A Systematic Evaluation of Machine Learning-based Biomarkers for Major Depressive Disorder across Modalities

Supplementary Materials

eMethods 1. Sample exclusion criteria

Participants with a history of neurological (e.g., concussion, stroke, tumor, neuro-inflammatory diseases) or medical conditions (e.g., cancer, chronic inflammatory or autoimmune diseases, heart diseases, diabetes mellitus, infections), as well as those who self-identified as non-Caucasian, were excluded from the analysis. Non-Caucasian participants were excluded since the FOR2107 MACS cohort was originally focused on genetic and neuroimaging analyses, thus providing greater genetic homogeneity. The exclusion criteria were the same for both the healthy and depressive participants. Additionally, healthy participants were further excluded if they had a current or past history of psychiatric illness. A sample of 1,801 participants remained for the analyses. Please note that the number of participants finally used in the machine learning models is reduced due to data availability and quality checks within the specific neuroimaging modality. Please see below for a detailed description of the number of participants used in each analysis.

eMethods 2. Diagnosis, remission status, and medication index

Each participant underwent a structured clinical interview for DSM-IV (SCID-I) to evaluate their current and lifetime psychopathological diagnoses.[1] For a Major Depressive Disorder (MDD) diagnosis, the participant had to meet the DSM-IV criteria, which includes experiencing at least five of nine core symptoms most of the day nearly every day for two weeks or more within the last four weeks, and must cause significant distress or impairment. At least one of the symptoms must either be a depressed mood or a markedly diminished interest or pleasure. Other symptoms include significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to concentrate or think clearly, and recurrent thoughts of death or suicide. Only participants with a primary MDD diagnosis were included in the MDD sample. MDD patients were not excluded if they fulfilled the criteria of an additional comorbid psychopathological diagnosis. Partial remission was defined either by (1) a presence of some major depressive symptoms, but full criteria are no longer met or (2) no major depressive symptoms, but the period of remission has been less than two months. Complete remission was defined as the absence of diagnostic criteria for depression for at least two consecutive months.

A medication load index was calculated expressing the combined dosage level of all current psychiatric medication. Trained personnel conducted interviews to assess current psychiatric medication, which were then classified categorized based on active ingredients (e.g. SSRIs, benzodiazepines). Psychiatric medication was coded based on established dosage-dependent cut-offs, with each active ingredient given a score of 0, 1, or 2.[2] The scores for all psychiatric medication were added together to create the final medication index. A similar procedure has been used in previous publications.[3,4]

eMethods 3. Definition of subgroups

In the secondary analyses that focused on acutely depressed patients, we excluded individuals with fully remitted MDD from the sample. In the secondary analyses that focused on recurrently depressed patients, we only included MDD subjects who had a history of at least two inpatient stays related to their depressive disorder. In addition, we ran analyses using only female or only male participants to reduce heterogeneity of the sample. We ran a final analysis using participants within a 5-year age range to reduce potential age effects confounding the classification analyses. To maximize the number of participants within a small age bin, we used an age range of 24 to 28, which showed the highest density of patients and controls.

eMethods 4. Assessment of childhood maltreatment and social support

The childhood trauma questionnaire (CTQ), a well-established tool, was used to evaluate childhood maltreatment in both patients and controls.[5] A sum score based on the five maltreatment subscales was computed and used in all analyses that included childhood maltreatment. No CTQ sum score was available for 13 individuals, resulting in a sample of N=1788 that could be used for the CTQ analysis.

The Social Support Questionnaire (F-SozU), an established German self-report measure, was used to evaluate perceived social support across three subscales (perceived emotional support, instrumental support, and social integration), with a sum score used in all analyses.[6] No social support sum score was available for 10 individuals, resulting in a sample of N=1791 that could be used for the social support analysis.

eMethods 5. Polygenic risk score for depression

Genetic data and preprocessing procedures have been described in previous publications.[7,8] Genome-wide genotyping was performed using the PsychArray BeadChip, followed by quality control (QC) and imputation using PLINK v1.9.[7,9–11] The genotype data were imputed to the 1000 Genomes phase 3 reference panel using SHAPEIT and IMPUTE2.[12,13] Genetic data were available for a total of n=1683 individuals. Related participants were identified using the PLINK command –genome and one individual of each related pair (PI-HAT ≥12.5) was excluded for a specific analysis. A total of 67 related participants were excluded for the main HC versus MDD analysis, resulting in a final sample of n=1616. Finally, a polygenic risk score (PRS) was calculated from the genetic data using the PRS-CS method and summary statistics from a recent depression GWAS, with the global shrinkage parameter phi estimated automatically using the PRS-CS-auto method ($\varphi=1\cdot30\times10^{-4}$).[14,15] This resulted in only a single PRS that was used in the present analysis. Note that the GWAS used for our PRS calculation investigated a wider depression phenotype which was not restricted to participants with a DSM MDD diagnosis. Therefore, we use the term 'depression PRS' throughout the manuscript. The FOR2107 MACS data used in this study were independent of the depression GWAS.

eMethods 6. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) data, protocol and preprocessing procedures (eMethods 6-12) have been described in a previous publication but are described here again to provide direct access to the relevant information.[8]

Data for all brain-based modalities using MRI were obtained through the use of two 3T whole body MRI scanners. The first scanner, located in Marburg, Germany, is the MAGNETOM Trio Tim with software version Syngo MR B17 (Siemens, Erlangen, Germany), equipped with a 12-channel head matrix Rx-coil. The second scanner, located in Münster, Germany, is the MAGNETOM Prisma with software version Syngo MR D13D (Siemens, Erlangen, Germany), equipped with a 20-channel head matrix Rx-coil. A GRAPPA acceleration factor of 2 was used during the acquisition process. Pulse sequence parameters were standardized across both sites to the extent possible (see below for differences between sites). More information on pulse sequence parameters, as well as quality assurance protocols, can be found in reference [16].

eMethods 7. T1-weighted MRI

The following parameters were used to acquire the structural MRI data: TE = 2.26ms (Marburg), TE = 2.28ms (Münster), TR = 1,900ms (Marburg), TR = 2,130ms (Münster), FoV = 256 mm, matrix = 256 × 256, slice thickness = 1 mm, distance factor = 50%, phase encoding direction anterior >> posterior, flip angle = 8°, bandwidth 200 Hz/Px, ascending acquisition, axial acquisition, 192 slices. Of the original sample of 1,801 subjects, 28 did not have a T1 scan available and 31 were excluded due to low image quality or artifacts, leaving a remaining sample of 1,742 subjects. Additionally, nine subjects were excluded from the Freesurfer analysis due to poor segmentation quality, leaving a final sample of 1,733 subjects. The quality of the images was assessed through visual inspection by a trained expert and by checking image homogeneity using the CAT12 toolbox. The voxel-based morphometry (VBM) was preprocessed using the default parameters in the CAT12 MATLAB toolbox (version r1450), which included bias correction, tissue segmentation, and normalization to MNI-space using linear and non-linear transformations.[17] Normalization was performed using a pre-computed high-dimensional DARTEL template, and the modulated gray matter images were smoothed with a Gaussian kernel of 8 mm FWHM. An absolute threshold masking value of 0.1 was used for all analyses, as recommended in the CAT12 manual (http://www.neuro.uni-jena.de/cat/).

Automated segmentation was performed using Freesurfer's (Version 5.3) cortical and subcortical parcellation stream based on the Desikan-Killiany atlas.[18] This allowed for the extraction of measures for 68 cortical regions (34 on each hemisphere), 14 subcortical regions (7 on each hemisphere), 4 ventricles (2 on each hemisphere), and total intracranial volume (ICV) for each participant. Global measures of cortical and subcortical surface, thickness, and volume were also calculated both per and across hemispheres, resulting in a total of 166 parameters that were used in the statistical analyses. Default parameters were used for the segmentation (https://surfer.nmr.mgh.harvard.edu/), and segmentation quality was reviewed visually and based on statistical outlier analysis following standardized protocols by the ENIGMA consortium.[19]

eMethods 8. Functional MRI image acquisition

The two functional MRI paradigms (face matching and resting-state) were based on a T_2*-weighted echo-planar imaging (EPI) sequence that was sensitive to blood oxygen level-dependent (BOLD) contrast. The following parameters were used: TE = 30 ms (Marburg), TE = 29ms (Münster), TR = 2,000 ms, FoV = 210 mm, matrix = 64 × 64, slice thickness = 3.8 mm, distance factor = 10%, phase encoding direction anterior >> posterior, flip angle = 90°, no parallel imaging, bandwidth 2,232 Hz/Px, ascending acquisition, axial acquisition, 33 slices, slice alignment parallel to AC-PC line tilted 20° in the dorsal direction. For resting-state fMRI, 237 interleaved and ascending measurements (8 minutes) were acquired, tilted with -20° against the anterior and posterior commission alignment (AC-PC alignment) and the following parameters: Base resolution=64, Bandwith=2,232 Hz/Px, Echo spacing=0.51ms, EPI factor=64, TR=2s). Participants were asked to keep their eyes closed until the end of the resting state session.

eMethods 9. Resting-State fMRI

Resting-state data was preprocessed using the CONN (v18b) MATLAB toolbox and its default volume-based MNI preprocessing pipeline.[20] The functional and structural images underwent several preprocessing steps, including functional realignment and unwarp, slice-timing correction, outlier identification based on the ART method, direct segmentation, and normalization of functional and structural images, as well as functional smoothing using an 8mm FWHM kernel. To regress out potential noise artefacts in the functional data, CONN's denoising step was used with default parameters. This process involved an anatomical component-based noise correction procedure (aCompCor), where cerebral white matter and cerebrospinal areas' noise components (5 PCA components), estimated subject-motion parameters (12 parameters including 6 motion parameters and their associated first-order derivatives), and identified outlier scans were regressed out.[21] Additionally, temporal band-pass filtering was applied to remove low frequencies under 0.008 Hz and high frequencies above 0.09 Hz.

Resting-state and T_1 data from 1372 subjects were available for the analyses. 14 subjects were excluded due to recent use of tranquilizers such as benzodiazepine or Z-drugs, which are known to affect functional MRI data. 16 subjects were excluded after visual quality checks revealed poor quality of the functional or structural segmentation and normalization or distribution of correlation values after denoising did not follow a normal distribution, as determined by quality assurance plots in the CONN toolbox. 11 subjects were excluded due to significant motion artifacts that resulted in fewer than 5 minutes of usable resting-state image time points after scrubbing. As a result, data from a total of 1331 subjects was available for the resting-state analyses.

The connectivity matrices for each participant were generated by computing the bivariate Pearson's correlation coefficient between the time-series of each region of the 17 networks Schaefer atlas (100 parcels). The Amplitude of Low-Frequency Fluctuations (ALFF) maps were computed from the resting-state time-series. The ALFF represents a measure of the BOLD signal power within the frequency band of interest, defined as the root mean square of the BOLD signal at each voxel after filtering.[22] To obtain a relative measure of BOLD signal power, the fractional ALFF (fALFF) was computed as the ratio of the root mean square of the BOLD signal at each voxel after versus before low- or band-pass filtering. Regional homogeneity was measured using the Local Correlation (LCOR) method, which is a more robust version of the original ReHo definition by Zang et al. (2004) across different data resolutions and neighboring sizes. LCOR is defined as the average of correlation coefficients between each individual voxel and a region of neighboring voxels.[20] For a more detailed description of the Integrated Local Correlation and a comparison to ReHo, see Deshpande et al. (2009).[23]

eMethods 10. Task-based fMRI

Functional MRI data from a well-established emotional face matching paradigm was used.[24] In summary, the experimental design involved presenting images of faces depicting fear or anger during the task, while geometric shapes served as the control condition. Each trial consisted of a target image presented at the top and two additional images displayed at the bottom left and right, one of which matched the target image. Participants were instructed to indicate which of the bottom images was identical to the target image by pressing the corresponding button. The preprocessing steps for this dataset have also been described previously.[25]

The same image acquisition parameters used for the resting-state scans were used for the emotional face matching paradigm. Subjects whose overall movement exceeded 2mm were excluded from the final sample to avoid motion artifacts, and a visual quality check was performed to exclude subjects with visible artifacts. Subjects under acute medication with tranquilizers were also excluded from the analyses. The fMRI responses for both the faces and shapes conditions were modeled using a block design and the canonical hemodynamic response function in SPM8, with high-pass filtering (cut-off frequency of 1/128 Hz) applied to attenuate low-frequency components. Contrast images were created by contrasting beta images of the faces and shapes conditions. Of the 1364 participants with available face matching fMRI data, 7 subjects under acute medication with tranquilizers were excluded, leaving a sample of 1357. An additional 109 subjects with more than 2mm of movement were excluded, leaving a sample of 1248. 14 subjects with low image quality or artifacts, as determined by visual inspection by a trained expert, were also excluded. Thus, a final sample of 1234 subjects was available for the face matching task-based fMRI analyses.

eMethods 11. DTI image acquisition and preprocessing

DTI data were acquired using a GRAPPA acceleration factor of two. 56 axial slices with no gap were measured with an isotropic voxel size of 2.5×2.5×2.5 mm3 (TE = 90 ms, TR = 7300 ms). Five non-DW images (*b* = 0 s/mm2) and 2 × 30 DW images with a *b*-value of 1000 s/mm2 were acquired.

The preprocessing procedure of the DTI images is described in more detail in a previous publication.[26] In summary, realignment and eddy correction of the Diffusion-weighted images (DWI) was done using FSL eddy.[27–30] Next, the reconstruction of the anatomical connectome was achieved using the CATO toolbox, which models the measured signal of a single voxel by a tensor describing the preferred diffusion direction per voxel.[31] CATO uses the RESTORE algorithm, which estimates the diffusion tensor while simultaneously identifying and removing outliers, thereby reducing the impact of physiological noise artifacts.[29,30] Deterministic tractography was used to reconstruct white matter paths. To this end, eight seeds were started per voxel, and for each seed, a tractography streamline was constructed by following the main diffusion direction from voxel to voxel. Stop criteria included reaching a voxel with a fractional anisotropy <0.1, making a sharp turn of >45°, reaching a gray matter voxel, or exiting the brain mask. Given the poorer DWI signal-to-noise ratio in subcortical regions and the dominant effect of subcortical regions on network properties, we decided to use the Lausanne parcellation including 114 cortical brain regions, a subdivision of FreeSurfer's Desikan Killiany Atlas, as we have done in previous work.[26,32–34] Matrix entries represent the weights of the graph edges. Network edges were weighted according to fractional anisotropy (FA), mean diffusivity (MD), and number of streamlines (NOS). In total, DTI data was available for 1558 participants. After quality control (see below), 55 subjects were excluded, resulting in a final sample of 1503 participants for all DTI-based analyses.

Outlier detection during quality checks were based on the following four metrics: the average number of streamlines, the average fractional anisotropy, the average prevalence of each subject's connections (low value if the subject has "odd" connections), and the average prevalence of each subjects connected brain regions (high value, if the participant misses commonly found connections). Then, quartiles (Q1, Q2, Q3) and the interquartile range (IQR=Q3-Q1) was computed for every metric across the group. A datapoint was declared an outlier if its value was below Q1-1.5*IQR or above Q3+1.5*IQR on any of the four metrics.

eMethods 12. Graph network parameters

To create the DTI and resting-state fMRI connectivity matrices, a binary adjacency matrix was produced using different methods. For DTI, a binary adjacency matrix was computed based on the number of streamlines, where all edges with less than three number of streamlines were set to 0 and all other edges were set to 1. For resting-state fMRI, a binary adjacency matrix was created by setting the top 15 percent of connections (highest correlation coefficient) to 1, and all other edges were set to 0. These adjacency matrices were then used to derive a variety of graph parameters using PHOTONAI Graph (https://github.com/wwu-mmll/photonai_graph). The selected graph metrics were global efficiency, local efficiency, clustering coefficient, degree centrality, betweenness centrality, and degree assortativity (for an introduction of graph metrics for brain connectivity, see [35]). Global efficiency was computed as the average inverse shortest path length between all node pairs, while local efficiency was computed on node neighborhoods. Clustering coefficient was defined as the average probability that the neighbors of a node are also mutually connected. Degree centrality was defined as the number of nodes connected to the node of interest, while betweenness centrality was defined as the proportion of shortest paths in the network that pass through the node of interest. Clustering coefficient, degree centrality, and betweenness centrality were calculated per node and additionally averaged across nodes, resulting in a total of 348 network parameters. For further information on graph metrics for brain connectivity, see (36).

eMethods 13. Reliability Analysis

The calculation of BACC from MCC requires information on prevalence ϕ and bias β as is described in [36]. In this context, prevalence measures the frequency of MDD cases in the test set while bias refers to how likely the classifier predicts an MDD label in the test set. We corrected MCC independently for all test sets of the 10 folds and converted it back to BACC using the frequency of MDD cases and frequency of MDD predictions in the corresponding test sets.

eMethods 14. Machine Learning Analysis

General

All ML analyses were done using Python 3.8, scikit-learn version 0.24.2 and photonai version 2.2.0. For all analyses, a strict nested cross-validation scheme with 10 inner and 10 outer folds was used to train, optimize, and evaluate the ML pipeline. Imputation, scaling, feature selection, and dimensionality reduction was always done on the training set and then applied to the validation or test set to ensure the independence assumption of the cross-validation. The inner cross-validation was used to optimize all hyperparameters. Once an optimal configuration based on mean balanced accuracy across the 10 validation sets was found, an ML pipeline with this configuration was trained on the complete training set and evaluated on the 10% test set. This was done for all 10 outer folds.

Imputation

The first step of the ML pipeline was an imputation of missing values. We used sklearn's SimpleImputer with default parameters. Missing values for a single feature of the training and test data were imputed with the mean of the training set. No hyperparameter tuning was performed for this pipeline element.

Scaling

The second step of the ML pipeline was an individual scaling of every feature using sklearn's RobustScaler method with default settings. This scaling method removes the median and scales the data according to the interquartile range. The interquartile is the range between the 1st quartile (25th quantile) and the 3rd quartile (75th quantile). Scaling of the features in the test set is done using the median and interquartile range of the training set to avoid data leakage.

Feature Selection and Dimensionality Reduction

The third step of the ML pipeline was a photonai Switch, an element that evaluates two or more other elements at the same position in the complete pipeline. In this case, the photonai Switch chose between a feature selection or a dimensionality reduction element. The selection of an ML element within a photonai Switch itself can be seen as a hyperparameter that is optimized by photonai. The feature selection was done using sklearn's f_classif() method that computes a statistical F-value from an ANOVA model differentiating between healthy participants and patients with MDD. This was combined with sklearn's selection method SelectPercentile, selecting a predefined percentage of features with the F-values. For our analyses, we used 5, 10, and 50 percent of the features as selection criterion. The dimensionality reduction as an alternative pipeline element was implemented using a Principal Component Analysis (PCA) from sklearn. A PCA is a linear dimensionality reduction method using Singular Value Decomposition to project the data into a lower dimensional space of orthogonal components. We used sklearn's default parameters to perform a full variance decomposition using all possible principal components. This will reduce the dimensionality of the data to either the number of features or the number of samples, depending on what is lower. The only hyperparameter of the PCA step was therefore whether to do the dimensionality reduction or not. In combination, this resulted in 6 possible hyperparameter configurations (4 for feature selection, 2 for dimensionality reduction).

Classification Algorithms

The last step of the ML pipeline consisted of one of six classification algorithms from different categories. First, a boosting ensemble method was evaluated using sklearn's GradientBoostingClassifier. It uses a decision tree classifier as base estimator and builds an additive model in a forward stage-wise fashion. As a hyperparameter, the number of boosting stages (n_estimators) was set to 10, 25, or 50. Second, a bagging ensemble implemented as a Random Forest was evaluated using sklearn's RandomForestClassifier. Two hyperparameters were optimized to control the amount of overfitting. The maximum number of features used for each split (max_features) was set to either the square root or log2 of the total number of features. The minimum samples required in a leaf of the individual decision trees was set to either 1%, 10%, or 20% of the total number of samples in the training set. Third, to evaluate the potential of linear models, we used a logistic regression as implemented in sklearn's LogisticRegression class. To control the amount of overfitting, we optimized the penalty added to the cost function using either L1 (lasso), L2 (ridge), or elastic net. In addition, we set the regularization parameter C to 0.0001, 0.01, 1, 100, or 10,000. Fourth, representing kernel methods which are very popular in multivariate neuroimaging data analysis, a support vector machine was evaluated using either the LinearSVM or SVM classes from sklearn. We used either a linear, polynomial, or radial basis function kernel with a C value of 10^{-8}, 10^{-6}, 10^{-4}, 10^{-2}, 1, 10^{2}, 10^{4}, 10^{6}, or 10^{8}. Fifth, a Gaussian naive Bayes classifier was evaluated as implemented in sklearn's GaussianNB class with default hyperparameters. Sixth, a k-nearest neighbour classification algorithm was evaluated as implemented in sklearn's KNeighborsClassifier class, optimizing the number of possible neighbours (5, 10, 15).

Number of Evaluated ML Pipelines

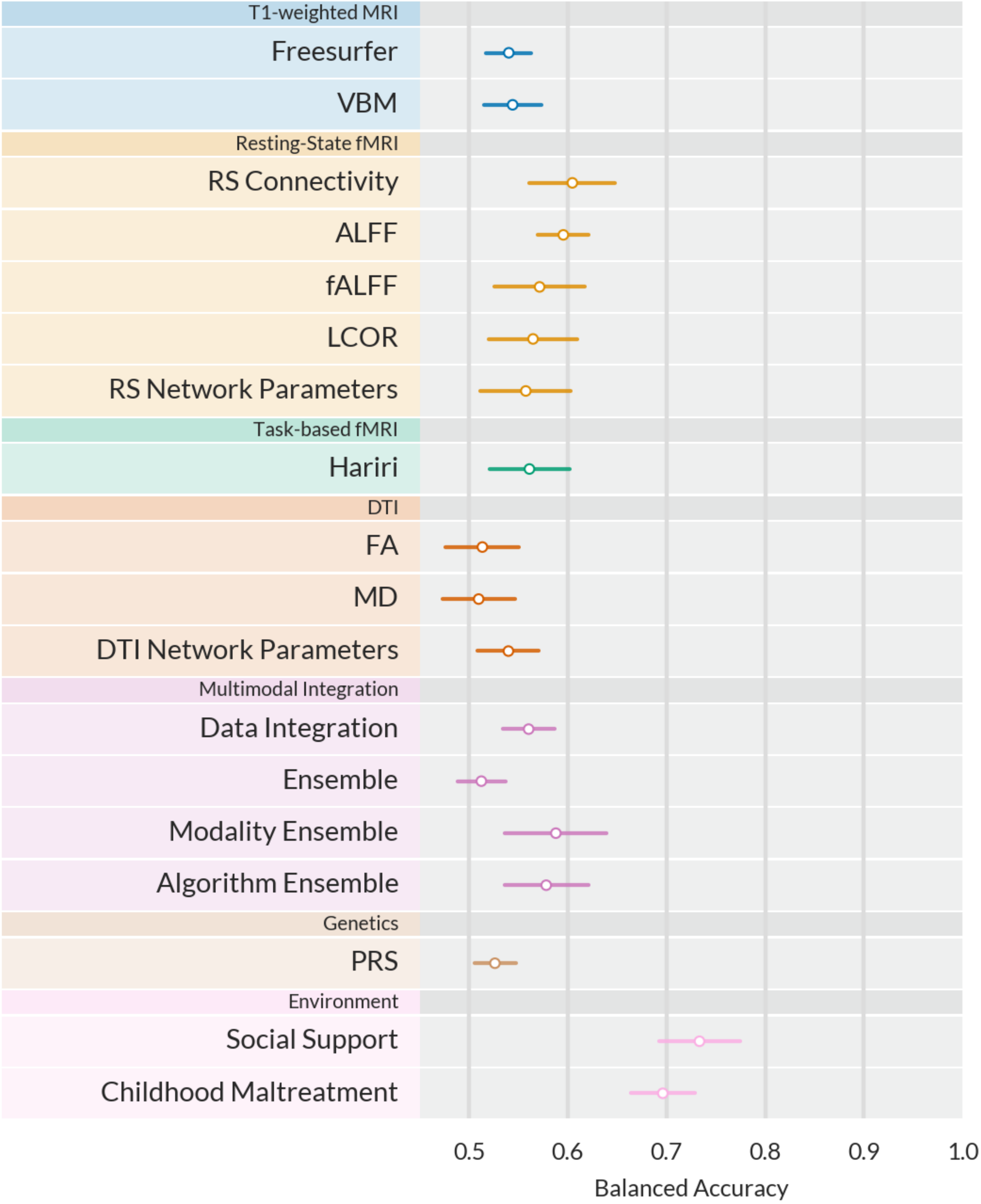
As reported in the main article, a total of about 2.4 million ML pipelines were trained in this project. The total number of pipelines are calculated below. Number of possible hyperparameter configurations are listed in parentheses next to the corresponding pipeline step.

1. [Imputation (1)] x [Scaling (1)] x [Feature Selection (4) + Dimensionality Reduction (2)] x [BC (3) + RF (6) + LR (15) + SVM (27) + NB (1) + kNN (3)] = 330 ML pipelines
2. 330 pipelines x 10 inner folds x 10 outer folds + 6 optimal configurations (one per classifier) x 10 outer folds = 33,060 pipelines
3. 33,060 pipelines x 12 modalities (11 unimodal and 1 PCA-based modality integration) = 396,720 pipelines
4. 396,720 pipelines x 6 subgroup analyses (all, acute, recurrent, male, female, age bin) = 2,380,320 pipelines

Modality Integration and Voting Ensemble

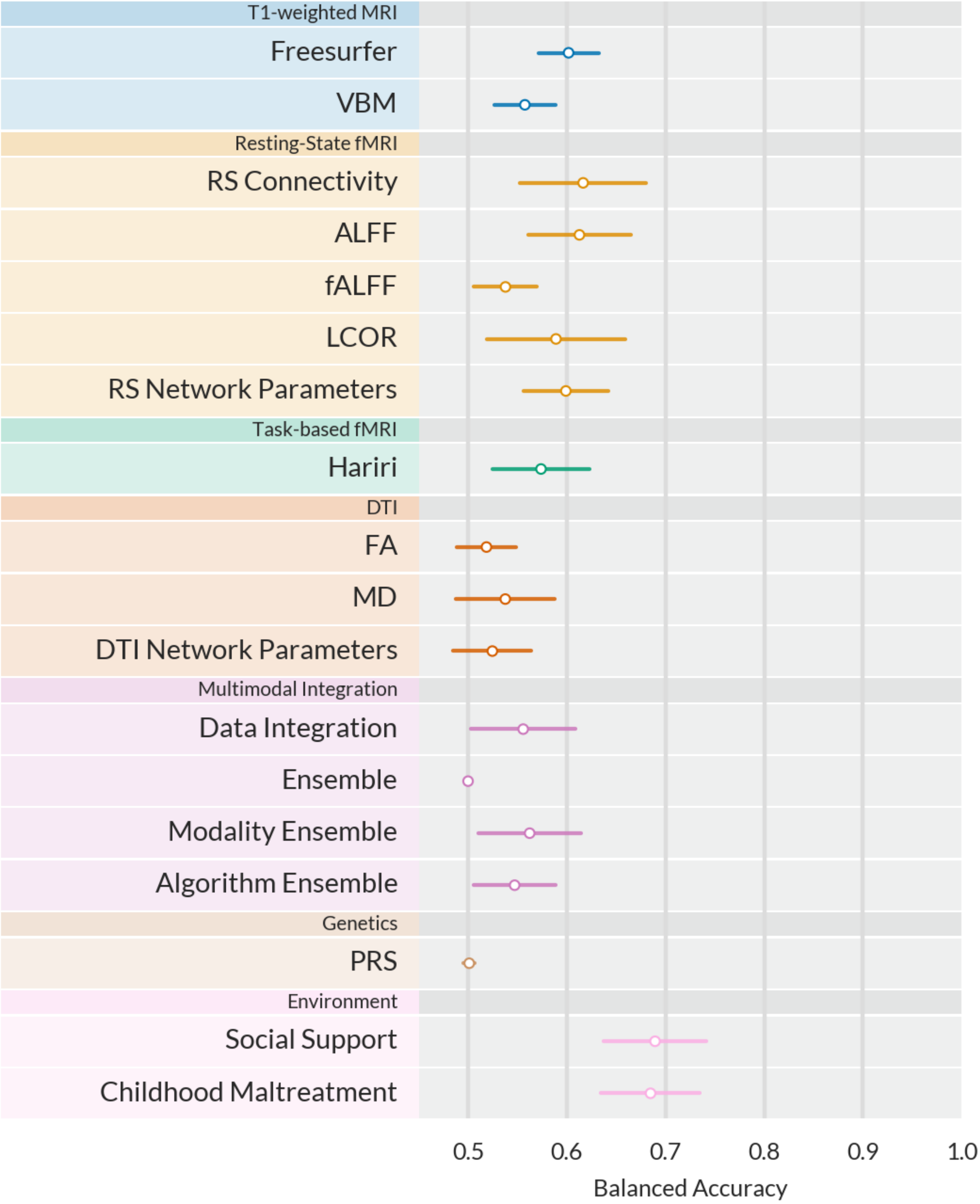
Modality integration was achieved using two different methods. First, the neuroimaging data was compressed and concatenated into one data matrix. Dimensionality reduction was implemented using a principal component analysis on every neuroimaging modality separately. All possible principal components were used to create the resulting data matrix, i.e. n_components of sklearn's PCA() method was set to "None" to allow for a full variance decomposition. The number of principal components was thus limited by either the training set sample size or the number of initial features, depending on the specific modality. The resulting data matrix was used as input to the ML pipelines described above. Importantly, this PCA-based modality integration was also done within the nested-cross validation, i.e. the PCA's were trained on the training set and applied to the test set. This was implemented using photonai's Stack and Branch pipeline elements. Second, an ensemble voting algorithm was used to combine predictions of all unimodal models. In order to build the voting ensemble, the optimized ML pipelines in every outer fold across neuroimaging modalities were used to classify between healthy participants and patients with MDD in the corresponding test set. For one participant, this resulted in 11 (modalities) x 6 (classification algorithm pipelines described above) predicted labels (HC or MDD). If data for a specific neuroimaging modality was not available for a participant, the number of usable predictions within the ensemble was thus reduced. A final prediction for every participant was calculated using a majority vote method. Simply put, the final prediction was determined by the most frequent prediction (HC or MDD). Finally, the classification metrics were calculated exactly as in the unimodal models and mean and standard deviation across the 10 outer folds are reported. Depending on which model predictions were used in the ensemble, different voting strategies could be evaluated. One ensemble model contained predictions from all algorithms and all modalities. Another aggregated across modalities only, keeping the classification algorithms separately which resulted in a final classification for every algorithm. A final ensemble model aggregated across classification algorithms but keeping the neuroimaging modalities separately. Note that this final method actually did not combine predictions across neuroimaging modalities and thus cannot be considered a modality integration analysis. Still, it evaluates the use of an algorithm ensemble for every modality.

eFigure 1. Classification results for healthy participants versus patients with acute MDD



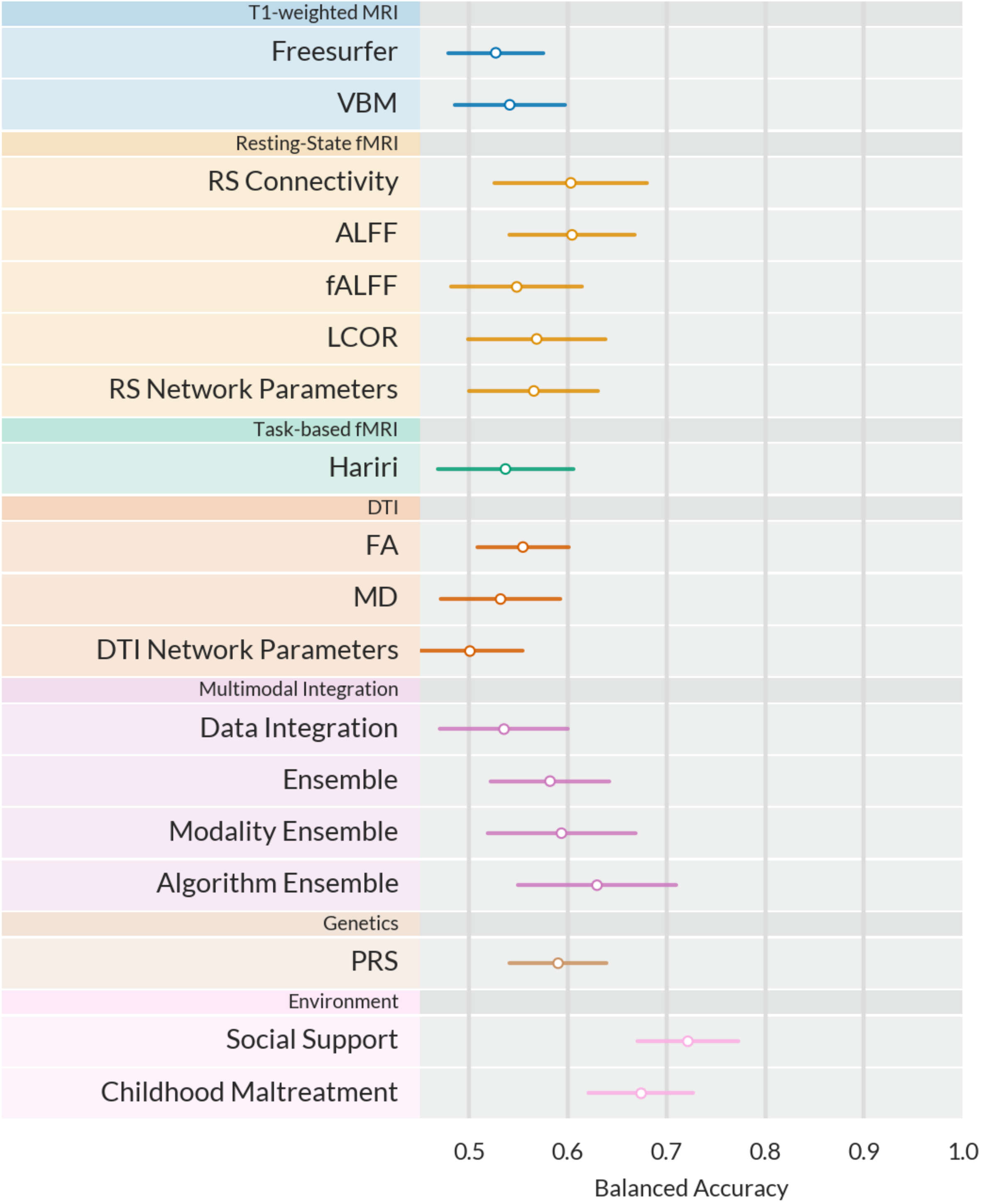
eFigure 1. Balanced accuracy for best machine learning pipeline in every modality. Error bars display +-1 standard deviation calculated across the 10 outer cross-validation folds. VBM=Voxel-based morphometry, ALFF=Amplitude of low-frequency fluctuations, fALFF=fractional ALFF, LCOR=Local correlation, FA=Fractional anisotropy, MD=Mean diffusivity, PRS=Polygenic risk score.

eFigure 2. Classification results for healthy participants versus patients with recurrent MDD



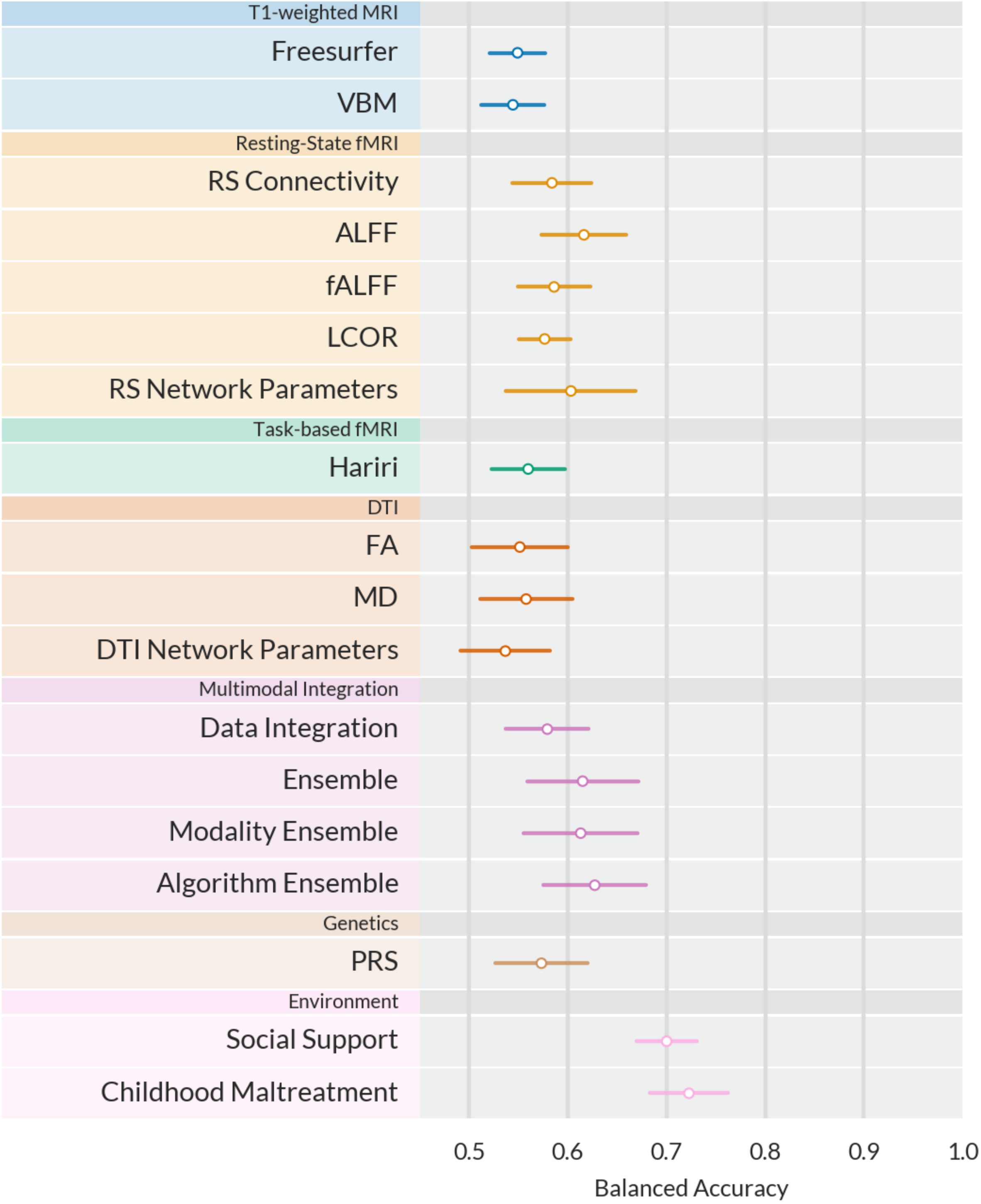
eFigure 2. Balanced accuracy for best machine learning pipeline in every modality. Error bars display +-1 standard deviation calculated across the 10 outer cross-validation folds. VBM=Voxel-based morphometry, ALFF=Amplitude of low-frequency fluctuations, fALFF=fractional ALFF, LCOR=Local correlation, FA=Fractional anisotropy, MD=Mean diffusivity, PRS=Polygenic risk score.

eFigure 3. Classification results for male participants only (HC versus MDD)



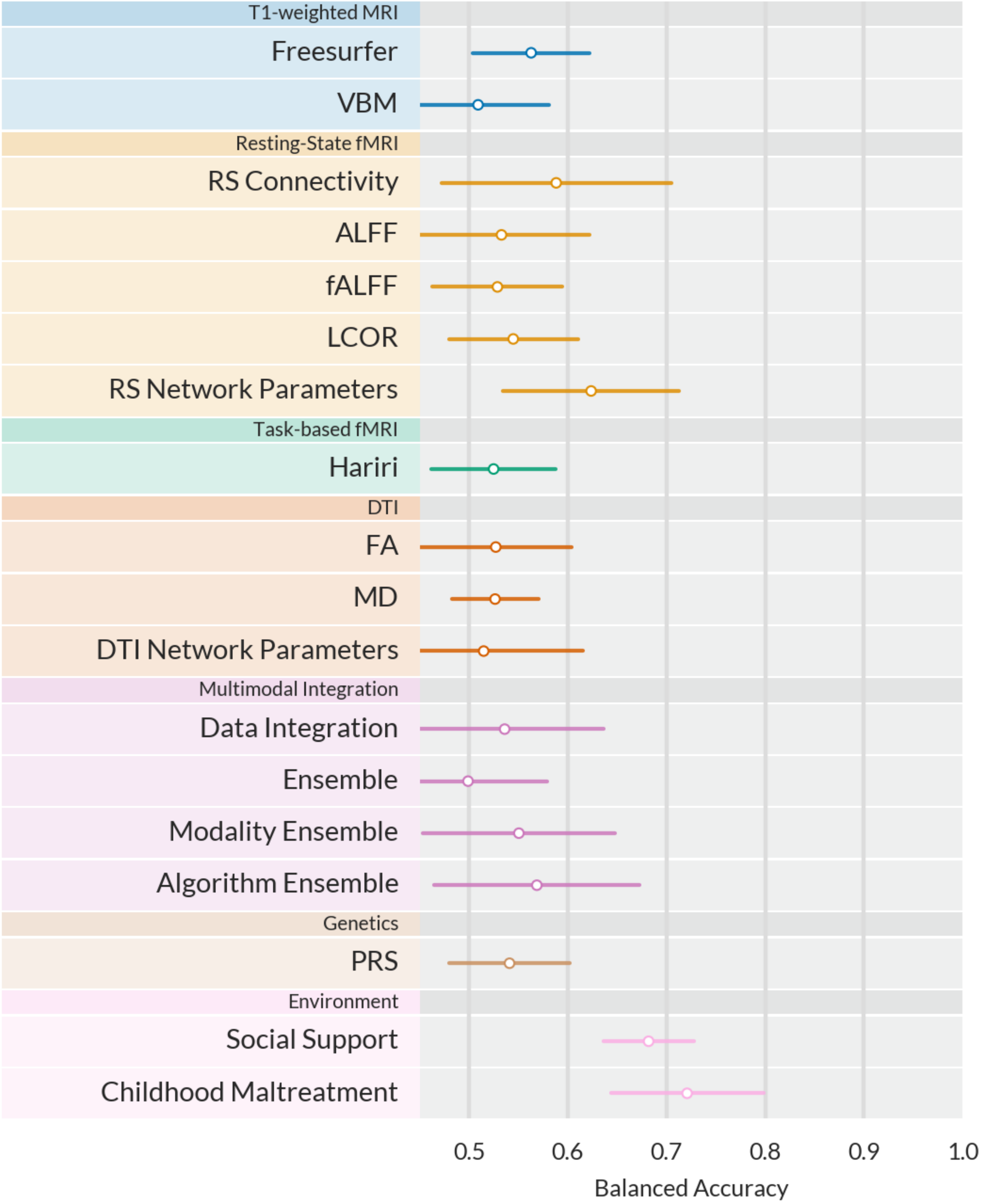
eFigure 3. Balanced accuracy for best machine learning pipeline in every modality. Error bars display +-1 standard deviation calculated across the 10 outer cross-validation folds. VBM=Voxel-based morphometry, ALFF=Amplitude of low-frequency fluctuations, fALFF=fractional ALFF, LCOR=Local correlation, FA=Fractional anisotropy, MD=Mean diffusivity, PRS=Polygenic risk score.

eFigure 4. Classification results for female participants only (HC versus MDD)



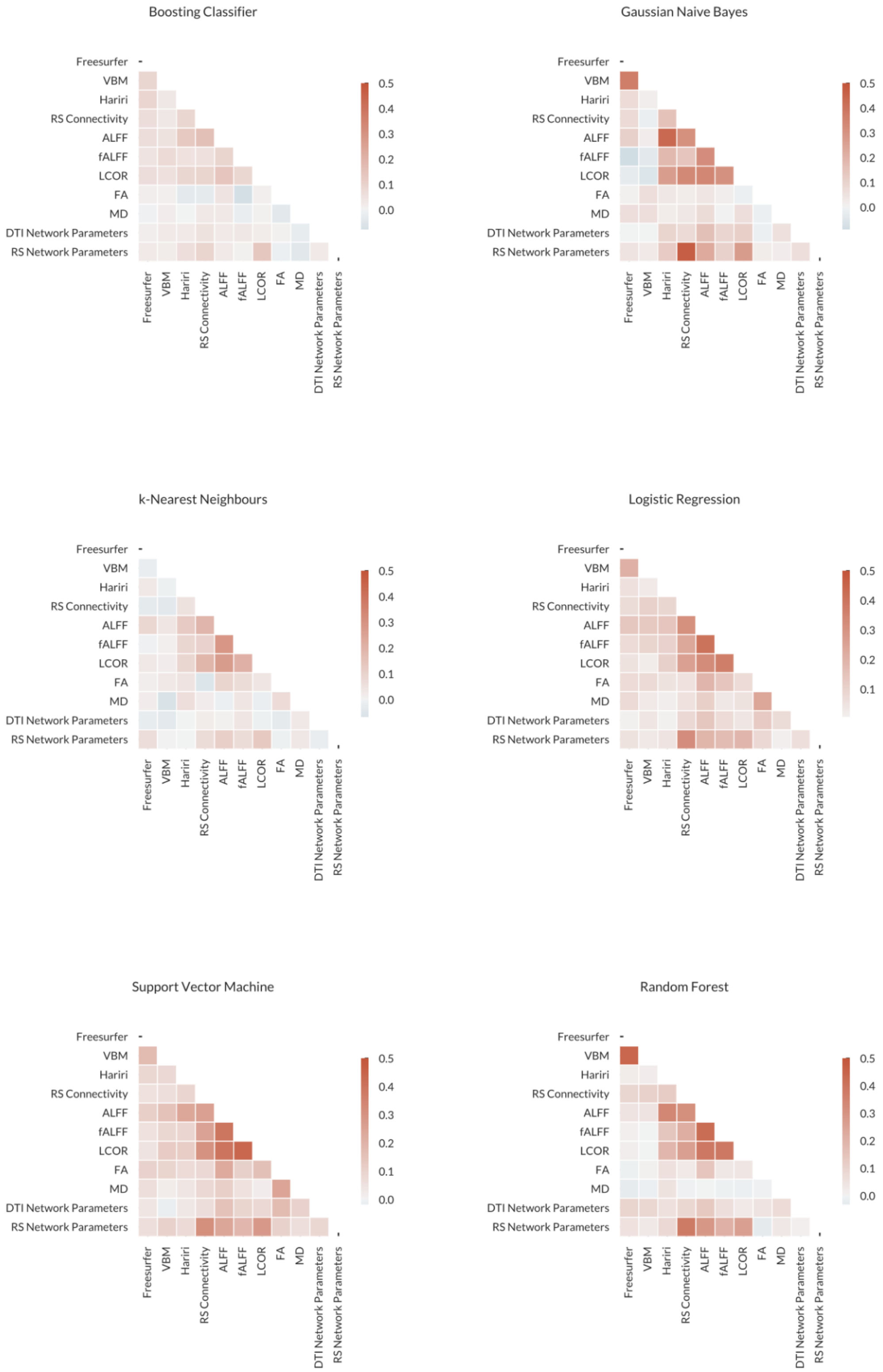
eFigure 4. Balanced accuracy for best machine learning pipeline in every modality. Error bars display +-1 standard deviation calculated across the 10 outer cross-validation folds. VBM=Voxel-based morphometry, ALFF=Amplitude of low-frequency fluctuations, fALFF=fractional ALFF, LCOR=Local correlation, FA=Fractional anisotropy, MD=Mean diffusivity, PRS=Polygenic risk score.

eFigure 5. Classification results for participants within an age range of 24 to 28 years (HC versus MDD)



eFigure 5. Balanced accuracy for best machine learning pipeline in every modality. Error bars display +-1 standard deviation calculated across the 10 outer cross-validation folds. VBM=Voxel-based morphometry, ALFF=Amplitude of low-frequency fluctuations, fALFF=fractional ALFF, LCOR=Local correlation, FA=Fractional anisotropy, MD=Mean diffusivity, PRS=Polygenic risk score**.**

eFigure 6. Correlations of model predictions across modalities for HC versus MDD.



eFigure 6. Correlation plots correlating model predictions for all six algorithms across neuroimaging modalities.

eTable 1. Classification accuracy for multivariate biomarkers based on structural MRI.

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Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
Freesurfer	Boosting Classifier	51.9% (2.8%)	52.6% (2.9%)	41.1% (8.2%)	62.8% (8.6%)	52.9% (3.7%)	0.04 (0.06)	920/813
	k-Nearest Neighbours	51.2% (4.8%)	51.8% (4.9%)	42.8% (6.2%)	59.7% (8.3%)	52.4% (5.2%)	0.03 (0.1)	920/813
	Logistic Regression	53.7% (3.1%)	54.5% (2.9%)	41.0% (9.2%)	66.4% (7.0%)	55.7% (3.8%)	0.08 (0.06)	920/813
	Gaussian Naive Bayes	54.5% (2.1%)	55.1% (2.1%)	46.4% (5.1%)	62.7% (4.7%)	56.0% (3.5%)	0.09 (0.04)	920/813
	Random Forest	53.5% (2.3%)	54.6% (2.3%)	34.8% (4.9%)	72.2% (4.7%)	55.1% (3.4%)	0.08 (0.05)	920/813
	Support Vector Machine	53.4% (2.7%)	54.4% (2.5%)	37.8% (9.6%)	69.0% (7.4%)	53.4% (2.7%)	0.07 (0.06)	920/813
VBM	Boosting Classifier	53.2% (3.6%)	53.6% (3.9%)	45.5% (4.3%)	60.8% (8.1%)	53.9% (3.6%)	0.07 (0.07)	924/817
	k-Nearest Neighbours	50.5% (2.5%)	51.4% (2.5%)	35.5% (6.1%)	65.5% (5.5%)	50.0% (3.2%)	0.01 (0.05)	924/817
	Logistic Regression	51.4% (3.2%)	49.7% (3.2%)	80.0% (8.3%)	22.8% (8.4%)	51.4% (4.1%)	0.04 (0.07)	924/817
	Gaussian Naive Bayes	52.5% (3.4%)	53.6% (2.8%)	34.4% (23.1%)	70.6% (18.6%)	54.8% (2.4%)	0.05 (0.07)	924/817
	Random Forest	55.3% (4.6%)	56.4% (4.7%)	37.9% (7.4%)	72.7% (7.8%)	57.4% (4.0%)	0.12 (0.1)	924/817
	Support Vector Machine	51.4% (3.3%)	51.2% (3.6%)	54.0% (6.7%)	48.8% (10.8%)	51.4% (3.3%)	0.03 (0.07)	924/817
DTI FA	Boosting Classifier	49.5% (3.5%)	50.6% (4.2%)	37.1% (14.3%)	61.9% (16.7%)	50.0% (4.3%)	-0.01 (0.07)	818/685
	k-Nearest Neighbours	51.8% (3.5%)	52.2% (3.5%)	47.7% (10.6%)	55.9% (9.4%)	51.8% (4.4%)	0.04 (0.07)	818/685
	Logistic Regression	51.0% (4.9%)	52.0% (4.7%)	39.7% (8.9%)	62.2% (6.8%)	53.0% (5.5%)	0.02 (0.1)	818/685
	Gaussian Naive Bayes	48.1% (3.6%)	46.8% (3.1%)	62.8% (28.5%)	33.5% (24.7%)	48.7% (3.8%)	-0.03 (0.08)	818/685
	Random Forest	49.5% (3.4%)	51.8% (4.0%)	23.8% (6.6%)	75.2% (10.7%)	49.7% (5.6%)	-0.01 (0.08)	818/685

	Support Vector Machine	54.9% (3.0%)	56.0% (2.9%)	41.9% (6.2%)	67.9% (4.4%)	54.9% (3.0%)	0.1 (0.06)	818/685
DTI MD	Boosting Classifier	49.4% (3.4%)	50.6% (3.8%)	36.5% (13.1%)	62.3% (14.2%)	47.4% (3.0%)	-0.01 (0.07)	818/685
	k-Nearest Neighbours	49.9% (4.8%)	51.1% (4.8%)	37.2% (8.5%)	62.7% (7.8%)	49.2% (5.8%)	-0.0 (0.1)	818/685
	Logistic Regression	50.8% (4.1%)	52.2% (4.6%)	35.4% (13.7%)	66.3% (16.2%)	51.3% (4.9%)	0.02 (0.09)	818/685
	Gaussian Naive Bayes	51.2% (2.4%)	52.5% (2.9%)	36.2% (9.7%)	66.2% (11.8%)	49.8% (4.0%)	0.03 (0.05)	818/685
	Random Forest	50.1% (2.6%)	52.6% (2.9%)	21.8% (5.5%)	78.5% (8.0%)	50.3% (4.9%)	0.01 (0.07)	818/685
	Support Vector Machine	51.8% (3.5%)	52.8% (3.7%)	40.3% (7.9%)	63.3% (9.4%)	51.8% (3.5%)	0.04 (0.07)	818/685
DTI Network Parameters	Boosting Classifier	52.8% (3.2%)	53.8% (3.4%)	40.5% (5.2%)	65.1% (7.7%)	54.0% (3.6%)	0.06 (0.07)	818/685
	k-Nearest Neighbours	51.1% (3.3%)	52.8% (3.3%)	32.8% (7.2%)	69.5% (7.2%)	51.4% (5.1%)	0.02 (0.07)	818/685
	Logistic Regression	54.4% (3.7%)	55.0% (3.6%)	48.2% (5.0%)	60.6% (4.1%)	57.8% (4.5%)	0.09 (0.07)	818/685
	Gaussian Naive Bayes	54.0% (4.9%)	54.0% (4.8%)	53.9% (8.8%)	54.0% (7.6%)	56.0% (4.3%)	0.08 (0.1)	818/685
	Random Forest	53.7% (1.8%)	56.0% (2.1%)	28.6% (7.1%)	78.9% (8.3%)	54.4% (3.8%)	0.09 (0.05)	818/685
	Support Vector Machine	53.3% (2.3%)	54.6% (1.9%)	39.3% (8.5%)	67.4% (5.7%)	53.3% (2.3%)	0.07 (0.05)	818/685

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 2. Classification accuracy for multivariate biomarkers based on functional MRI.

eTable 2. Classification accuracy for multivariate biomarkers based on functional MRI.

Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
Face Matching Task	Boosting Classifier	53.0% (4.1%)	53.3% (4.0%)	48.8% (7.5%)	57.2% (4.8%)	52.9% (5.6%)	0.06 (0.08)	654/580
	k-Nearest Neighbours	51.5% (5.7%)	52.5% (5.4%)	34.7% (12.7%)	68.3% (5.9%)	51.9% (5.6%)	0.03 (0.12)	654/580
	Logistic Regression	53.3% (6.0%)	53.5% (5.9%)	49.1% (10.6%)	57.4% (7.8%)	54.8% (5.8%)	0.07 (0.12)	654/580
	Gaussian Naive Bayes	54.9% (4.7%)	54.8% (4.7%)	56.4% (7.9%)	53.4% (8.2%)	55.6% (4.9%)	0.1 (0.09)	654/580
	Random Forest	55.6% (4.5%)	56.5% (4.5%)	41.9% (6.3%)	69.4% (5.6%)	59.1% (5.7%)	0.12 (0.09)	654/580
	Support Vector Machine	54.0% (5.3%)	54.2% (5.5%)	50.0% (15.5%)	58.0% (16.0%)	54.0% (5.3%)	0.08 (0.11)	654/580
RS Connectivity	Boosting Classifier	51.5% (7.1%)	51.7% (7.1%)	48.5% (10.1%)	54.6% (8.5%)	54.5% (7.4%)	0.03 (0.14)	700/631
	k-Nearest Neighbours	56.1% (6.3%)	56.9% (6.1%)	40.3% (11.5%)	71.9% (7.2%)	59.1% (7.3%)	0.13 (0.13)	700/631
	Logistic Regression	59.7% (3.7%)	60.2% (3.8%)	49.5% (7.1%)	69.9% (7.8%)	62.7% (4.4%)	0.2 (0.08)	700/631
	Gaussian Naive Bayes	59.0% (3.6%)	59.1% (3.7%)	56.6% (6.4%)	61.4% (8.2%)	60.4% (2.9%)	0.18 (0.07)	700/631
	Random Forest	59.1% (3.1%)	59.6% (2.9%)	49.3% (11.0%)	68.9% (7.2%)	61.3% (3.1%)	0.19 (0.06)	700/631
	Support Vector Machine	61.5% (3.4%)	61.8% (3.3%)	55.3% (7.2%)	67.7% (5.0%)	61.5% (3.4%)	0.23 (0.07)	700/631
ALFF	Boosting Classifier	56.6% (4.2%)	56.8% (4.4%)	52.8% (7.5%)	60.5% (10.5%)	60.4% (6.0%)	0.13 (0.08)	701/631
	k-Nearest Neighbours	60.3% (4.3%)	60.7% (4.4%)	53.4% (5.8%)	67.2% (6.4%)	63.2% (4.6%)	0.21 (0.09)	701/631
	Logistic Regression	61.0% (4.7%)	61.3% (4.6%)	55.8% (8.7%)	66.2% (6.1%)	64.3% (4.2%)	0.22 (0.09)	701/631
	Gaussian Naive Bayes	59.1% (4.3%)	59.2% (4.3%)	55.8% (7.7%)	62.4% (8.7%)	59.7% (4.6%)	0.18 (0.09)	701/631
	Random Forest	59.8% (3.5%)	60.4% (3.5%)	49.9% (7.4%)	69.8% (6.5%)	63.9% (4.1%)	0.2 (0.07)	701/631
	Support Vector Machine	60.2% (3.4%)	60.7% (3.3%)	52.1% (8.2%)	68.3% (6.0%)	60.2% (3.4%)	0.21 (0.07)	701/631
fALFF	Boosting Classifier	52.7% (4.4%)	52.9% (4.3%)	47.7% (9.9%)	57.6% (9.2%)	53.3% (5.7%)	0.05 (0.09)	701/631

	k-Nearest Neighbours	55.6% (3.2%)	56.6% (3.2%)	36.6% (6.7%)	74.6% (5.7%)	57.3% (4.7%)	0.12 (0.07)	701/631
	Logistic Regression	58.7% (4.0%)	59.1% (4.0%)	51.8% (6.2%)	65.6% (6.1%)	61.6% (5.5%)	0.18 (0.08)	701/631
	Gaussian Naive Bayes	54.7% (4.4%)	54.8% (4.3%)	52.5% (6.8%)	56.9% (4.7%)	54.9% (4.5%)	0.09 (0.09)	701/631
	Random Forest	54.4% (3.0%)	55.1% (3.0%)	40.3% (6.4%)	68.5% (5.3%)	55.9% (3.5%)	0.09 (0.06)	701/631
	Support Vector Machine	56.5% (3.3%)	56.9% (3.3%)	48.8% (5.6%)	64.2% (4.5%)	56.5% (3.3%)	0.13 (0.07)	701/631
LCOR	Boosting Classifier	51.5% (4.3%)	51.9% (4.2%)	44.4% (8.3%)	58.6% (5.8%)	53.2% (3.4%)	0.03 (0.09)	701/631
	k-Nearest Neighbours	55.7% (3.6%)	56.2% (3.5%)	45.3% (10.5%)	66.1% (7.9%)	57.1% (3.0%)	0.12 (0.08)	701/631
	Logistic Regression	55.8% (2.4%)	56.2% (2.3%)	48.6% (4.4%)	62.9% (3.3%)	58.4% (3.9%)	0.12 (0.05)	701/631
	Gaussian Naive Bayes	55.6% (4.7%)	55.7% (4.7%)	54.0% (6.8%)	57.2% (6.6%)	56.0% (4.7%)	0.11 (0.09)	701/631
	Random Forest	53.8% (5.1%)	54.4% (5.2%)	42.3% (6.8%)	65.2% (7.7%)	56.5% (5.4%)	0.08 (0.11)	701/631
	Support Vector Machine	55.7% (2.2%)	56.2% (2.1%)	47.5% (4.8%)	63.9% (2.6%)	55.7% (2.2%)	0.12 (0.04)	701/631
RS Network Parameters	Boosting Classifier	53.5% (3.6%)	54.0% (3.5%)	44.2% (6.8%)	62.9% (5.5%)	55.0% (4.8%)	0.07 (0.07)	700/631
	k-Nearest Neighbours	53.6% (4.6%)	54.4% (4.5%)	38.8% (8.0%)	68.4% (5.9%)	56.0% (5.6%)	0.08 (0.1)	700/631
	Logistic Regression	56.6% (2.6%)	57.1% (2.8%)	47.7% (6.7%)	65.6% (8.8%)	57.6% (3.4%)	0.14 (0.06)	700/631
	Gaussian Naive Bayes	56.3% (3.1%)	56.4% (3.1%)	54.7% (6.2%)	57.9% (6.5%)	57.5% (3.9%)	0.13 (0.06)	700/631
	Random Forest	56.8% (3.0%)	57.6% (3.1%)	40.6% (6.5%)	73.0% (7.0%)	58.3% (4.7%)	0.15 (0.06)	700/631
	Support Vector Machine	56.9% (3.0%)	57.4% (3.0%)	46.8% (7.9%)	67.0% (7.3%)	56.9% (3.0%)	0.14 (0.06)	700/631

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 3. Classification accuracy for multivariate biomarkers using neuroimaging modality integration.

eTable 3. Classification accuracy for multivariate biomarkers using neuroimaging modality integration.

Modality Integration	Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
PCA-based	all	Boosting Classifier	54.1% (4.1%)	54.9% (4.4%)	45.4% (11.6%)	62.7% (12.6%)	55.2% (5.4%)	0.09 (0.08)	567/471
		k-Nearest Neighbours	50.3% (3.9%)	51.7% (3.9%)	35.0% (8.4%)	65.6% (8.0%)	50.0% (5.1%)	0.01 (0.08)	567/471
		Logistic Regression	51.1% (3.0%)	52.1% (4.5%)	40.0% (44.2%)	62.3% (43.0%)	51.4% (5.2%)	0.05 (0.12)	567/471
		Gaussian Naive Bayes	51.3% (3.6%)	54.6% (3.2%)	15.9% (24.7%)	86.7% (20.8%)	50.4% (4.6%)	0.04 (0.13)	567/471
		Random Forest	57.2% (4.4%)	59.8% (4.4%)	29.1% (8.3%)	85.4% (6.1%)	62.0% (4.8%)	0.18 (0.11)	567/471
		Support Vector Machine	50.1% (4.0%)	49.2% (5.3%)	60.2% (46.5%)	40.0% (45.0%)	50.1% (4.0%)	0.01 (0.15)	567/471
Voting	all	all	61.1% (4.4%)	63.3% (4.4%)	37.6% (6.7%)	84.6% (5.0%)	65.3% (4.2%)	0.26 (0.1)	567/471
Voting	all	Boosting Classifier	55.5% (4.2%)	57.4% (4.3%)	34.8% (6.9%)	34.8% (6.9%)	57.4% (5.3%)	0.12 (0.1)	567/471
		k-Nearest Neighbours	56.3% (3.2%)	58.9% (3.3%)	28.7% (3.3%)	28.7% (3.3%)	62.2% (5.5%)	0.16 (0.08)	567/471
		Logistic Regression	60.9% (4.2%)	62.1% (4.2%)	47.2% (8.1%)	47.2% (8.1%)	63.7% (4.0%)	0.23 (0.09)	567/471
		Gaussian Naive Bayes	60.6% (5.8%)	61.4% (5.9%)	51.8% (7.2%)	51.8% (7.2%)	62.7% (4.1%)	0.22 (0.12)	567/471
		Random Forest	59.5% (3.5%)	62.3% (3.3%)	29.5% (6.3%)	29.5% (6.3%)	63.3% (4.2%)	0.24 (0.08)	567/471
		Support Vector Machine	60.3% (3.8%)	62.0% (3.6%)	42.1% (8.0%)	42.1% (8.0%)	64.9% (3.6%)	0.22 (0.08)	567/471
Voting	Freesurfer	all	53.1% (4.4%)	55.0% (4.3%)	31.9% (6.5%)	31.9% (6.5%)	54.3% (5.7%)	0.07 (0.1)	567/471
	VBM		54.2% (4.6%)	56.0% (4.5%)	35.1% (8.2%)	35.1% (8.2%)	54.5% (6.0%)	0.09 (0.1)	567/471
	DTI FA		52.0% (5.4%)	54.5% (5.4%)	25.1% (7.3%)	25.1% (7.3%)	52.4% (7.5%)	0.05 (0.13)	567/471
	DTI MD		50.6% (4.1%)	53.6% (4.1%)	18.5% (4.3%)	18.5% (4.3%)	52.1% (6.3%)	0.02 (0.11)	567/471

	DTI Network Parameters		55.7% (3.8%)	58.1% (3.6%)	29.5% (6.9%)	29.5% (6.9%)	56.3% (5.6%)	0.13 (0.09)	567/471
	Face Matching Task		55.6% (5.7%)	57.2% (5.7%)	37.6% (7.4%)	37.6% (7.4%)	57.2% (6.0%)	0.12 (0.12)	567/471
	RS Connectivity		60.2% (4.6%)	61.5% (4.7%)	46.1% (6.6%)	46.1% (6.6%)	62.2% (5.6%)	0.21 (0.1)	567/471
	ALFF		62.0% (4.8%)	63.3% (4.7%)	48.2% (7.5%)	48.2% (7.5%)	64.7% (5.5%)	0.25 (0.1)	567/471
	fALFF		55.9% (4.5%)	57.4% (4.2%)	39.3% (9.0%)	39.3% (9.0%)	58.5% (5.5%)	0.12 (0.09)	567/471
	LCOR		54.7% (3.4%)	56.3% (3.4%)	38.2% (6.1%)	38.2% (6.1%)	58.2% (3.4%)	0.1 (0.07)	567/471
	RS Network Parameters		57.5% (4.9%)	59.4% (4.8%)	37.8% (6.9%)	37.8% (6.9%)	60.7% (5.2%)	0.16 (0.11)	567/471

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 4. Associations of symptom severity and misclassification frequency.

eTable 4. Associations of symptom severity and misclassification frequency.

	MDD			**HC**		
	N	**r**	***p***	**N**	**r**	***p***
Age	631	-0.057	0.156	700	0.011	0.774
BDI	621	-0.152	<0.001			
HAMD	628	-0.197	<0.001			
GAF	620	0.171	<0.001	690	-0.102	0.007
Number of Hospitalizations	622	-0.102	0.011			

Note: BDI = Beck’s Depression Inventory, HAMD = Hamilton Depression Rating Scale, GAF = Global Assessment of Functioning.

eTable 5. Classification accuracy based on structural MRI for HC vs acute MDD.

eTable 5. Classification accuracy for multivariate biomarkers based on structural MRI for HC vs acute MDD.

Modality	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
Freesurfer	Boosting Classifier	52.7% (2.1%)	58.7% (2.1%)	27.1% (6.7%)	78.3% (5.5%)	54.7% (2.6%)	0.06 (0.05)	920/568
	k-Nearest Neighbours	51.4% (3.4%)	57.5% (3.7%)	25.7% (9.5%)	77.1% (8.6%)	55.4% (5.0%)	0.03 (0.07)	920/568
	Logistic Regression	53.5% (4.5%)	55.2% (4.2%)	46.0% (9.1%)	61.0% (6.1%)	54.0% (5.2%)	0.07 (0.09)	920/568
	Gaussian Naive Bayes	54.0% (2.4%)	58.0% (2.2%)	37.3% (8.0%)	70.8% (5.9%)	55.4% (4.2%)	0.08 (0.05)	920/568
	Random Forest	52.5% (1.3%)	61.7% (1.3%)	13.6% (3.2%)	91.4% (2.6%)	57.2% (3.4%)	0.08 (0.04)	920/568
	Support Vector Machine	51.4% (3.2%)	57.1% (4.1%)	27.0% (11.1%)	75.8% (11.2%)	51.4% (3.2%)	0.03 (0.07)	920/568
VBM	Boosting Classifier	54.4% (3.1%)	58.7% (3.0%)	36.4% (5.0%)	72.4% (3.9%)	56.4% (3.6%)	0.09 (0.06)	924/571
	k-Nearest Neighbours	49.1% (1.7%)	55.5% (1.5%)	21.9% (7.3%)	76.3% (5.4%)	49.2% (5.6%)	-0.02 (0.04)	924/571
	Logistic Regression	51.1% (3.4%)	45.5% (6.1%)	74.9% (15.8%)	27.4% (18.1%)	52.5% (2.9%)	0.03 (0.08)	924/571
	Gaussian Naive Bayes	52.2% (2.7%)	58.9% (3.0%)	23.7% (21.4%)	80.8% (17.3%)	53.3% (4.4%)	0.05 (0.07)	924/571
	Random Forest	52.1% (3.2%)	61.0% (3.0%)	14.4% (4.6%)	89.8% (3.6%)	59.0% (2.8%)	0.06 (0.09)	924/571
	Support Vector Machine	49.7% (1.7%)	49.3% (11.0%)	51.4% (45.6%)	48.0% (45.7%)	49.7% (1.7%)	-0.01 (0.07)	924/571
DTI FA	Boosting Classifier	51.0% (4.5%)	57.7% (4.6%)	25.0% (9.0%)	77.0% (7.8%)	49.1% (6.0%)	0.02 (0.11)	818/484
	k-Nearest Neighbours	48.8% (2.4%)	55.4% (3.4%)	23.1% (6.9%)	74.5% (8.1%)	48.7% (3.5%)	-0.03 (0.05)	818/484
	Logistic Regression	49.1% (3.7%)	53.9% (3.6%)	30.6% (9.1%)	67.7% (7.0%)	49.6% (4.0%)	-0.02 (0.08)	818/484
	Gaussian Naive Bayes	48.7% (3.6%)	55.6% (3.8%)	21.7% (11.4%)	75.7% (9.8%)	48.2% (6.7%)	-0.04 (0.08)	818/484
	Random Forest	49.7% (1.4%)	61.9% (1.3%)	2.1% (2.6%)	97.3% (2.0%)	49.4% (5.0%)	-0.02 (0.07)	818/484

	Support Vector Machine	51.4% (3.9%)	56.1% (3.9%)	32.8% (11.7%)	69.9% (9.2%)	51.4% (3.9%)	0.03 (0.08)	818/484
DTI MD	Boosting Classifier	48.5% (3.4%)	55.5% (3.9%)	21.3% (11.3%)	75.7% (10.1%)	46.4% (4.1%)	-0.04 (0.07)	818/484
	k-Nearest Neighbours	51.0% (3.9%)	59.7% (3.6%)	17.1% (7.5%)	84.8% (5.2%)	51.4% (5.2%)	0.02 (0.11)	818/484
	Logistic Regression	48.4% (4.5%)	55.1% (5.7%)	22.2% (12.8%)	74.6% (13.7%)	50.1% (5.2%)	-0.04 (0.1)	818/484
	Gaussian Naive Bayes	48.6% (3.3%)	56.4% (4.6%)	18.2% (11.0%)	79.0% (11.8%)	49.3% (4.9%)	-0.03 (0.08)	818/484
	Random Forest	48.9% (1.6%)	60.7% (2.1%)	2.7% (2.2%)	95.1% (4.1%)	46.9% (5.4%)	-0.04 (0.08)	818/484
	Support Vector Machine	51.0% (4.1%)	56.6% (5.4%)	29.1% (8.1%)	72.9% (11.3%)	51.0% (4.1%)	0.03 (0.09)	818/484
DTI Network Parameters	Boosting Classifier	51.9% (3.6%)	57.4% (3.0%)	30.7% (14.3%)	73.1% (10.0%)	51.8% (4.7%)	0.04 (0.08)	818/484
	k-Nearest Neighbours	49.3% (2.4%)	58.1% (1.9%)	14.8% (7.1%)	83.7% (4.5%)	50.5% (5.5%)	-0.02 (0.07)	818/484
	Logistic Regression	54.0% (3.3%)	58.7% (3.1%)	35.7% (7.6%)	72.2% (5.5%)	55.3% (3.4%)	0.08 (0.07)	818/484
	Gaussian Naive Bayes	52.0% (5.3%)	53.4% (5.2%)	46.8% (15.1%)	57.2% (11.7%)	53.9% (5.3%)	0.04 (0.11)	818/484
	Random Forest	51.7% (2.7%)	61.8% (2.8%)	12.2% (2.9%)	91.2% (3.3%)	53.0% (4.7%)	0.06 (0.09)	818/484
	Support Vector Machine	52.9% (4.7%)	59.4% (4.3%)	27.7% (6.8%)	78.1% (4.1%)	52.9% (4.7%)	0.07 (0.11)	818/484

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew's Correlation Coefficient.

eTable 6. Classification accuracy based on functional MRI for HC vs acute MDD.

eTable 6. Classification accuracy for multivariate biomarkers based on functional MRI for HC vs acute MDD.

Modality	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
Face Matching Task	Boosting Classifier	53.2% (3.7%)	57.7% (3.8%)	34.3% (5.8%)	72.0% (5.6%)	56.1% (3.2%)	0.07 (0.08)	654/402
	k-Nearest Neighbours	51.1% (2.7%)	58.1% (2.9%)	21.9% (8.7%)	80.4% (7.4%)	53.4% (5.1%)	0.03 (0.07)	654/402
	Logistic Regression	56.1% (4.3%)	59.7% (3.7%)	41.0% (9.2%)	71.2% (5.1%)	59.9% (4.2%)	0.13 (0.09)	654/402
	Gaussian Naive Bayes	55.0% (5.1%)	56.4% (5.0%)	49.1% (11.8%)	60.9% (9.4%)	55.4% (4.4%)	0.1 (0.1)	654/402
	Random Forest	51.6% (2.0%)	61.5% (1.6%)	10.5% (6.5%)	92.8% (4.0%)	57.7% (4.9%)	0.06 (0.07)	654/402
	Support Vector Machine	53.4% (5.5%)	56.8% (6.2%)	39.0% (11.5%)	67.7% (12.1%)	53.4% (5.5%)	0.07 (0.11)	654/402
RS Connectivity	Boosting Classifier	53.8% (5.0%)	57.0% (4.9%)	40.1% (7.5%)	67.6% (5.9%)	55.8% (5.8%)	0.08 (0.1)	700/439
	k-Nearest Neighbours	55.7% (3.8%)	62.4% (3.8%)	26.6% (5.9%)	84.9% (5.0%)	58.7% (5.4%)	0.14 (0.09)	700/439
	Logistic Regression	58.7% (5.7%)	61.5% (5.4%)	46.7% (10.4%)	70.7% (7.1%)	62.2% (6.0%)	0.18 (0.11)	700/439
	Gaussian Naive Bayes	59.4% (3.9%)	60.6% (3.4%)	54.4% (10.6%)	64.4% (7.1%)	61.6% (4.5%)	0.19 (0.08)	700/439
	Random Forest	54.4% (3.1%)	61.5% (3.0%)	23.5% (6.0%)	85.3% (4.8%)	61.3% (5.2%)	0.11 (0.08)	700/439
	Support Vector Machine	60.5% (4.6%)	64.7% (5.0%)	41.9% (5.7%)	79.0% (7.5%)	60.5% (4.6%)	0.23 (0.1)	700/439
ALFF	Boosting Classifier	54.9% (3.6%)	59.1% (3.5%)	36.4% (7.3%)	73.3% (5.5%)	58.5% (4.0%)	0.1 (0.08)	701/439
	k-Nearest Neighbours	55.9% (5.1%)	60.5% (4.9%)	35.7% (8.1%)	76.0% (5.7%)	59.9% (5.0%)	0.13 (0.11)	701/439
	Logistic Regression	59.6% (2.7%)	61.2% (2.6%)	52.4% (9.7%)	66.7% (7.5%)	63.7% (4.5%)	0.19 (0.05)	701/439
	Gaussian Naive Bayes	58.5% (6.0%)	59.9% (5.3%)	52.6% (12.4%)	64.5% (7.6%)	59.1% (5.8%)	0.17 (0.12)	701/439
	Random Forest	58.0% (2.9%)	63.6% (3.4%)	33.9% (4.2%)	82.2% (5.7%)	63.3% (4.8%)	0.19 (0.07)	701/439
	Support Vector Machine	57.4% (2.9%)	61.5% (3.0%)	39.4% (4.9%)	75.3% (4.7%)	57.4% (2.9%)	0.16 (0.06)	701/439
fALFF	Boosting Classifier	52.6% (4.5%)	56.9% (5.3%)	33.9% (8.2%)	71.3% (10.2%)	56.2% (5.2%)	0.06 (0.1)	701/439

	k-Nearest Neighbours	53.7% (3.3%)	62.2% (3.4%)	16.8% (6.9%)	90.6% (6.6%)	57.8% (5.0%)	0.12 (0.12)	701/439
	Logistic Regression	57.2% (4.8%)	60.9% (4.9%)	41.0% (10.1%)	73.3% (8.8%)	60.5% (6.2%)	0.15 (0.1)	701/439
	Gaussian Naive Bayes	54.5% (5.3%)	55.0% (5.1%)	52.2% (8.2%)	56.8% (5.9%)	54.8% (6.1%)	0.09 (0.1)	701/439
	Random Forest	50.8% (2.4%)	60.2% (2.7%)	10.2% (3.9%)	91.4% (4.5%)	57.5% (5.2%)	0.03 (0.07)	701/439
	Support Vector Machine	54.7% (3.9%)	59.6% (3.3%)	33.3% (9.0%)	76.2% (5.1%)	54.7% (3.9%)	0.1 (0.08)	701/439
LCOR	Boosting Classifier	51.1% (3.8%)	55.8% (2.8%)	30.5% (9.5%)	71.6% (4.1%)	49.9% (7.2%)	0.02 (0.08)	701/439
	k-Nearest Neighbours	53.3% (4.6%)	58.5% (4.0%)	30.8% (9.6%)	75.9% (5.4%)	57.3% (6.0%)	0.07 (0.1)	701/439
	Logistic Regression	56.5% (4.8%)	60.4% (4.6%)	39.7% (8.3%)	73.3% (6.1%)	58.2% (6.0%)	0.14 (0.1)	701/439
	Gaussian Naive Bayes	55.9% (6.3%)	56.6% (6.1%)	52.9% (9.1%)	58.9% (7.5%)	55.9% (6.4%)	0.12 (0.12)	701/439
	Random Forest	50.8% (3.9%)	58.9% (3.6%)	16.0% (8.0%)	85.7% (5.0%)	56.9% (8.3%)	0.02 (0.11)	701/439
	Support Vector Machine	53.9% (5.3%)	58.2% (5.2%)	35.3% (8.6%)	72.5% (6.3%)	53.9% (5.3%)	0.08 (0.12)	701/439
RS Network Parameters	Boosting Classifier	54.9% (4.6%)	59.1% (4.2%)	36.7% (7.8%)	73.1% (4.4%)	55.5% (6.0%)	0.1 (0.09)	700/439
	k-Nearest Neighbours	52.0% (3.8%)	58.0% (4.8%)	25.5% (7.2%)	78.4% (10.0%)	53.9% (5.8%)	0.05 (0.1)	700/439
	Logistic Regression	55.5% (3.2%)	59.9% (2.5%)	36.2% (10.7%)	74.7% (6.8%)	57.2% (3.5%)	0.12 (0.07)	700/439
	Gaussian Naive Bayes	55.3% (7.1%)	57.4% (7.0%)	46.2% (10.8%)	64.4% (9.1%)	57.7% (6.6%)	0.11 (0.14)	700/439
	Random Forest	55.8% (4.8%)	63.3% (4.5%)	22.8% (6.9%)	88.7% (3.9%)	58.0% (6.7%)	0.15 (0.13)	700/439
	Support Vector Machine	54.8% (4.1%)	60.8% (3.7%)	28.5% (10.0%)	81.1% (6.8%)	54.8% (4.1%)	0.11 (0.1)	700/439

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 7. Classification accuracy using neuroimaging modality integration for HC vs acute MDD.

eTable 7. Classification accuracy for multivariate biomarkers using neuroimaging modality integration for HC vs acute MDD.

Modality Integration	**Modality**	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
PCA-based	all	Boosting Classifier	56.0% (2.7%)	62.2% (3.3%)	32.7% (11.1%)	79.4% (9.7%)	58.2% (4.5%)	0.14 (0.07)	567/330
		k-Nearest Neighbours	49.8% (3.8%)	56.7% (3.6%)	23.6% (8.4%)	76.0% (6.2%)	50.6% (6.8%)	-0.01 (0.09)	567/330
		Logistic Regression	49.3% (2.3%)	55.0% (9.6%)	27.6% (37.7%)	71.0% (36.7%)	49.2% (3.0%)	-0.01 (0.08)	567/330
		Gaussian Naive Bayes	50.6% (4.7%)	60.8% (3.8%)	12.1% (10.8%)	89.1% (5.6%)	49.5% (7.9%)	0.0 (0.13)	567/330
		Random Forest	50.1% (2.2%)	62.4% (3.2%)	3.3% (3.0%)	96.8% (5.9%)	57.6% (10.8%)	0.03 (0.11)	567/330
		Support Vector Machine	49.0% (2.0%)	44.5% (12.7%)	66.1% (46.0%)	31.9% (46.7%)	49.0% (2.0%)	-0.04 (0.1)	567/330
Voting	all	all	51.3% (2.6%)	63.4% (2.0%)	5.2% (5.0%)	97.4% (1.9%)	64.7% (5.3%)	0.05 (0.12)	567/330
Voting	all	Boosting Classifier	52.0% (2.8%)	63.0% (2.4%)	10.3% (5.2%)	93.7% (2.1%)	60.3% (3.5%)	0.07 (0.1)	567/330
		k-Nearest Neighbours	51.9% (3.1%)	64.1% (2.3%)	5.8% (6.0%)	98.1% (1.8%)	57.1% (7.8%)	0.09 (0.12)	567/330
		Logistic Regression	58.8% (5.4%)	65.4% (5.8%)	33.6% (5.6%)	84.0% (7.6%)	64.4% (5.0%)	0.21 (0.13)	567/330
		Gaussian Naive Bayes	58.4% (5.6%)	64.2% (5.4%)	36.4% (8.5%)	80.4% (6.6%)	60.2% (5.9%)	0.19 (0.12)	567/330
		Random Forest	50.3% (1.0%)	63.2% (0.7%)	1.2% (2.1%)	99.3% (0.9%)	59.4% (6.1%)	0.01 (0.07)	567/330
		Support Vector Machine	56.8% (2.7%)	66.2% (2.5%)	21.2% (6.1%)	92.4% (4.1%)	61.3% (6.8%)	0.2 (0.07)	567/330
Voting	Freesurfer	all	51.6% (3.4%)	60.9% (2.8%)	16.7% (7.2%)	86.6% (3.6%)	53.5% (6.2%)	0.04 (0.09)	567/330
	VBM		51.8% (2.3%)	62.0% (2.3%)	13.0% (4.5%)	90.5% (3.7%)	52.1% (4.2%)	0.06 (0.08)	567/330
	DTI FA		49.8% (1.9%)	61.3% (2.3%)	6.4% (1.7%)	93.3% (3.3%)	51.0% (7.3%)	0.0 (0.07)	567/330
	DTI MD		49.5% (3.0%)	61.6% (3.1%)	3.6% (3.7%)	95.4% (4.1%)	47.8% (4.1%)	-0.02 (0.13)	567/330

	DTI Network Parameters		51.0% (4.1%)	61.1% (3.7%)	12.7% (6.0%)	89.3% (3.2%)	53.7% (3.2%)	0.03 (0.12)	567/330
	Face Matching Task		53.9% (3.4%)	63.4% (2.7%)	17.9% (7.5%)	89.9% (3.5%)	57.2% (6.4%)	0.11 (0.09)	567/330
	RS Connectivity		57.8% (4.5%)	65.3% (3.8%)	29.4% (7.7%)	86.2% (3.6%)	62.6% (8.0%)	0.19 (0.11)	567/330
	ALFF		57.8% (4.9%)	64.8% (4.2%)	31.5% (8.6%)	84.1% (3.8%)	64.3% (5.9%)	0.18 (0.11)	567/330
	fALFF		54.6% (3.4%)	63.8% (3.3%)	20.0% (5.9%)	89.2% (4.2%)	59.0% (3.1%)	0.13 (0.1)	567/330
	LCOR		52.8% (5.1%)	61.3% (4.5%)	20.6% (9.9%)	85.0% (5.6%)	57.6% (6.2%)	0.07 (0.13)	567/330
	RS Network Parameters		56.3% (2.5%)	65.1% (2.1%)	23.0% (4.8%)	89.6% (1.9%)	59.3% (5.3%)	0.17 (0.06)	567/330

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew's Correlation Coefficient.

eTable 8. Classification accuracy based on structural MRI for HC vs recurrent MDD.

eTable 8. Classification accuracy for multivariate biomarkers based on structural MRI for HC vs recurrent MDD.

Modality	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
Freesurfer	Boosting Classifier	51.1% (2.6%)	70.9% (2.8%)	13.8% (5.2%)	88.4% (3.7%)	55.1% (6.9%)	0.03 (0.07)	920/282
	k-Nearest Neighbours	51.5% (3.9%)	73.0% (2.4%)	11.0% (7.8%)	92.0% (2.4%)	55.0% (7.0%)	0.04 (0.11)	920/282
	Logistic Regression	60.2% (3.2%)	60.9% (3.6%)	58.8% (7.3%)	61.5% (5.4%)	63.3% (5.0%)	0.17 (0.05)	920/282
	Gaussian Naive Bayes	59.1% (5.8%)	62.6% (4.0%)	52.5% (11.2%)	65.7% (4.3%)	62.6% (5.5%)	0.16 (0.1)	920/282
	Random Forest	51.5% (2.0%)	76.1% (1.1%)	5.0% (4.2%)	97.9% (0.8%)	60.9% (5.9%)	0.06 (0.09)	920/282
	Support Vector Machine	53.8% (4.7%)	66.1% (5.7%)	30.5% (20.2%)	77.1% (12.8%)	53.8% (4.7%)	0.07 (0.09)	920/282
VBM	Boosting Classifier	55.8% (3.3%)	73.5% (2.6%)	22.1% (8.4%)	89.4% (4.3%)	61.0% (6.8%)	0.14 (0.07)	924/285
	k-Nearest Neighbours	50.7% (2.7%)	73.9% (2.6%)	6.7% (5.7%)	94.7% (3.1%)	52.8% (5.0%)	0.02 (0.09)	924/285
	Logistic Regression	54.8% (3.1%)	49.7% (9.1%)	64.3% (18.5%)	45.3% (17.1%)	52.7% (4.9%)	0.09 (0.05)	924/285
	Gaussian Naive Bayes	55.4% (4.1%)	67.9% (6.5%)	31.6% (20.4%)	79.1% (14.3%)	58.8% (6.4%)	0.1 (0.09)	924/285
	Random Forest	50.1% (1.3%)	75.8% (1.0%)	1.4% (3.0%)	98.7% (1.1%)	63.8% (5.8%)	-0.01 (0.08)	924/285
	Support Vector Machine	51.6% (2.5%)	64.6% (19.4%)	27.0% (39.0%)	76.2% (37.3%)	51.6% (2.5%)	0.06 (0.09)	924/285
DTI FA	Boosting Classifier	49.9% (3.9%)	70.5% (5.2%)	12.9% (9.4%)	86.9% (8.0%)	49.8% (6.1%)	-0.0 (0.08)	818/233
	k-Nearest Neighbours	51.4% (2.7%)	74.0% (3.3%)	10.7% (4.2%)	92.0% (3.9%)	51.9% (4.2%)	0.05 (0.09)	818/233
	Logistic Regression	50.4% (3.0%)	69.8% (4.1%)	15.5% (7.8%)	85.3% (6.2%)	51.8% (6.1%)	0.01 (0.07)	818/233
	Gaussian Naive Bayes	51.0% (6.1%)	68.8% (4.8%)	19.2% (14.3%)	82.9% (7.3%)	50.7% (7.1%)	0.02 (0.14)	818/233
	Random Forest	50.0% (0.0%)	77.8% (0.4%)	0.0% (0.0%)	100.0% (0.0%)	51.5% (5.7%)	0.0 (0.0)	818/233

	Support Vector Machine	51.9% (3.2%)	68.7% (6.5%)	21.6% (13.7%)	82.2% (11.7%)	51.9% (3.2%)	0.04 (0.08)	818/233
DTI MD	Boosting Classifier	51.1% (3.8%)	74.0% (4.4%)	10.0% (8.0%)	92.3% (6.2%)	52.9% (6.1%)	0.04 (0.13)	818/233
	k-Nearest Neighbours	50.9% (4.5%)	75.4% (2.7%)	6.9% (9.8%)	94.9% (3.9%)	49.9% (9.3%)	0.02 (0.14)	818/233
	Logistic Regression	53.8% (5.3%)	69.4% (5.6%)	25.7% (7.0%)	81.8% (6.8%)	52.8% (8.6%)	0.09 (0.12)	818/233
	Gaussian Naive Bayes	49.5% (2.2%)	73.9% (5.3%)	5.6% (6.2%)	93.4% (8.3%)	50.7% (8.2%)	-0.01 (0.07)	818/233
	Random Forest	50.0% (0.0%)	77.8% (0.4%)	0.0% (0.0%)	100.0% (0.0%)	56.7% (9.5%)	0.0 (0.0)	818/233
	Support Vector Machine	51.1% (7.1%)	66.6% (9.0%)	23.4% (17.8%)	78.8% (14.0%)	51.1% (7.1%)	0.03 (0.16)	818/233
DTI Network Parameters	Boosting Classifier	49.1% (3.0%)	69.7% (3.4%)	12.0% (6.3%)	86.2% (4.7%)	50.1% (6.1%)	-0.02 (0.08)	818/233
	k-Nearest Neighbours	50.6% (2.0%)	75.6% (1.5%)	5.6% (5.4%)	95.6% (2.7%)	52.5% (4.7%)	0.01 (0.07)	818/233
	Logistic Regression	52.5% (4.2%)	70.9% (3.8%)	19.3% (6.0%)	85.6% (3.9%)	58.6% (6.5%)	0.06 (0.1)	818/233
	Gaussian Naive Bayes	50.1% (3.8%)	63.9% (5.7%)	25.3% (9.6%)	74.9% (8.7%)	50.1% (6.2%)	0.0 (0.08)	818/233
	Random Forest	50.2% (0.7%)	77.9% (0.6%)	0.4% (1.4%)	100.0% (0.0%)	54.8% (5.5%)	0.02 (0.06)	818/233
	Support Vector Machine	49.2% (5.7%)	64.2% (5.2%)	22.0% (14.8%)	76.3% (8.4%)	49.2% (5.7%)	-0.02 (0.11)	818/233

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 9. Classification accuracy based on functional MRI for HC vs recurrent MDD.

eTable 9. Classification accuracy for multivariate biomarkers based on functional MRI for HC vs recurrent MDD.

Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
Face Matching Task	Boosting Classifier	53.4% (5.3%)	72.3% (3.0%)	19.4% (12.2%)	87.3% (4.0%)	58.2% (5.3%)	0.07 (0.12)	654/185
	k-Nearest Neighbours	49.7% (2.9%)	74.7% (2.4%)	4.9% (5.4%)	94.5% (2.8%)	47.6% (7.6%)	-0.01 (0.1)	654/185
	Logistic Regression	54.0% (6.6%)	69.1% (3.5%)	27.0% (13.1%)	81.0% (3.5%)	52.9% (9.6%)	0.08 (0.14)	654/185
	Gaussian Naive Bayes	57.4% (5.2%)	68.3% (4.8%)	37.9% (8.2%)	76.9% (5.3%)	58.2% (5.0%)	0.14 (0.1)	654/185
	Random Forest	49.9% (0.2%)	77.8% (0.8%)	0.0% (0.0%)	99.8% (0.5%)	55.4% (9.3%)	-0.01 (0.02)	654/185
	Support Vector Machine	53.7% (4.7%)	65.9% (5.1%)	31.9% (12.5%)	75.5% (8.3%)	53.7% (4.7%)	0.07 (0.09)	654/185
RS Connectivity	Boosting Classifier	52.8% (3.7%)	70.9% (2.1%)	19.4% (9.1%)	86.1% (3.4%)	57.2% (8.3%)	0.06 (0.09)	700/207
	k-Nearest Neighbours	50.4% (3.7%)	74.3% (3.7%)	6.3% (5.2%)	94.4% (4.3%)	56.9% (9.6%)	0.03 (0.14)	700/207
	Logistic Regression	57.1% (6.0%)	70.2% (4.6%)	32.9% (10.6%)	81.3% (5.1%)	61.4% (6.7%)	0.15 (0.12)	700/207
	Gaussian Naive Bayes	61.7% (6.7%)	66.8% (7.1%)	52.2% (9.7%)	71.1% (8.5%)	62.4% (7.7%)	0.21 (0.13)	700/207
	Random Forest	50.6% (1.3%)	77.3% (1.0%)	1.5% (2.3%)	99.7% (0.6%)	62.3% (8.9%)	0.05 (0.1)	700/207
	Support Vector Machine	55.9% (6.6%)	70.2% (4.0%)	29.5% (14.0%)	82.3% (4.8%)	55.9% (6.6%)	0.12 (0.13)	700/207
ALFF	Boosting Classifier	55.8% (5.2%)	72.6% (5.1%)	25.1% (9.5%)	86.6% (6.5%)	60.2% (6.3%)	0.14 (0.12)	701/207
	k-Nearest Neighbours	55.1% (4.7%)	77.0% (2.2%)	14.9% (11.3%)	95.3% (3.3%)	63.2% (4.6%)	0.16 (0.14)	701/207
	Logistic Regression	61.3% (5.5%)	67.6% (4.6%)	49.7% (8.8%)	72.9% (5.0%)	66.8% (5.8%)	0.2 (0.1)	701/207
	Gaussian Naive Bayes	55.0% (6.0%)	63.2% (4.8%)	40.0% (11.9%)	70.0% (6.0%)	55.1% (6.8%)	0.09 (0.11)	701/207
	Random Forest	52.4% (2.3%)	77.3% (1.5%)	6.7% (4.6%)	98.1% (1.8%)	66.5% (7.2%)	0.13 (0.11)	701/207
	Support Vector Machine	56.1% (5.5%)	72.4% (3.9%)	26.1% (10.3%)	86.0% (4.5%)	56.1% (5.5%)	0.14 (0.13)	701/207
fALFF	Boosting Classifier	50.3% (7.1%)	69.0% (5.4%)	16.0% (12.6%)	84.7% (5.2%)	51.4% (12.2%)	0.01 (0.16)	701/207

	k-Nearest Neighbours	50.9% (2.6%)	76.8% (1.5%)	3.3% (5.0%)	98.4% (1.3%)	53.8% (6.1%)	0.04 (0.13)	701/207
	Logistic Regression	53.8% (3.4%)	66.7% (5.8%)	30.0% (14.0%)	77.6% (10.9%)	56.2% (6.8%)	0.08 (0.07)	701/207
	Gaussian Naive Bayes	53.0% (10.2%)	56.2% (8.2%)	47.3% (16.2%)	58.8% (7.9%)	53.8% (10.5%)	0.05 (0.18)	701/207
	Random Forest	50.0% (0.0%)	77.2% (0.5%)	0.0% (0.0%)	100.0% (0.0%)	55.5% (8.2%)	0.0 (0.0)	701/207
	Support Vector Machine	52.9% (3.2%)	69.4% (3.5%)	22.7% (6.7%)	83.2% (5.0%)	52.9% (3.2%)	0.07 (0.07)	701/207
LCOR	Boosting Classifier	53.6% (4.8%)	71.2% (3.3%)	21.4% (9.0%)	85.9% (3.0%)	56.5% (8.4%)	0.08 (0.11)	701/207
	k-Nearest Neighbours	52.5% (2.8%)	75.2% (1.9%)	10.6% (6.4%)	94.3% (2.4%)	55.6% (8.1%)	0.07 (0.09)	701/207
	Logistic Regression	57.2% (3.7%)	66.7% (4.2%)	39.6% (13.2%)	74.8% (8.5%)	58.7% (5.0%)	0.13 (0.06)	701/207
	Gaussian Naive Bayes	58.9% (7.4%)	62.0% (4.8%)	53.2% (16.0%)	64.6% (6.3%)	58.9% (7.4%)	0.15 (0.13)	701/207
	Random Forest	50.2% (1.6%)	76.7% (1.6%)	1.5% (2.3%)	98.9% (1.9%)	58.6% (8.6%)	0.02 (0.09)	701/207
	Support Vector Machine	53.5% (5.5%)	69.7% (3.9%)	23.7% (11.3%)	83.3% (4.7%)	53.5% (5.5%)	0.07 (0.13)	701/207
RS Network Parameters	Boosting Classifier	52.2% (3.3%)	72.2% (3.1%)	15.4% (5.7%)	89.0% (4.0%)	55.1% (4.0%)	0.06 (0.1)	700/207
	k-Nearest Neighbours	53.1% (2.9%)	73.5% (2.6%)	15.5% (6.7%)	90.7% (3.8%)	57.3% (6.4%)	0.08 (0.08)	700/207
	Logistic Regression	52.2% (5.2%)	69.0% (2.9%)	21.2% (10.7%)	83.1% (2.8%)	57.5% (4.6%)	0.04 (0.11)	700/207
	Gaussian Naive Bayes	59.9% (4.5%)	68.0% (4.7%)	45.0% (6.9%)	74.9% (5.8%)	62.1% (5.3%)	0.18 (0.09)	700/207
	Random Forest	50.3% (0.8%)	77.1% (0.4%)	1.0% (2.0%)	99.6% (0.7%)	62.7% (6.0%)	0.01 (0.05)	700/207
	Support Vector Machine	54.8% (4.7%)	69.2% (4.6%)	28.1% (10.5%)	81.4% (6.9%)	54.8% (4.7%)	0.1 (0.1)	700/207

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew's Correlation Coefficient.

eTable 10. Classification accuracy using neuroimaging modality integration for HC vs recurrent MDD.

eTable 10. Classification accuracy for multivariate biomarkers using neuroimaging modality integration for HC vs recurrent MDD.

Modality Integration	**Modality**	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
PCA-based	all	Boosting Classifier	55.6% (5.6%)	77.2% (3.2%)	19.5% (12.6%)	91.7% (4.1%)	62.7% (10.0%)	0.14 (0.14)	567/143
		k-Nearest Neighbours	50.3% (4.0%)	77.2% (3.4%)	5.5% (7.7%)	95.2% (3.7%)	48.4% (6.6%)	0.01 (0.14)	567/143
		Logistic Regression	52.2% (4.9%)	71.4% (17.7%)	19.8% (27.8%)	84.5% (28.5%)	49.6% (8.0%)	0.07 (0.15)	567/143
		Gaussian Naive Bayes	49.9% (3.3%)	73.5% (3.4%)	10.4% (8.2%)	89.4% (5.2%)	47.6% (7.5%)	-0.01 (0.09)	567/143
		Random Forest	50.4% (1.3%)	79.3% (1.2%)	2.0% (3.3%)	98.8% (1.2%)	49.8% (9.0%)	0.01 (0.07)	567/143
		Support Vector Machine	51.2% (3.2%)	40.4% (27.3%)	69.3% (45.0%)	33.2% (45.4%)	51.2% (3.2%)	0.04 (0.16)	567/143
Voting	all	all	50.0% (0.0%)	79.9% (0.7%)	0.0% (0.0%)	100.0% (0.0%)	68.3% (6.7%)	0.0 (0.0)	567/143
Voting	all	Boosting Classifier	50.1% (1.0%)	79.6% (1.0%)	0.7% (2.3%)	99.5% (0.9%)	60.1% (7.2%)	0.0 (0.05)	567/143
		k-Nearest Neighbours	50.0% (0.0%)	79.9% (0.7%)	0.0% (0.0%)	100.0% (0.0%)	59.6% (4.8%)	0.0 (0.0)	567/143
		Logistic Regression	56.2% (5.9%)	78.7% (3.3%)	18.6% (11.7%)	93.8% (3.9%)	66.7% (7.9%)	0.18 (0.17)	567/143
		Gaussian Naive Bayes	56.2% (5.4%)	76.6% (3.5%)	22.2% (10.4%)	90.3% (3.5%)	65.6% (8.5%)	0.15 (0.13)	567/143
		Random Forest	50.0% (0.0%)	79.9% (0.7%)	0.0% (0.0%)	100.0% (0.0%)	53.5% (3.6%)	0.0 (0.0)	567/143
		Support Vector Machine	51.5% (2.4%)	79.0% (1.9%)	5.6% (4.3%)	97.5% (1.9%)	61.6% (6.0%)	0.07 (0.11)	567/143
Voting	Freesurfer	all	51.1% (4.2%)	75.9% (2.9%)	9.7% (8.1%)	92.6% (3.6%)	57.3% (7.8%)	0.03 (0.14)	567/143
	VBM		51.8% (2.7%)	79.3% (2.1%)	5.6% (4.5%)	97.9% (2.0%)	57.4% (6.4%)	0.09 (0.13)	567/143
	DTI FA		50.5% (2.8%)	79.0% (1.9%)	2.8% (4.8%)	98.2% (1.9%)	52.9% (10.3%)	0.03 (0.15)	567/143
	DTI MD		49.5% (0.7%)	79.0% (1.6%)	0.0% (0.0%)	98.9% (1.5%)	55.2% (8.3%)	-0.03 (0.04)	567/143

	DTI Network Parameters		49.3% (1.2%)	78.3% (2.0%)	0.7% (2.3%)	97.9% (2.3%)	50.4% (10.2%)	-0.04 (0.05)	567/143
	Face Matching Task		51.3% (2.6%)	79.0% (2.9%)	4.9% (3.4%)	97.7% (2.9%)	57.5% (6.6%)	0.09 (0.14)	567/143
	RS Connectivity		53.2% (4.6%)	79.2% (2.6%)	9.8% (8.8%)	96.6% (2.0%)	63.7% (7.0%)	0.11 (0.16)	567/143
	ALFF		54.7% (4.4%)	80.0% (1.6%)	12.4% (8.9%)	97.0% (1.7%)	65.8% (5.7%)	0.16 (0.16)	567/143
	fALFF		50.7% (1.8%)	78.5% (1.9%)	4.1% (3.6%)	97.2% (2.6%)	54.8% (9.0%)	0.04 (0.1)	567/143
	LCOR		52.2% (4.4%)	78.0% (3.1%)	8.9% (7.7%)	95.4% (3.3%)	59.4% (6.1%)	0.08 (0.14)	567/143
	RS Network Parameters		50.7% (2.7%)	78.5% (1.6%)	4.2% (6.0%)	97.2% (1.7%)	62.9% (7.3%)	0.01 (0.11)	567/143

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 11. Classification accuracy based on structural MRI for HC vs MDD (male).

eTable 11. Classification accuracy for multivariate biomarkers based on structural MRI for HC vs MDD (male).

Modality	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
Freesurfer	Boosting Classifier	46.8% (4.4%)	47.6% (4.8%)	36.8% (5.8%)	56.9% (11.1%)	47.4% (3.5%)	-0.06 (0.09)	327/280
	k-Nearest Neighbours	52.7% (5.0%)	54.5% (5.0%)	28.9% (6.8%)	76.5% (7.5%)	51.9% (7.1%)	0.06 (0.11)	327/280
	Logistic Regression	50.3% (6.9%)	51.6% (7.3%)	34.3% (8.3%)	66.4% (14.0%)	49.4% (5.8%)	0.01 (0.14)	327/280
	Gaussian Naive Bayes	50.1% (5.2%)	50.9% (5.5%)	38.9% (8.8%)	61.2% (11.2%)	50.3% (4.4%)	0.0 (0.11)	327/280
	Random Forest	48.3% (4.0%)	49.9% (4.4%)	27.5% (6.5%)	69.1% (10.6%)	50.6% (5.3%)	-0.03 (0.09)	327/280
	Support Vector Machine	49.4% (3.8%)	50.7% (3.9%)	32.1% (8.2%)	66.7% (8.7%)	49.4% (3.8%)	-0.01 (0.08)	327/280
VBM	Boosting Classifier	53.2% (5.2%)	53.8% (5.3%)	45.2% (8.6%)	61.2% (9.6%)	53.0% (6.1%)	0.07 (0.11)	330/281
	k-Nearest Neighbours	47.9% (4.1%)	49.4% (4.3%)	28.1% (5.0%)	67.6% (8.1%)	47.3% (6.9%)	-0.05 (0.09)	330/281
	Logistic Regression	51.3% (5.5%)	50.9% (5.8%)	56.9% (15.9%)	45.8% (17.2%)	52.1% (5.5%)	0.03 (0.12)	330/281
	Gaussian Naive Bayes	50.1% (3.0%)	52.7% (4.6%)	17.5% (24.2%)	82.7% (27.7%)	51.5% (6.2%)	0.02 (0.1)	330/281
	Random Forest	54.1% (5.9%)	56.1% (5.6%)	29.2% (11.2%)	79.1% (5.8%)	56.5% (5.4%)	0.09 (0.15)	330/281
	Support Vector Machine	51.7% (3.2%)	50.4% (4.4%)	66.4% (42.2%)	37.0% (41.7%)	51.7% (3.2%)	0.06 (0.12)	330/281
DTI FA	Boosting Classifier	49.3% (6.5%)	49.9% (6.9%)	42.9% (7.5%)	55.6% (11.8%)	48.3% (7.8%)	-0.01 (0.13)	291/238
	k-Nearest Neighbours	51.7% (9.8%)	52.0% (9.6%)	48.4% (13.3%)	55.0% (9.5%)	53.1% (7.4%)	0.03 (0.2)	291/238
	Logistic Regression	50.6% (6.6%)	51.6% (6.5%)	39.5% (10.9%)	61.6% (9.2%)	50.8% (6.8%)	0.01 (0.13)	291/238
	Gaussian Naive Bayes	55.4% (6.1%)	55.4% (5.7%)	55.1% (14.5%)	55.7% (8.7%)	55.7% (6.2%)	0.11 (0.12)	291/238
	Random Forest	55.5% (4.9%)	57.7% (4.5%)	33.6% (10.2%)	77.4% (6.1%)	57.9% (5.8%)	0.12 (0.1)	291/238
	Support Vector Machine	52.1% (5.4%)	52.8% (5.8%)	45.0% (5.1%)	59.1% (10.7%)	52.1% (5.4%)	0.04 (0.11)	291/238

DTI MD	Boosting Classifier	49.5% (9.6%)	50.3% (9.8%)	41.2% (11.5%)	57.7% (12.9%)	51.3% (11.0%)	-0.01 (0.19)	291/238
	k-Nearest Neighbours	53.2% (6.4%)	54.3% (6.8%)	42.1% (13.7%)	64.3% (16.1%)	55.8% (7.5%)	0.07 (0.13)	291/238
	Logistic Regression	49.7% (4.4%)	51.2% (4.8%)	33.3% (13.3%)	66.0% (14.8%)	49.3% (6.9%)	-0.0 (0.1)	291/238
	Gaussian Naive Bayes	50.0% (6.5%)	51.4% (7.3%)	36.2% (13.1%)	63.9% (19.1%)	53.6% (8.3%)	0.02 (0.16)	291/238
	Random Forest	49.8% (4.2%)	52.7% (4.4%)	19.8% (6.7%)	79.8% (8.7%)	52.5% (5.9%)	-0.0 (0.1)	291/238
	Support Vector Machine	51.0% (6.3%)	52.2% (6.4%)	39.9% (10.1%)	62.2% (10.7%)	51.0% (6.3%)	0.02 (0.13)	291/238
DTI Network Parameters	Boosting Classifier	47.0% (6.9%)	47.6% (7.1%)	39.9% (12.6%)	54.0% (14.1%)	45.9% (8.1%)	-0.06 (0.14)	291/238
	k-Nearest Neighbours	47.9% (6.5%)	49.9% (6.2%)	28.1% (11.3%)	67.7% (9.1%)	50.3% (4.9%)	-0.05 (0.15)	291/238
	Logistic Regression	48.0% (5.7%)	49.1% (5.4%)	36.6% (10.8%)	59.5% (6.7%)	47.7% (7.8%)	-0.04 (0.12)	291/238
	Gaussian Naive Bayes	50.1% (5.6%)	50.7% (5.2%)	44.2% (12.6%)	56.0% (8.3%)	51.7% (7.1%)	0.0 (0.11)	291/238
	Random Forest	48.9% (4.7%)	51.2% (5.4%)	25.6% (12.0%)	72.1% (15.1%)	46.9% (8.1%)	-0.02 (0.12)	291/238
	Support Vector Machine	49.8% (6.0%)	50.3% (5.7%)	44.6% (12.5%)	55.0% (8.5%)	49.8% (6.0%)	-0.01 (0.12)	291/238

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 12. Classification accuracy based on functional MRI for HC vs MDD (male).

eTable 12. Classification accuracy for multivariate biomarkers based on functional MRI for HC vs MDD (male).

Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
Face Matching Task	Boosting Classifier	52.2% (8.8%)	52.6% (8.8%)	47.1% (12.0%)	57.3% (11.2%)	51.1% (9.5%)	0.05 (0.18)	227/195
	k-Nearest Neighbours	48.4% (9.7%)	49.3% (9.8%)	34.5% (10.9%)	62.3% (16.3%)	48.2% (8.8%)	-0.03 (0.21)	227/195
	Logistic Regression	53.7% (7.2%)	53.6% (7.3%)	54.0% (9.9%)	53.4% (10.8%)	55.0% (10.7%)	0.07 (0.15)	227/195
	Gaussian Naive Bayes	51.6% (9.5%)	51.5% (9.5%)	52.0% (17.9%)	51.2% (16.6%)	52.6% (12.0%)	0.04 (0.2)	227/195
	Random Forest	50.5% (5.4%)	52.2% (5.3%)	27.2% (15.8%)	73.8% (16.4%)	52.8% (9.3%)	0.01 (0.12)	227/195
	Support Vector Machine	48.3% (7.8%)	47.6% (7.5%)	58.3% (25.0%)	38.3% (22.2%)	48.3% (7.8%)	-0.05 (0.18)	227/195
RS Connectivity	Boosting Classifier	52.9% (8.2%)	53.5% (8.4%)	46.4% (12.9%)	59.4% (13.3%)	51.9% (10.7%)	0.06 (0.17)	249/209
	k-Nearest Neighbours	54.3% (7.8%)	55.4% (7.7%)	41.1% (13.2%)	67.4% (8.3%)	55.6% (9.3%)	0.09 (0.16)	249/209
	Logistic Regression	57.6% (8.6%)	58.1% (8.4%)	52.1% (13.1%)	63.0% (8.4%)	60.2% (9.0%)	0.15 (0.17)	249/209
	Gaussian Naive Bayes	57.8% (5.9%)	58.3% (6.0%)	53.5% (14.6%)	62.2% (13.9%)	59.5% (7.9%)	0.16 (0.13)	249/209
	Random Forest	58.9% (5.7%)	60.3% (5.3%)	44.4% (13.1%)	73.4% (6.8%)	60.6% (9.0%)	0.19 (0.11)	249/209
	Support Vector Machine	60.3% (8.1%)	61.1% (7.6%)	51.2% (17.9%)	69.4% (9.7%)	60.3% (8.1%)	0.21 (0.17)	249/209
ALFF	Boosting Classifier	55.6% (6.6%)	55.9% (6.3%)	51.7% (12.9%)	59.5% (7.7%)	58.1% (8.6%)	0.11 (0.13)	249/209
	k-Nearest Neighbours	57.3% (3.5%)	58.3% (3.8%)	46.4% (7.7%)	68.2% (8.5%)	59.8% (4.9%)	0.15 (0.08)	249/209
	Logistic Regression	60.4% (6.7%)	61.2% (6.7%)	52.2% (8.2%)	68.7% (7.9%)	62.5% (10.2%)	0.21 (0.14)	249/209
	Gaussian Naive Bayes	59.8% (5.7%)	60.1% (5.9%)	57.8% (11.2%)	61.8% (11.9%)	59.5% (5.6%)	0.2 (0.12)	249/209
	Random Forest	59.0% (4.9%)	60.5% (4.7%)	42.6% (10.1%)	75.4% (7.0%)	62.5% (9.5%)	0.19 (0.1)	249/209
	Support Vector Machine	59.1% (8.6%)	60.1% (8.8%)	47.4% (11.0%)	70.7% (13.8%)	59.1% (8.6%)	0.19 (0.18)	249/209
fALFF	Boosting Classifier	52.7% (7.6%)	53.3% (7.6%)	46.9% (13.4%)	58.6% (12.9%)	51.7% (9.1%)	0.06 (0.16)	249/209

	k-Nearest Neighbours	50.0% (8.6%)	51.1% (8.8%)	37.3% (10.5%)	62.7% (13.8%)	52.2% (8.7%)	0.0 (0.18)	249/209
	Logistic Regression	54.2% (7.2%)	55.0% (7.2%)	45.0% (9.8%)	63.5% (9.6%)	56.3% (11.5%)	0.09 (0.15)	249/209
	Gaussian Naive Bayes	54.8% (7.0%)	55.0% (6.9%)	52.6% (9.8%)	57.0% (7.0%)	55.7% (7.6%)	0.1 (0.14)	249/209
	Random Forest	53.5% (8.8%)	55.2% (8.8%)	34.0% (12.3%)	73.1% (11.8%)	55.7% (9.4%)	0.08 (0.19)	249/209
	Support Vector Machine	53.6% (7.7%)	55.0% (7.6%)	36.9% (13.5%)	70.3% (11.6%)	53.6% (7.7%)	0.08 (0.17)	249/209
LCOR	Boosting Classifier	51.0% (5.5%)	51.5% (6.0%)	45.0% (13.1%)	57.0% (16.1%)	51.2% (3.2%)	0.02 (0.11)	249/209
	k-Nearest Neighbours	56.9% (7.4%)	57.4% (7.0%)	50.7% (13.7%)	63.0% (6.7%)	59.0% (6.6%)	0.14 (0.15)	249/209
	Logistic Regression	52.2% (7.1%)	52.8% (6.7%)	45.5% (17.1%)	59.0% (12.1%)	55.0% (4.1%)	0.04 (0.15)	249/209
	Gaussian Naive Bayes	53.5% (5.6%)	53.5% (5.4%)	53.5% (10.3%)	53.4% (6.7%)	53.0% (5.5%)	0.07 (0.11)	249/209
	Random Forest	51.8% (6.2%)	53.3% (5.8%)	34.9% (16.0%)	68.6% (10.3%)	54.9% (6.7%)	0.04 (0.13)	249/209
	Support Vector Machine	52.8% (7.4%)	53.7% (6.8%)	42.1% (18.5%)	63.4% (10.8%)	52.8% (7.4%)	0.05 (0.15)	249/209
RS Network Parameters	Boosting Classifier	52.4% (6.9%)	53.3% (6.9%)	43.5% (10.6%)	61.4% (10.2%)	53.6% (7.1%)	0.05 (0.14)	249/209
	k-Nearest Neighbours	51.8% (7.1%)	53.3% (6.7%)	35.3% (15.7%)	68.2% (11.8%)	53.2% (11.4%)	0.03 (0.16)	249/209
	Logistic Regression	52.5% (6.9%)	54.1% (7.0%)	33.9% (7.7%)	71.0% (9.0%)	56.0% (9.1%)	0.05 (0.15)	249/209
	Gaussian Naive Bayes	56.6% (6.9%)	56.8% (6.4%)	54.9% (13.6%)	58.2% (6.8%)	58.1% (7.5%)	0.13 (0.14)	249/209
	Random Forest	56.0% (6.1%)	57.6% (6.1%)	36.8% (11.5%)	75.1% (9.3%)	58.7% (8.7%)	0.13 (0.13)	249/209
	Support Vector Machine	53.5% (5.5%)	54.6% (5.6%)	42.0% (17.9%)	65.1% (17.8%)	53.5% (5.5%)	0.08 (0.12)	249/209

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 13. Classification accuracy using neuroimaging modality integration for HC vs MDD (male).

eTable 13. Classification accuracy for multivariate biomarkers using neuroimaging modality integration for HC vs MDD (male).

Modality Integration	**Modality**	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
PCA-based	all	Boosting Classifier	49.7% (11.0%)	50.6% (10.8%)	40.6% (17.0%)	58.7% (14.3%)	48.9% (14.5%)	-0.01 (0.24)	196/158
		k-Nearest Neighbours	48.1% (9.3%)	50.0% (9.7%)	29.2% (12.7%)	66.9% (17.3%)	48.7% (10.6%)	-0.04 (0.2)	196/158
		Logistic Regression	49.1% (4.1%)	48.3% (7.2%)	56.7% (44.1%)	41.5% (46.6%)	53.0% (9.0%)	-0.05 (0.15)	196/158
		Gaussian Naive Bayes	51.1% (7.6%)	50.8% (7.9%)	51.0% (34.9%)	51.2% (31.8%)	51.2% (8.9%)	0.01 (0.18)	196/158
		Random Forest	53.5% (6.9%)	56.8% (7.3%)	23.5% (15.4%)	83.6% (16.0%)	55.6% (9.6%)	0.09 (0.18)	196/158
		Support Vector Machine	48.9% (4.3%)	46.6% (5.0%)	67.3% (38.5%)	30.4% (36.3%)	48.9% (4.3%)	-0.03 (0.14)	196/158
Voting	all	all	58.2% (6.3%)	61.6% (5.8%)	27.7% (10.5%)	88.7% (6.0%)	64.6% (8.8%)	0.21 (0.16)	196/158
Voting	all	Boosting Classifier	54.8% (6.4%)	56.5% (6.2%)	39.2% (10.5%)	70.4% (9.5%)	54.6% (10.1%)	0.1 (0.14)	196/158
		k-Nearest Neighbours	55.5% (5.3%)	59.1% (5.0%)	22.7% (10.0%)	88.3% (5.8%)	59.8% (6.3%)	0.14 (0.14)	196/158
		Logistic Regression	55.4% (6.1%)	57.6% (6.3%)	35.3% (9.5%)	75.4% (11.7%)	62.7% (9.8%)	0.13 (0.14)	196/158
		Gaussian Naive Bayes	59.4% (7.9%)	61.3% (7.3%)	42.2% (13.6%)	76.5% (8.1%)	63.5% (6.3%)	0.2 (0.17)	196/158
		Random Forest	53.1% (3.3%)	57.3% (3.4%)	13.3% (6.2%)	92.8% (4.9%)	64.5% (12.8%)	0.11 (0.11)	196/158
		Support Vector Machine	57.2% (9.2%)	59.0% (9.3%)	39.9% (10.7%)	74.4% (10.4%)	61.1% (7.9%)	0.15 (0.2)	196/158
Voting	Freesurfer	all	52.4% (6.8%)	55.1% (7.3%)	27.8% (9.4%)	76.9% (12.8%)	52.6% (9.9%)	0.06 (0.16)	196/158
	VBM		51.5% (5.1%)	55.3% (4.9%)	16.3% (10.7%)	86.7% (10.3%)	56.2% (7.2%)	0.05 (0.18)	196/158
	DTI FA		54.0% (5.6%)	56.5% (5.7%)	31.0% (5.1%)	77.1% (7.8%)	56.2% (7.0%)	0.09 (0.13)	196/158
	DTI MD		52.1% (7.1%)	55.7% (7.3%)	20.2% (8.1%)	84.1% (12.6%)	54.1% (11.4%)	0.07 (0.19)	196/158

	DTI Network Parameters		49.5% (6.0%)	52.0% (6.2%)	27.1% (8.1%)	71.9% (8.3%)	47.4% (9.5%)	-0.01 (0.13)	196/158
	Face Matching Task		49.9% (6.8%)	52.3% (6.8%)	27.8% (11.0%)	71.9% (12.2%)	52.3% (9.2%)	0.0 (0.17)	196/158
	RS Connectivity		61.3% (7.3%)	63.0% (7.6%)	45.0% (9.0%)	77.5% (11.3%)	63.3% (10.8%)	0.24 (0.16)	196/158
	ALFF		63.0% (8.4%)	64.9% (8.1%)	45.5% (12.7%)	80.5% (8.3%)	65.2% (9.5%)	0.28 (0.18)	196/158
	fALFF		53.2% (7.0%)	55.6% (7.5%)	29.8% (9.1%)	76.5% (11.1%)	54.1% (7.0%)	0.08 (0.17)	196/158
	LCOR		52.6% (7.7%)	54.2% (7.7%)	36.8% (9.4%)	68.4% (8.4%)	52.3% (7.8%)	0.05 (0.16)	196/158
	RS Network Parameters		54.4% (6.4%)	56.8% (6.3%)	32.8% (9.8%)	76.1% (10.2%)	56.6% (4.7%)	0.1 (0.14)	196/158

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 14. Classification accuracy based on structural MRI for HC vs MDD (female).

eTable 14. Classification accuracy for multivariate biomarkers based on structural MRI for HC vs MDD (female).

Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
Freesurfer	Boosting Classifier	54.3% (6.1%)	54.6% (5.9%)	48.0% (11.4%)	60.6% (7.3%)	55.6% (6.4%)	0.09 (0.12)	593/533
	k-Nearest Neighbours	51.4% (4.8%)	51.7% (4.8%)	46.9% (9.1%)	56.0% (8.2%)	51.6% (5.2%)	0.03 (0.1)	593/533
	Logistic Regression	53.5% (3.7%)	54.0% (3.8%)	45.0% (8.7%)	62.1% (9.5%)	56.0% (3.0%)	0.07 (0.08)	593/533
	Gaussian Naive Bayes	53.9% (3.5%)	53.8% (3.6%)	54.4% (5.9%)	53.3% (6.8%)	56.4% (3.5%)	0.08 (0.07)	593/533
	Random Forest	53.1% (5.2%)	53.8% (5.1%)	38.8% (8.4%)	67.3% (6.7%)	55.6% (3.9%)	0.06 (0.11)	593/533
	Support Vector Machine	54.9% (2.9%)	55.6% (2.8%)	42.0% (13.8%)	67.8% (12.6%)	54.9% (2.9%)	0.11 (0.06)	593/533
VBM	Boosting Classifier	53.1% (2.5%)	53.1% (2.4%)	52.2% (6.2%)	53.9% (4.1%)	53.1% (3.3%)	0.06 (0.05)	594/536
	k-Nearest Neighbours	49.6% (4.2%)	50.4% (4.3%)	33.8% (7.9%)	65.5% (10.7%)	51.1% (5.9%)	-0.01 (0.09)	594/536
	Logistic Regression	51.8% (4.4%)	50.9% (4.7%)	67.8% (16.6%)	35.8% (18.0%)	52.0% (4.8%)	0.04 (0.09)	594/536
	Gaussian Naive Bayes	51.0% (3.8%)	51.9% (3.4%)	31.5% (24.6%)	70.4% (21.5%)	50.7% (6.2%)	0.02 (0.09)	594/536
	Random Forest	54.5% (3.4%)	55.0% (3.4%)	42.9% (5.5%)	66.0% (6.0%)	57.2% (4.6%)	0.09 (0.07)	594/536
	Support Vector Machine	53.5% (4.1%)	53.3% (4.3%)	58.0% (15.1%)	49.0% (17.2%)	53.5% (4.1%)	0.07 (0.08)	594/536
DTI FA	Boosting Classifier	54.4% (6.9%)	54.7% (6.7%)	51.2% (11.7%)	57.7% (8.1%)	56.3% (7.2%)	0.09 (0.14)	527/447
	k-Nearest Neighbours	50.8% (3.2%)	51.4% (3.1%)	43.2% (8.3%)	58.5% (7.6%)	50.7% (3.9%)	0.02 (0.06)	527/447
	Logistic Regression	52.8% (5.3%)	53.3% (5.1%)	46.6% (9.0%)	59.0% (5.8%)	54.5% (5.3%)	0.06 (0.11)	527/447
	Gaussian Naive Bayes	49.5% (3.6%)	49.3% (4.5%)	51.9% (21.3%)	47.1% (23.7%)	49.8% (2.6%)	-0.01 (0.08)	527/447
	Random Forest	55.2% (5.1%)	56.9% (5.2%)	34.0% (6.8%)	76.3% (8.0%)	58.0% (5.3%)	0.12 (0.11)	527/447

	Support Vector Machine	54.6% (5.3%)	55.3% (5.2%)	45.4% (13.0%)	63.7% (11.0%)	54.6% (5.3%)	0.09 (0.11)	527/447
DTI MD	Boosting Classifier	55.8% (4.9%)	56.4% (4.8%)	48.4% (9.9%)	63.2% (7.9%)	55.6% (5.3%)	0.12 (0.1)	527/447
	k-Nearest Neighbours	52.4% (4.4%)	53.5% (4.2%)	39.5% (14.9%)	65.2% (13.4%)	51.7% (2.9%)	0.05 (0.1)	527/447
	Logistic Regression	52.8% (3.3%)	53.4% (3.3%)	45.2% (7.0%)	60.3% (5.4%)	53.5% (3.8%)	0.06 (0.07)	527/447
	Gaussian Naive Bayes	53.5% (4.8%)	53.0% (4.8%)	60.2% (8.6%)	46.9% (7.2%)	56.6% (4.2%)	0.07 (0.1)	527/447
	Random Forest	55.0% (3.0%)	56.9% (3.0%)	31.6% (7.3%)	78.4% (7.6%)	56.6% (3.8%)	0.11 (0.07)	527/447
	Support Vector Machine	53.0% (5.2%)	53.6% (4.9%)	46.3% (10.2%)	59.8% (3.0%)	53.0% (5.2%)	0.06 (0.11)	527/447
DTI Network Parameters	Boosting Classifier	49.2% (5.0%)	49.6% (5.2%)	45.0% (8.3%)	53.5% (11.0%)	49.8% (4.4%)	-0.01 (0.1)	527/447
	k-Nearest Neighbours	50.7% (4.0%)	52.0% (4.1%)	35.8% (9.4%)	65.7% (9.3%)	51.2% (6.3%)	0.02 (0.09)	527/447
	Logistic Regression	53.7% (4.8%)	54.4% (4.9%)	44.9% (7.3%)	62.4% (8.8%)	54.2% (5.1%)	0.08 (0.1)	527/447
	Gaussian Naive Bayes	52.4% (3.2%)	52.5% (3.5%)	51.3% (9.2%)	53.5% (10.7%)	54.4% (3.2%)	0.05 (0.07)	527/447
	Random Forest	50.1% (3.8%)	52.4% (3.7%)	23.0% (11.6%)	77.2% (9.9%)	53.6% (7.3%)	-0.0 (0.09)	527/447
	Support Vector Machine	52.2% (4.1%)	52.9% (4.1%)	43.8% (7.2%)	60.6% (6.7%)	52.2% (4.1%)	0.04 (0.08)	527/447

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 15. Classification accuracy based on functional MRI for HC vs MDD (female).

eTable 15. Classification accuracy for multivariate biomarkers based on functional MRI for HC vs MDD (female).

Modality	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
Face Matching Task	Boosting Classifier	52.8% (5.6%)	53.0% (5.6%)	49.1% (5.2%)	56.4% (7.6%)	53.0% (4.7%)	0.06 (0.11)	427/385
	k-Nearest Neighbours	51.2% (5.9%)	52.1% (5.9%)	33.8% (13.7%)	68.7% (12.4%)	52.5% (5.7%)	0.02 (0.13)	427/385
	Logistic Regression	50.5% (6.2%)	50.7% (5.9%)	45.2% (16.2%)	55.8% (9.6%)	51.7% (7.0%)	0.01 (0.13)	427/385
	Gaussian Naive Bayes	56.0% (3.9%)	55.2% (4.3%)	71.0% (11.1%)	41.0% (13.3%)	57.5% (4.2%)	0.13 (0.08)	427/385
	Random Forest	55.6% (5.9%)	56.5% (5.8%)	37.4% (7.3%)	73.8% (7.7%)	57.3% (6.6%)	0.12 (0.13)	427/385
	Support Vector Machine	51.4% (6.4%)	51.6% (6.6%)	47.8% (11.8%)	55.0% (16.2%)	51.4% (6.4%)	0.03 (0.13)	427/385
RS Connectivity	Boosting Classifier	53.2% (4.1%)	53.3% (4.1%)	50.9% (5.0%)	55.4% (8.1%)	55.2% (4.2%)	0.06 (0.08)	451/422
	k-Nearest Neighbours	55.6% (5.1%)	56.0% (5.2%)	42.9% (5.7%)	68.3% (8.8%)	58.6% (7.0%)	0.12 (0.11)	451/422
	Logistic Regression	58.4% (4.2%)	58.5% (4.3%)	54.3% (5.7%)	62.5% (8.7%)	62.3% (4.6%)	0.17 (0.09)	451/422
	Gaussian Naive Bayes	57.4% (5.1%)	57.6% (5.0%)	51.9% (7.6%)	63.0% (5.5%)	59.7% (6.2%)	0.15 (0.1)	451/422
	Random Forest	56.9% (4.5%)	57.2% (4.5%)	47.9% (5.9%)	65.8% (6.4%)	61.0% (4.4%)	0.14 (0.09)	451/422
	Support Vector Machine	58.1% (3.6%)	58.3% (3.6%)	51.5% (6.8%)	64.7% (7.8%)	58.1% (3.6%)	0.16 (0.07)	451/422
ALFF	Boosting Classifier	57.4% (5.6%)	57.5% (5.7%)	55.3% (7.7%)	59.6% (8.7%)	59.3% (7.0%)	0.15 (0.11)	452/422
	k-Nearest Neighbours	59.2% (4.8%)	59.5% (4.8%)	51.4% (6.3%)	67.0% (6.7%)	60.9% (6.9%)	0.19 (0.1)	452/422
	Logistic Regression	59.1% (5.9%)	59.3% (5.7%)	54.3% (11.9%)	64.0% (5.7%)	62.4% (6.0%)	0.19 (0.12)	452/422
	Gaussian Naive Bayes	60.3% (4.5%)	60.4% (4.5%)	54.8% (7.6%)	65.8% (7.7%)	60.1% (4.3%)	0.21 (0.09)	452/422
	Random Forest	60.5% (6.8%)	60.7% (6.7%)	55.7% (10.1%)	65.3% (6.0%)	63.3% (5.4%)	0.21 (0.14)	452/422
	Support Vector Machine	61.6% (4.5%)	61.8% (4.5%)	56.9% (7.7%)	66.4% (5.1%)	61.6% (4.5%)	0.23 (0.09)	452/422
fALFF	Boosting Classifier	54.4% (6.0%)	54.5% (6.1%)	53.3% (9.1%)	55.6% (9.9%)	55.6% (4.8%)	0.09 (0.12)	452/422

	k-Nearest Neighbours	56.0% (5.1%)	56.6% (5.0%)	35.8% (11.2%)	76.1% (6.5%)	58.7% (6.0%)	0.13 (0.11)	452/422
	Logistic Regression	57.9% (4.1%)	58.0% (4.1%)	53.3% (6.1%)	62.4% (7.5%)	59.8% (3.9%)	0.16 (0.08)	452/422
	Gaussian Naive Bayes	55.3% (2.7%)	55.4% (2.6%)	53.1% (6.0%)	57.5% (4.4%)	56.1% (3.3%)	0.11 (0.05)	452/422
	Random Forest	55.4% (4.7%)	55.8% (4.7%)	43.1% (8.3%)	67.7% (9.2%)	58.9% (6.1%)	0.11 (0.1)	452/422
	Support Vector Machine	58.6% (3.9%)	58.8% (3.9%)	53.1% (5.0%)	64.2% (6.9%)	58.6% (3.9%)	0.17 (0.08)	452/422
LCOR	Boosting Classifier	50.8% (4.9%)	51.0% (4.7%)	45.5% (11.8%)	56.2% (6.7%)	51.8% (8.1%)	0.01 (0.1)	452/422
	k-Nearest Neighbours	56.2% (6.5%)	56.5% (6.6%)	46.7% (9.2%)	65.7% (10.7%)	59.7% (4.6%)	0.13 (0.14)	452/422
	Logistic Regression	57.7% (2.7%)	57.8% (2.7%)	54.5% (5.5%)	60.8% (4.1%)	59.3% (4.8%)	0.15 (0.05)	452/422
	Gaussian Naive Bayes	55.9% (4.4%)	56.1% (4.3%)	52.8% (9.7%)	59.1% (5.0%)	55.8% (4.3%)	0.12 (0.09)	452/422
	Random Forest	54.5% (5.7%)	54.8% (5.5%)	47.4% (11.6%)	61.7% (3.1%)	59.4% (6.4%)	0.09 (0.11)	452/422
	Support Vector Machine	56.5% (3.8%)	56.6% (3.7%)	51.4% (8.2%)	61.5% (7.3%)	56.5% (3.8%)	0.13 (0.08)	452/422
RS Network Parameters	Boosting Classifier	50.5% (4.9%)	50.7% (4.8%)	41.3% (10.9%)	59.6% (5.1%)	52.6% (5.3%)	0.01 (0.1)	451/422
	k-Nearest Neighbours	52.9% (3.8%)	53.4% (3.9%)	38.6% (7.6%)	67.2% (8.9%)	55.6% (3.8%)	0.06 (0.08)	451/422
	Logistic Regression	57.8% (5.0%)	58.0% (5.0%)	52.6% (7.2%)	63.0% (6.2%)	61.6% (6.0%)	0.16 (0.1)	451/422
	Gaussian Naive Bayes	53.1% (6.8%)	53.2% (6.8%)	50.9% (7.4%)	55.2% (7.9%)	54.5% (7.9%)	0.06 (0.14)	451/422
	Random Forest	56.2% (5.0%)	56.5% (5.1%)	47.2% (7.2%)	65.2% (8.5%)	57.8% (6.4%)	0.13 (0.1)	451/422
	Support Vector Machine	60.3% (6.9%)	60.5% (7.0%)	55.4% (7.1%)	65.2% (9.2%)	60.3% (6.9%)	0.21 (0.14)	451/422

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 16. Classification accuracy using neuroimaging modality integration for HC vs MDD (female).

eTable 16. Classification accuracy for multivariate biomarkers using neuroimaging modality integration for HC vs MDD (female).

Modality Integration	**Modality**	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
PCA-based	all	Boosting Classifier	57.9% (4.4%)	58.6% (4.3%)	49.6% (10.6%)	66.3% (7.7%)	56.3% (5.0%)	0.16 (0.09)	371/313
		k-Nearest Neighbours	51.7% (4.6%)	52.9% (4.7%)	37.4% (9.9%)	66.0% (9.8%)	53.6% (7.5%)	0.04 (0.1)	371/313
		Logistic Regression	50.7% (2.3%)	53.7% (3.1%)	15.7% (20.8%)	85.7% (21.0%)	50.8% (5.4%)	0.03 (0.08)	371/313
		Gaussian Naive Bayes	50.5% (2.9%)	53.4% (3.2%)	18.1% (25.0%)	83.0% (24.0%)	53.4% (5.2%)	0.03 (0.11)	371/313
		Random Forest	54.1% (5.9%)	56.6% (5.8%)	25.2% (10.0%)	83.0% (8.5%)	58.2% (9.3%)	0.11 (0.16)	371/313
		Support Vector Machine	49.0% (2.4%)	49.1% (5.6%)	46.8% (48.4%)	51.3% (50.3%)	49.0% (2.4%)	-0.03 (0.1)	371/313
Voting	all	all	61.5% (5.9%)	63.0% (5.3%)	43.8% (13.7%)	79.2% (4.0%)	65.9% (5.6%)	0.25 (0.12)	371/313
Voting	all	Boosting Classifier	56.6% (6.1%)	57.6% (6.0%)	44.1% (10.7%)	69.0% (6.5%)	59.8% (5.3%)	0.14 (0.13)	371/313
		k-Nearest Neighbours	57.4% (4.8%)	59.5% (4.5%)	32.0% (10.1%)	82.7% (6.7%)	60.1% (6.9%)	0.17 (0.11)	371/313
		Logistic Regression	60.2% (4.4%)	61.0% (4.1%)	50.5% (10.4%)	69.8% (6.3%)	63.1% (5.8%)	0.21 (0.09)	371/313
		Gaussian Naive Bayes	60.8% (5.9%)	61.3% (5.7%)	54.7% (10.9%)	66.8% (6.1%)	62.6% (7.7%)	0.22 (0.12)	371/313
		Random Forest	59.0% (5.4%)	61.1% (4.9%)	34.5% (11.6%)	83.6% (4.4%)	64.1% (5.5%)	0.21 (0.11)	371/313
		Support Vector Machine	61.3% (6.1%)	62.4% (5.9%)	48.2% (10.1%)	74.4% (5.9%)	65.3% (6.0%)	0.23 (0.12)	371/313
Voting	Freesurfer	all	49.7% (7.7%)	51.0% (7.7%)	34.2% (8.5%)	65.2% (8.9%)	52.6% (9.8%)	-0.0 (0.16)	371/313
	VBM		52.6% (5.0%)	53.8% (4.6%)	38.7% (10.0%)	66.6% (5.1%)	53.8% (6.4%)	0.05 (0.1)	371/313
	DTI FA		53.8% (4.6%)	55.7% (4.5%)	31.3% (8.3%)	76.3% (7.0%)	55.6% (6.2%)	0.09 (0.1)	371/313
	DTI MD		56.1% (5.8%)	58.0% (5.7%)	33.2% (8.5%)	79.0% (7.6%)	56.4% (3.9%)	0.14 (0.13)	371/313

	DTI Network Parameters		51.5% (7.6%)	53.8% (7.8%)	24.3% (8.0%)	78.7% (9.8%)	52.9% (5.0%)	0.04 (0.17)	371/313
	Face Matching Task		54.6% (3.8%)	56.0% (3.5%)	37.7% (10.7%)	71.4% (7.6%)	56.8% (6.0%)	0.1 (0.08)	371/313
	RS Connectivity		58.0% (4.5%)	59.2% (4.2%)	43.1% (8.8%)	72.8% (4.8%)	61.7% (5.7%)	0.17 (0.09)	371/313
	ALFF		62.7% (5.5%)	63.6% (5.4%)	52.7% (9.3%)	72.8% (6.7%)	64.8% (6.0%)	0.26 (0.11)	371/313
	fALFF		59.5% (5.4%)	60.7% (5.2%)	45.4% (8.8%)	73.6% (5.7%)	60.6% (6.0%)	0.2 (0.11)	371/313
	LCOR		56.8% (4.7%)	58.0% (4.7%)	42.5% (7.2%)	71.2% (7.1%)	59.5% (6.3%)	0.14 (0.1)	371/313
	RS Network Parameters		58.4% (7.1%)	59.8% (6.9%)	42.5% (9.9%)	74.4% (5.4%)	59.8% (7.9%)	0.18 (0.15)	371/313

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew's Correlation Coefficient.

eTable 17. Classification accuracy based on structural MRI for HC vs MDD (age 24 - 28).

eTable 17. Classification accuracy for multivariate biomarkers based on structural MRI for HC vs MDD (age 24 -28).

Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
Freesurfer	Boosting Classifier	53.5% (8.5%)	55.1% (8.7%)	41.8% (14.0%)	65.3% (14.0%)	51.5% (12.9%)	0.07 (0.17)	224/166
	k-Nearest Neighbours	50.0% (5.9%)	52.8% (6.5%)	30.8% (8.2%)	69.1% (9.8%)	51.6% (5.6%)	0.0 (0.13)	224/166
	Logistic Regression	52.4% (6.9%)	55.9% (6.9%)	28.9% (11.7%)	75.9% (11.6%)	57.6% (6.0%)	0.06 (0.16)	224/166
	Gaussian Naive Bayes	52.8% (7.8%)	54.6% (8.0%)	39.4% (15.2%)	66.1% (13.8%)	56.2% (9.6%)	0.06 (0.16)	224/166
	Random Forest	56.3% (6.2%)	59.2% (5.7%)	36.3% (14.6%)	76.3% (8.4%)	56.8% (11.1%)	0.13 (0.14)	224/166
	Support Vector Machine	47.9% (8.3%)	50.3% (9.2%)	33.1% (17.3%)	62.8% (20.7%)	47.9% (8.3%)	-0.03 (0.2)	224/166
VBM	Boosting Classifier	49.0% (8.3%)	49.9% (7.9%)	42.9% (12.7%)	55.0% (6.9%)	49.0% (7.3%)	-0.02 (0.17)	225/166
	k-Nearest Neighbours	50.9% (7.5%)	52.2% (7.7%)	42.8% (9.8%)	59.0% (10.0%)	49.9% (10.7%)	0.02 (0.15)	225/166
	Logistic Regression	49.6% (6.6%)	46.8% (7.0%)	67.0% (32.7%)	32.2% (29.6%)	45.4% (6.0%)	0.0 (0.16)	225/166
	Gaussian Naive Bayes	48.5% (5.6%)	51.1% (10.5%)	29.8% (32.7%)	67.3% (40.6%)	50.5% (10.3%)	-0.04 (0.17)	225/166
	Random Forest	49.6% (6.7%)	55.0% (6.4%)	13.9% (10.8%)	85.4% (7.7%)	51.5% (13.5%)	-0.01 (0.19)	225/166
	Support Vector Machine	48.3% (5.4%)	46.0% (9.0%)	63.5% (42.2%)	33.1% (43.4%)	48.3% (5.4%)	-0.05 (0.19)	225/166
DTI FA	Boosting Classifier	46.7% (9.2%)	47.7% (9.5%)	40.4% (11.4%)	52.9% (14.2%)	47.2% (11.1%)	-0.07 (0.18)	204/144
	k-Nearest Neighbours	47.0% (8.4%)	50.2% (8.8%)	29.0% (9.8%)	65.0% (11.3%)	47.9% (9.4%)	-0.06 (0.18)	204/144
	Logistic Regression	46.5% (4.6%)	50.3% (6.8%)	24.4% (14.1%)	68.6% (19.2%)	48.6% (4.1%)	-0.07 (0.1)	204/144
	Gaussian Naive Bayes	52.7% (8.1%)	54.3% (8.0%)	43.0% (13.4%)	62.4% (11.6%)	52.2% (9.1%)	0.06 (0.17)	204/144
	Random Forest	51.5% (4.9%)	58.4% (5.6%)	11.9% (7.6%)	91.2% (7.6%)	46.7% (8.1%)	0.06 (0.17)	204/144
	Support Vector Machine	52.0% (6.1%)	54.3% (7.1%)	39.0% (7.0%)	65.1% (13.0%)	52.0% (6.1%)	0.05 (0.13)	204/144

DTI MD	Boosting Classifier	52.6% (6.5%)	55.2% (6.4%)	37.4% (11.6%)	67.8% (11.0%)	51.7% (9.6%)	0.05 (0.14)	204/144
	k-Nearest Neighbours	50.0% (6.6%)	54.3% (6.7%)	25.5% (13.0%)	74.5% (11.8%)	49.1% (10.4%)	-0.0 (0.15)	204/144
	Logistic Regression	47.5% (4.3%)	50.3% (4.0%)	31.3% (14.4%)	63.8% (11.4%)	45.6% (7.6%)	-0.06 (0.1)	204/144
	Gaussian Naive Bayes	52.6% (4.6%)	54.0% (5.0%)	44.0% (9.6%)	61.3% (9.4%)	53.9% (5.3%)	0.05 (0.1)	204/144
	Random Forest	48.0% (5.8%)	54.6% (6.6%)	10.3% (8.0%)	85.8% (11.7%)	50.2% (12.5%)	-0.05 (0.18)	204/144
	Support Vector Machine	46.8% (7.2%)	49.1% (7.2%)	33.3% (15.7%)	60.3% (14.0%)	46.8% (7.2%)	-0.07 (0.15)	204/144
DTI Network Parameters	Boosting Classifier	51.5% (10.6%)	53.4% (10.3%)	40.8% (15.4%)	62.2% (11.5%)	51.8% (12.1%)	0.03 (0.21)	204/144
	k-Nearest Neighbours	49.5% (7.2%)	53.8% (7.8%)	24.4% (14.2%)	74.5% (15.3%)	47.2% (8.0%)	-0.01 (0.18)	204/144
	Logistic Regression	47.6% (4.7%)	54.3% (6.7%)	7.8% (12.4%)	87.4% (18.2%)	43.7% (10.2%)	-0.05 (0.11)	204/144
	Gaussian Naive Bayes	48.2% (8.3%)	52.3% (8.8%)	25.4% (15.2%)	71.0% (16.5%)	44.8% (11.5%)	-0.03 (0.18)	204/144
	Random Forest	50.2% (5.7%)	55.5% (5.2%)	19.4% (14.3%)	81.0% (10.0%)	45.3% (7.8%)	0.01 (0.14)	204/144
	Support Vector Machine	46.5% (7.5%)	49.4% (8.1%)	30.3% (17.1%)	62.7% (17.7%)	46.5% (7.5%)	-0.07 (0.15)	204/144

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

eTable 18. Classification accuracy based on functional MRI for HC vs MDD (age 24 - 28).

eTable 18. Classification accuracy for multivariate biomarkers based on functional MRI for HC vs MDD (age 24 - 28).

Modality	**Algorithm**	**BACC**	**ACC**	**Sensitivity**	**Specificity**	**AUC**	**MCC**	**n (HC/MDD)**
Face Matching Task	Boosting Classifier	49.1% (10.9%)	50.0% (10.7%)	40.2% (17.5%)	58.1% (13.2%)	47.2% (11.6%)	-0.02 (0.22)	148/116
	k-Nearest Neighbours	50.3% (7.8%)	53.1% (7.6%)	28.4% (15.6%)	72.3% (11.5%)	49.5% (7.1%)	-0.0 (0.18)	148/116
	Logistic Regression	46.2% (12.0%)	48.1% (12.5%)	31.3% (10.1%)	61.2% (17.7%)	46.0% (12.0%)	-0.08 (0.24)	148/116
	Gaussian Naive Bayes	52.5% (6.6%)	52.7% (7.0%)	49.3% (12.2%)	55.7% (15.7%)	52.4% (6.5%)	0.05 (0.14)	148/116
	Random Forest	51.6% (4.7%)	54.6% (4.7%)	25.3% (11.0%)	77.9% (9.8%)	52.0% (10.6%)	0.04 (0.11)	148/116
	Support Vector Machine	48.5% (8.0%)	50.0% (9.5%)	36.4% (31.4%)	60.6% (32.8%)	48.5% (8.0%)	-0.01 (0.19)	148/116
RS Connectivity	Boosting Classifier	57.4% (7.1%)	58.7% (6.7%)	45.3% (14.5%)	69.6% (8.2%)	59.7% (9.0%)	0.15 (0.15)	155/126
	k-Nearest Neighbours	56.3% (7.0%)	58.0% (7.1%)	38.9% (13.0%)	73.7% (15.8%)	60.2% (9.6%)	0.15 (0.16)	155/126
	Logistic Regression	58.8% (12.3%)	59.8% (12.3%)	49.2% (20.2%)	68.5% (19.5%)	60.0% (16.8%)	0.19 (0.25)	155/126
	Gaussian Naive Bayes	56.8% (12.2%)	57.6% (12.2%)	49.8% (12.6%)	63.9% (14.1%)	59.0% (12.6%)	0.14 (0.25)	155/126
	Random Forest	58.5% (6.2%)	60.5% (6.3%)	38.9% (8.9%)	78.0% (8.3%)	58.2% (10.3%)	0.19 (0.13)	155/126
	Support Vector Machine	54.5% (7.6%)	55.1% (8.1%)	47.1% (13.8%)	62.0% (16.8%)	54.5% (7.6%)	0.1 (0.16)	155/126
ALFF	Boosting Classifier	50.5% (9.9%)	51.6% (9.4%)	39.7% (16.0%)	61.2% (8.2%)	46.4% (12.7%)	0.01 (0.2)	155/126
	k-Nearest Neighbours	52.4% (9.9%)	54.1% (9.7%)	38.5% (16.7%)	66.3% (14.5%)	52.5% (11.8%)	0.05 (0.21)	155/126
	Logistic Regression	53.3% (9.4%)	54.1% (9.0%)	45.1% (13.7%)	61.5% (10.2%)	56.9% (11.7%)	0.07 (0.19)	155/126
	Gaussian Naive Bayes	48.4% (12.8%)	48.4% (13.1%)	49.7% (18.2%)	47.1% (20.6%)	49.1% (11.8%)	-0.04 (0.27)	155/126
	Random Forest	51.3% (7.7%)	54.1% (8.0%)	25.3% (10.9%)	77.3% (11.3%)	53.9% (11.8%)	0.03 (0.19)	155/126
	Support Vector Machine	49.2% (7.5%)	50.9% (7.1%)	33.3% (11.4%)	65.2% (8.0%)	49.2% (7.5%)	-0.02 (0.16)	155/126
fALFF	Boosting Classifier	50.6% (11.0%)	50.9% (10.5%)	48.2% (18.4%)	52.9% (11.6%)	52.5% (13.3%)	0.01 (0.23)	155/126

	k-Nearest Neighbours	47.7% (5.8%)	50.2% (6.5%)	23.7% (9.4%)	71.7% (15.7%)	45.5% (8.7%)	-0.04 (0.16)	155/126
	Logistic Regression	51.1% (7.6%)	51.9% (8.1%)	43.5% (15.3%)	58.7% (20.6%)	50.5% (9.7%)	0.03 (0.17)	155/126
	Gaussian Naive Bayes	52.9% (7.0%)	53.4% (7.9%)	50.5% (13.7%)	55.2% (21.6%)	52.0% (9.7%)	0.05 (0.16)	155/126
	Random Forest	51.3% (7.0%)	54.1% (7.1%)	24.6% (12.1%)	78.1% (14.3%)	56.5% (8.1%)	0.03 (0.18)	155/126
	Support Vector Machine	49.0% (6.3%)	51.6% (7.0%)	24.6% (14.5%)	73.4% (18.4%)	49.0% (6.3%)	-0.02 (0.16)	155/126
LCOR	Boosting Classifier	52.9% (12.2%)	54.1% (12.1%)	42.1% (19.1%)	63.7% (16.3%)	53.8% (13.9%)	0.06 (0.26)	155/126
	k-Nearest Neighbours	54.5% (6.9%)	55.8% (6.7%)	41.9% (11.7%)	67.0% (9.6%)	55.8% (9.2%)	0.09 (0.14)	155/126
	Logistic Regression	51.9% (11.2%)	53.3% (11.6%)	38.1% (9.6%)	65.6% (14.8%)	49.9% (11.3%)	0.04 (0.23)	155/126
	Gaussian Naive Bayes	52.7% (4.6%)	53.0% (4.8%)	52.1% (15.7%)	53.4% (15.0%)	52.0% (5.1%)	0.06 (0.1)	155/126
	Random Forest	53.6% (10.1%)	55.5% (10.1%)	35.6% (13.0%)	71.6% (12.7%)	53.6% (9.5%)	0.08 (0.21)	155/126
	Support Vector Machine	49.9% (7.7%)	51.6% (8.3%)	33.3% (4.9%)	66.4% (14.4%)	49.9% (7.7%)	0.0 (0.16)	155/126
RS Network Parameters	Boosting Classifier	59.2% (10.7%)	59.8% (10.5%)	52.5% (16.0%)	65.9% (13.4%)	61.3% (14.0%)	0.19 (0.22)	155/126
	k-Nearest Neighbours	53.0% (5.1%)	54.8% (5.3%)	35.0% (12.0%)	71.0% (12.1%)	51.4% (5.1%)	0.07 (0.11)	155/126
	Logistic Regression	52.4% (11.2%)	53.7% (11.4%)	41.0% (11.9%)	63.7% (16.5%)	54.7% (13.0%)	0.05 (0.24)	155/126
	Gaussian Naive Bayes	53.6% (6.7%)	54.1% (6.8%)	48.5% (12.1%)	58.7% (13.6%)	53.4% (9.1%)	0.08 (0.14)	155/126
	Random Forest	62.4% (9.4%)	64.1% (9.5%)	45.4% (12.1%)	79.3% (9.6%)	61.3% (12.8%)	0.27 (0.21)	155/126
	Support Vector Machine	58.5% (9.9%)	60.1% (9.8%)	43.5% (12.2%)	73.5% (12.4%)	58.5% (9.9%)	0.18 (0.21)	155/126

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew's Correlation Coefficient.

eTable 19. Classification accuracy using neuroimaging modality integration for HC vs MDD (age 24 - 28).

eTable 19. Classification accuracy for multivariate biomarkers using neuroimaging modality integration for HC vs MDD (age 24 - 28).

Modality Integration	Modality	Algorithm	BACC	ACC	Sensitivity	Specificity	AUC	MCC	n (HC/MDD)
PCA-based	all	Boosting Classifier	53.6% (10.6%)	55.4% (11.3%)	42.6% (20.3%)	64.7% (23.0%)	50.6% (12.1%)	0.08 (0.24)	133/94
		k-Nearest Neighbours	48.2% (10.5%)	52.9% (10.6%)	22.9% (16.3%)	73.5% (15.0%)	54.7% (8.5%)	-0.04 (0.26)	133/94
		Logistic Regression	48.6% (7.5%)	48.6% (12.1%)	50.3% (33.0%)	46.9% (40.9%)	41.9% (13.9%)	-0.04 (0.21)	133/94
		Gaussian Naive Bayes	46.9% (10.4%)	49.7% (9.9%)	29.4% (24.1%)	64.3% (19.1%)	48.2% (17.2%)	-0.08 (0.23)	133/94
		Random Forest	53.2% (9.2%)	58.1% (8.5%)	26.1% (23.7%)	80.2% (17.2%)	55.8% (12.7%)	0.06 (0.24)	133/94
		Support Vector Machine	52.0% (3.3%)	53.7% (7.2%)	43.1% (49.1%)	60.8% (46.0%)	52.0% (3.3%)	0.08 (0.14)	133/94
Voting	all	all	49.9% (8.4%)	56.3% (8.9%)	12.7% (9.9%)	87.1% (12.5%)	56.5% (14.8%)	0.03 (0.23)	133/94
Voting	all	Boosting Classifier	55.1% (10.2%)	58.5% (8.3%)	34.9% (23.6%)	75.2% (7.7%)	58.3% (11.5%)	0.09 (0.23)	133/94
		k-Nearest Neighbours	49.9% (5.6%)	56.8% (5.6%)	10.4% (9.7%)	89.5% (8.0%)	52.8% (13.1%)	-0.0 (0.18)	133/94
		Logistic Regression	50.6% (8.5%)	54.6% (8.7%)	26.8% (15.2%)	74.3% (15.2%)	50.4% (12.9%)	0.01 (0.19)	133/94
		Gaussian Naive Bayes	54.1% (10.3%)	56.7% (9.8%)	38.3% (17.8%)	69.8% (13.1%)	56.6% (11.8%)	0.09 (0.21)	133/94
		Random Forest	50.8% (3.4%)	58.2% (3.5%)	7.6% (7.4%)	94.0% (5.9%)	59.5% (15.8%)	0.03 (0.15)	133/94
		Support Vector Machine	48.7% (9.4%)	52.8% (8.3%)	24.4% (16.4%)	73.0% (8.7%)	49.0% (14.8%)	-0.03 (0.22)	133/94
Voting	Freesurfer	all	53.5% (7.9%)	59.0% (7.5%)	22.1% (12.8%)	84.9% (7.1%)	51.1% (14.7%)	0.09 (0.2)	133/94
	VBM		48.3% (8.1%)	53.4% (8.9%)	19.3% (8.6%)	77.4% (10.3%)	48.8% (9.3%)	-0.04 (0.19)	133/94
	DTI FA		48.8% (9.6%)	54.5% (9.4%)	14.8% (13.0%)	82.8% (13.1%)	47.2% (15.6%)	-0.04 (0.24)	133/94
	DTI MD		47.7% (8.9%)	52.8% (8.6%)	17.9% (11.2%)	77.4% (12.5%)	48.2% (10.4%)	-0.05 (0.24)	133/94

	DTI Network Parameters		48.9% (6.7%)	56.3% (6.7%)	5.2% (7.6%)	92.5% (10.2%)	48.8% (12.6%)	-0.02 (0.21)	133/94
	Face Matching Task		51.1% (10.8%)	56.8% (10.0%)	18.0% (17.6%)	84.2% (5.7%)	50.2% (13.5%)	0.0 (0.29)	133/94
	RS Connectivity		53.3% (6.7%)	56.8% (6.4%)	33.9% (14.7%)	72.8% (12.7%)	59.1% (9.3%)	0.07 (0.17)	133/94
	ALFF		51.6% (9.7%)	54.6% (9.7%)	35.0% (17.0%)	68.1% (13.0%)	51.2% (10.1%)	0.04 (0.21)	133/94
	fALFF		50.9% (9.5%)	54.6% (9.0%)	29.0% (16.6%)	72.9% (9.9%)	51.9% (13.7%)	0.01 (0.21)	133/94
	LCOR		53.1% (9.7%)	56.0% (8.5%)	36.2% (18.1%)	70.0% (6.7%)	53.8% (11.3%)	0.06 (0.21)	133/94
	RS Network Parameters		56.9% (10.9%)	60.3% (9.6%)	36.2% (19.7%)	77.5% (8.3%)	60.4% (13.2%)	0.14 (0.23)	133/94

Note: HC = Healthy Controls, MDD = Major Depressive Disorder, BACC = Balanced Accuracy, ACC = Accuracy, AUC = Area Under The Receiver Operating Characteristic Curve, MCC = Matthew’s Correlation Coefficient.

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