Identifying Shared Neural Markers Across Positive and Negative Valence for Depression and Anxiety

1. INTRODUCTION

Depression and anxiety disorders (DP and AX) are heterogeneous and etiologically complex psychiatric syndromes. Although considered by Diagnostic and Statistical Manual of Mental Disorders (DSM) as two separate disorders, depression and anxiety involve dysregulation of identical neurotransmitter systems and may share the neural underpinnings in a continuum of psychopathology.

Tremendous progress has been made in characterizing the neural mechanisms of emotional and cognitive impairments (1–3) in DP/AX. For instance, dysfunctions in the positive valence system (PVS) (4) and negative valence system (NVS) (5), and executive control (EC) (6), such as working memory (7,8), have been frequently observed in DP/AX patients. Studies have successfully employed magnetic resonance imaging (MRI) to quantify structural and functional brain differences between individuals with DP or AX and healthy controls (HCs). For instance, an earlier work reviewed salience, affective (threat and reward) processing, attention, and cognitive control network dysfunction and highlighted over-activity of the saliency circuit (anterior cingulate and insula) and under-activity of executive control circuit in DP/AX (2). Other investigations found the roles of the default mode network (9,11) or dysfunctional reward circuit (13–16) in DP/AX.

Among the MRI data, task fMRI (tfMRIs) offers unique data where a behavioral paradigm can capture multiple psychological constructs, and seemingly different behavioral paradigms may yield contrasts of brain activities that reflect the same construct. For instance, in the Human Connectome Project (HCP) dataset (17), with the gambling task, investigators have identified the behavioral and neural correlates of both PVS (win) and NVS (loss) (18). Although innovative machine learning and statistical approaches has been applied to characterize the conceptual overlap in constructs across the component contrasts of different behavioral tasks, and the circuit-based taxonomy that captures the transdiagnostic heterogeneity of DP/AX (19,20), no studies have investigated how seemingly different PVS and NVS construct may speak to the same neural markers pertinent to the transdiagnostic

heterogeneity of DP/AX, and new analytics is needed to innovate the way to model task fMRI data so we can connect multiple construct-related behaviors.

Here, we select the gambling win and loss tfMRI in the Human Connectome Project (HCP) (10) dataset to represent positive and negative emotion valences, and to validate the neural basis of DP/AX with a novel artificial neural network (ANN). In the ANN model, we jointly inferred DP and AX via multi-task learning (MTL) (21), a machine learning principle jointly estimating models for multiple inferential goals when the goals (here, predicting DP and AX) are assumed to be related. Besides, with gambling win and loss tasks as the input, multi-view learning framework (MVL) (22) as utilized in the ANN model to predict DP and AX with neural science knowledge extracted from both PVS and NVS. After fitting the model, we employed the Shapley additive explanations (SHAP) (23), a game theoretic approach to explain the output of any machine learning model, to interpret the proposed ANN by identifying critical FC markers of win and loss tasks that differentiate DP/AX from HC.

2. METHOD AND MATERIALS

2.1 Subjects and clinical assessments

We curated data from the HCP S1200 Subjects Release, which contains clinical and 3T magnetic resonance imaging (MRI) scans of 1,206 young adults (age 22-35). A total of 231 subjects were excluded from analyses because of missing depression and/or anxiety scores (n = 6), incomplete gambling task functional MRI scans (n = 126), or questionable image quality/excessive head movements (n = 99). The final sample consisted of 975 participants (xxx women).

Participants were assessed with the Achenbach Adult Self Report (ASR) (24). We used the data of the DSM-oriented subscales of depression and anxiety in the ASR. Specifically, the age- and sex-adjusted depression and anxiety *T* scores ≥ 65 were identified as the depression (DEP; n = 65) and anxiety (AX; n = 46) groups, respectively, with 26 participants included in both depression and anxiety groups. The remaining 860 participants with both depression and anxiety *T* scores < 65 were identified as the healthy control (HC) group (see **Supplementary Table S2** for demographic statistics).

2.2 Imaging protocol and fMRI scans

HCP imaging protocol and data processing have been described in detail by Barch et al (1).

Briefly, MRI was done using a customized 3 T Siemens Connectome Skyra with a standard 32-channel Siemens receiver head coil and a body transmission coil. T1-weighted high-resolution structural images were acquired using a 3D MPRAGE sequence with 0.7 mm isotropic resolution (FOV = 224 × 224 mm, matrix = 320 × 320, 256 sagittal slices, TR = 2400 msec, TE = 2.14 msec, TI = 1000 msec, FA = 8°) and used to register functional MRI data to a standard brain space. Tasks fMRI data were collected using gradient-echo echo-planar imaging (EPI) with 2.0 mm isotropic resolution (FOV = 208 × 180 mm, matrix = 104 × 90, 72 slices, TR = 720 msec, TE = 33.1 msec, FA = 52°, multi-band factor = 8).

In the gambling task, participants guessed if a mystery card (with a number 1-9) was higher or lower than 5 to win money, with feedback of win, loss, or even (when the number is "5") provided. The task was presented in blocks of 8 trials that are either mostly win (6 win trials pseudo randomly interleaved with either 1 neutral and 1 loss trial, 2 neutral trials, or 2 loss trials) or mostly loss (6 loss trials interleaved with either 1 neutral and 1 win trial, 2 neutral trials, or 2 reward trials). In each of the two runs, there were 2 mostly win and 2 mostly loss blocks, interleaved with 4 fixation blocks (15 s each). All the participants are provided with money as a result of completing the task, though it is a standard amount across subjects.

2.3 Imaging data preprocessing and functional connectivity metrics

As described in our prior work (25), imaging data were analyzed with Statistical Parametric Mapping (SPM8, Welcome Department of Imaging Neuroscience, University College London, U.K.). Images of each individual subject were first realigned (motion corrected). A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high-resolution structural MPRAGE image and then segmented for normalization with affine registration followed by nonlinear transformation. The normalization parameters determined for the structural volume were then applied to the corresponding functional image volumes for each subject. The voxel is of 2×2×2 mm^3 after spatial normalization. Finally, the images were smoothed with a Gaussian kernel of 4 mm at Full Width at Half Maximum.

We used Shen's 268 nodes (12) defined through groupwise graph theory-based parcellation clustering of whole-brain connectivity matrices, as the template of the whole brain. For each participant,

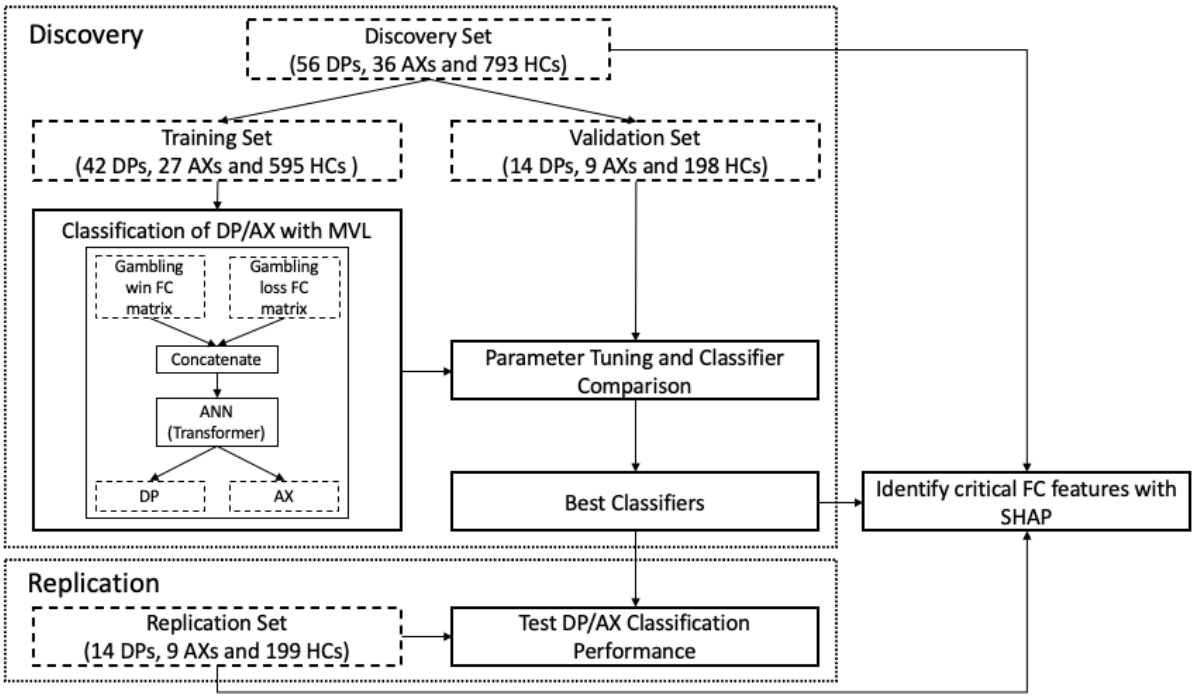
we extracted the average time series data of the 268 ROIs and calculated 268×268 functional connection (FC) matrices for win, loss, and baseline blocks, respectively. To identify the correlation of the positive (win) and negative (loss) valence to the DP/AX, the z-transformed baseline FC matric were subtracted from the z-transformed win and loss FC matrices, and the differences were used in the following analysis.

2.4 Machine learning analysis

2.4.1 Overall analytic goals and routines

Of the 865 subjects, 649 (75%, with 42 DP subjects, 27 AX subjects (with 15 comorbid DP and AX), and 595 HCs) were used for discovery and 216 (14 DP subjects, 9 AX subjects (with 5 comorbid DP and AX), and 198 HCs) for replication. The discovery set was further split into training (n=432, 28 DP subjects, 18 AX subjects (with 10 comorbid DP and AX), and 396 HCs) and validation (n=217, 14 DP, 9 AX subjects (with 5 comorbid DP and AX), and 199 HCs) sets to allow validation of the classifiers without involving the replication set. **Supplementary Table S3** shows the demographic and clinical characteristics of the training and replication samples and the statistics.

Figure 1 shows the analytic procedures. Although sex is a critical factor, because sex-stratified analyses reduce the available statistical power, we accounted for covariate effects (ref) in the computation of each FC feature by regressing out age and sex in a linear model of the training data. Validation and replication datasets were corrected using the same linear models of training data. The training sample was used to create classifiers to differentiate DP or AX subjects from HCs. The validation sample was used to compare classifiers and select model's hyper-parameter setting achieving the highest classification accuracy. During replication, the classifier was trained with the discovery set under the validated hyper-parameter setting, and the fitted classifier were applied to the replication sample to assess classification accuracy. Finally, SHAP analysis was employed to interpret the importance of task-evoked fMRI functional connectivity features (FCs) on DP/AX prediction within the classifier.



2.4.2 Differentiating depressed and anxiety individuals from controls

We constructed an ANN that performed multi-view learning (MVL) and multi-task learning (MTL) to differentiate DP or AX subjects from HCs simultaneously (workflow shown in Supplementary Figure S1). The MVL enables the ANN to predict DP/AX with both positive and negative emotional valence simultaneously, while the MTL allows the ANN to be trained using both DP and AX samples and both win and loss FC matrices.

In the MVL framework, DP/AX was predicted from two views, i.e., win and loss tasks. Each of the task FC matrices was transformed into a set of low-dimensional representations of brain networks with a FC matrix decomposition method proved to be effective on predicting alcoholism based on FC features in our early works (2). Specifically, each of the FC matrices involving the 268 ROIs was divided into 8 within-network and 28 between-network FC sub-matrices following the definition in (ref). An ANN module was used to transfer each of the brain network into a low-dimensional representation. Then we utilized the Transformer (26) to highlight subject-specific correlations between brain networks in both win and loss tasks with its self-attention mechanism, and to compress the processed low-dimensional presentations into the low dimensional representation of the whole-brain network. Finally, a ANN module was attached after the Transformer to predict DP and AX jointly with the MTL framework.

To examine whether MVL and/or MTL improved the classification, three ANNs were trained and their performance compared: (i) a model with MVL but without MTL, i.e., an ANN trained to classify DP/AX subjects separately from HCs directly with both win and loss FC matrices; (ii) a model without MVL but with MTL, i.e., an ANN trained to classify DP/AX jointly with win or loss FC matrix; and (iii) our approach with both MVL and MTL. To train the MTL model, we minimized the objective function measuring the overall DP and AX (vs. HC) classification error. Objective functions of the other two models are described in **Supplementary Methods**. By training the ANN model with the training set, and comparing the area under the receiver operating characteristic curves (AUCs) of the resultant DP and AX classifiers on the validation sample, we selected the best hyper-parameter setting for the ANN model. Under the selected hyper-parameter setting, the proposed ANN model was retrained with the discovery set, and evaluated with the replication set.

Statistical significance was estimated by permutation-testing whether any of the above three classifiers performed significantly better than chance. We randomly permuted the DP, AX and HC labels in the discovery and replication sets. For each permuted discovery dataset, we trained ANN classifiers using the above-mentioned training procedure, classified DP/AX in the replication sample, and tested whether the permuted classification performance was significantly worse than the non-permuted ANNs. We repeated this procedure 1000 times and report the statistical significance of classification accuracy.

2.4.3 Model interpretation

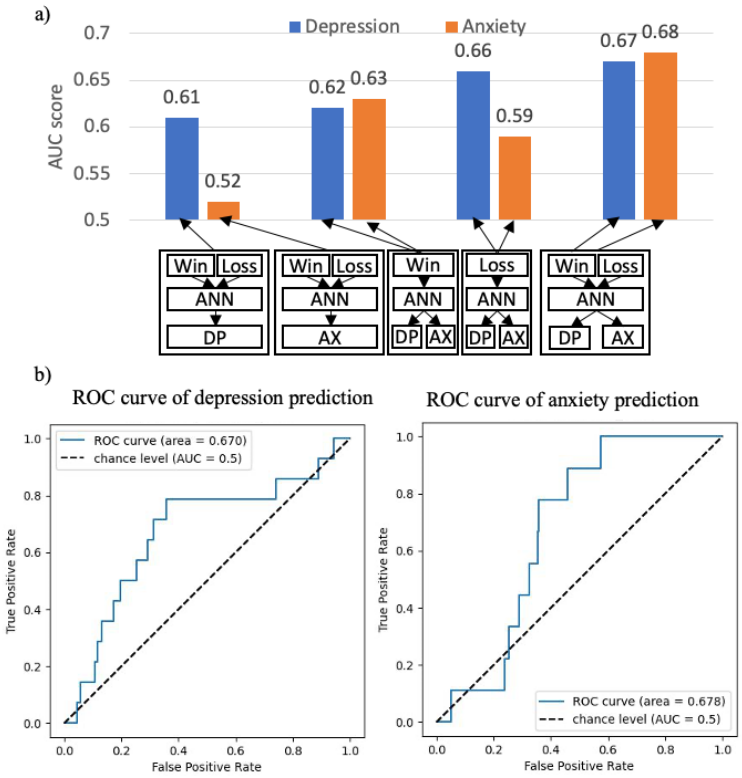
SHAP analysis was performed to interpret the predictive model, which employs the DeepLIFT algorithm to infer the contribution of FCs on the DP/AX predictions in the ANN model for each feature and each subject in discovery and replication datasets. A single SHAP value is a real number that refers to a single feature of a subject for an output of the ANN model (DP or AX prediction), and the sign of the SHAP value shows the direction of the FC drives the prediction of a specific subject, while the absolute value means the impact of that FC. The sum of all SHAP values of DP/AX in the win and loss FC matrices for a given subject provides the difference between the prediction of DP/AX and the average of the samples' outcomes.

The mean of the absolute SHAP value across subjects was computed to quantify the influence of each FC feature on DP/AX prediction. For both the win and loss FC matrices, the Wilcoxon signed-rank test was applied to assess whether the mean of the absolute SHAP value for each FC is significantly greater ($P > 0.05$, with Bonferroni correction) than the average absolute SHAP value calculated over all FCs within the respective FC matrix.

3. RESULTS

3.1 Distinguishing DP and AX from HC: the effects of MVL and MTL

We conducted an ablation study to investigate the impact of MTL and the combined effect of positive and negative valences on DP/AX prediction. Specifically, we contrasted the AUC scores for DP and AX prediction in the replication set. This was done between the ANN with both MVL and MTL, and the ANN with MTL/MVL. Figure X shows the ANN model with both MVL and MTL achieved the highest AUC in predicting both DP (0.67, $P < 0.05$, permutation test) and AX (0.68, $P < 0.05$). Without MTL, the proposed ANN can't get any significant DP and AX prediction, which shows that the shared neural markers between DP and AX could greatly improve ANN's DP and AX prediction performance. For the MTL ANN without MVL, only significant DP prediction (0.66, $P < 0.05$) with the loss FC matrix can be achieved, which highlighted the importance of the negative emotional valence in DP prediction, and the combination of positive and negative emotional valences in DP/AX prediction.



3.2 Interpretation of ANN model

The focus of the current study is to identify critical FC features in the ANN with MVL and MTL. After calculating all SHAP value for each FC and each subject, we selected critical FC features following the method descripted in section 2.4.3. We identified A and B DP- and AX-related FCs in the win FC matrix, and for the loss FC matrix, C and D were found. Figure Y exhibits a visual representation of the top-5 FCs for each task and each disorder. In the win task, 4 out of 5 FCs are fusiform-related FCs for both DP and AX, while for the loss task, cerebellum-related FCs were identified in all 5 and 4 out of 5 FCs in AX and DP, respectively. Besides, we observed that FCs between cerebellum and visuomotor existed in each of the four sets of top-5 FCs. All selected FCs were visualized in the heatmap Figure Xa and table SX in the supplementary material.

Two triangular matrices in Figure Xa are rather symmetric, indicating shared FC features across DP/AX, with A (win) and B (loss) features distinguishing both DP and AX from HC, and X and Y shared win/loss FC features for DP (across the bottom-left matrices) and AX (top-right matrices) respectively (refer to Table SX in the supplementary materal for details). These findings support the scientific premise of the study and the hypothesis that DP and AX may represent a continuum of shared

neuropathology. In addition to the shared FCs, we found that for win, features shared between DP and AX were identified in the cerebellum-fusiform gyrus (blue box) and cerebellum-visuomotor (green box) networks, while for loss, FCs in visual cortex (red box) and between the visual cortical regions and cerebellum (purple box) were found.

To examine the importance of brain regions' importance in predicting DP/AX in win/loss task, we group 268 ROIs into X BAs according to (ref) and present the BA's importance with the summation of the ROIs' absolute SHAP values in each of the BAs in Figure Xb. As shown in Figure Xb, win task plays more important roles in distinguishing subjects with DP/AX from HCs, and most critical features in win/loss tfMRI were in visuomotor regions, secondary visual cortex, associative visual cortex, fusiform gyrus, and cerebellum. To check the importance of brain regions' importance in the shared FCs between DP and AX or between win and loss, we calculated the summation of the ROIs' degrees in each BA, and listed the top-5 BAs in Figure Xc. We found that most FC features shared between DP and AX are located in the visuomotor regions, fusiform gyruns, associative visual cortex and cerebellum. Figures Xb and Xc are consistant with our observations on Figure Xa.

DISCUSSION

We designed and implemented an Artificial Neural Network (ANN) diagnosing DP and AX by analyzing FC features from gambling tasks, associating wins with positive and losses with negative emotional valences. After fitting the ANN model, we identified critical emotional valence-related neural markers in predicting DP and AX with the machine learning explanation model SHAP. The findings add to the effort to develop diagnostic biomarkers of DP and AX.

FC features show highly non-linear relationships with psychiatric diagnose (27,28). By conducted nested non-linear transformations on the win and loss FCs in the ANN model, features partake in the DP and AX classification in a non-linear manner. In our ANN model, MVL and MTL were used to improve the DP/AX classification performance. MVL facilitates us to predict DP/AX with both positive and negative emotional valences, and analyze the knowledge cross-learned from win and loss tasks. The MTL framework enables our ANN model to capture neural markers shared by win and loss tasks. Both MVL and MTL improved the accuracy of ANN in differentiating DP and AX subjects

from HCs as evidenced by the superior AUC in predicting DP/AX as compared to the analyses without MTL/MVL in the replication results.

The SHAP value of FC features shows that many of the FC features in support of DP and AX prediction involved the visuomotor regions, fusiform gyruns, and cerebellum. Emotion can be encoded visually and experienced in imagery, and the visual areas, particularly the lingual gyrus, are known to show higher activity during emotion memory encoding and retrieval (29–31). For example, studies implicated emotional imagery during rumination and altered lingual gyrus activation during emotion memory in DP/AX (32–34). A recent study showed that in the cambridge gambling task, activation was found in the visual cortex, the visuo-motor cortex, as expected from the task requirement (choosing a color by pressing a button). Although evidence is less consistent to implicate the altered visual and visuomotor networks in DP/AX during the gambling task, research showed that premorbid anxiety and/or depression perform worse on visual motor speed components of neurocognitive testing, which might be caused by the potential alter neural networks on visual and visuomotor networks (35). Early studies observed that increased fusiform gyrus activity exists for subjects in gambling task (36), and for subjects with pathological gambling or problem gambling, abnormal neural markers in fusiform gyrus were identified (37). Based on the observations that fusiform gyrus showed altered activity during both facial and non-facial emotion processing in DP/AX (38–42), it's reasonable to observe altered neural activities in DP/AX in the gambling tasks. The cerebellum has long been known for its role in motor functions (43), but newer research have also revealed the cerebellum's critical role in modulating cognition and emotions (44). For example, gambling associated risk-taking decision was found to be closely related with damage to the cerebellum (45,46). Besides, the cerebellum is known for its role in emotion processing and the pathophysiology of depression and anxiety (47–50). Most studies on DP/AX and the cerebellum suggest a hyperactivity of the cerebellum, which might be caused by the attention impairments observed in both disorders, or areas contributing to the contrasting deficits that characterize each disorder (48).

In addition to shared FC features, the SHAP analysis revealed unique functional connectivity (FC) patterns. Specifically, the loss task exhibited fewer altered FC features in the cerebellum compared to the win task. This aligns with previous findings that, unlike healthy individuals, those with cerebellar damage show diminished pleasurable emotional experiences in response to positive stimuli, yet maintain normal emotional reactions to stimuli that induce fear (24). Besides, we also found that compared with the win task, the secondary visual cortex plays a more important role in the loss task on distinguishing DP/AX subjects from HCs. It's aligned with the findings that altered secondary virtual cortex is observed on both DP (51) and AX (52) subjects, and the observations that depressed patients have increased activation to emotive, especially negative, visual stimuli (53), and anxiety increases sensitivity to errors and negative feedback over time (54).

Our study has limitations. First, the discovery and replication samples were recruited from a single study; an independent test sample is needed to eliminate potential study-specific confounds. To maximize objectivity in validating the findings, we excluded the replication set from classifier training. Second, despite the large size of the training set, only a small subset of subjects is DP/AX. Third, the HCP did not contain clinically-verified depression or anxiety, and self-reported depression and anxiety scores could have limited the analysis. Fourth, the present study is cross-sectional, and it remains to be seen whether the identified connectivity features remain stable in classifying DP and AX. Finally, we did not consider behavioral measures in model prediction.

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LEGENDS FOR TABLES AND FIGURES