Prediction of remission among patients with a major depressive disorder based on the resting-state functional connectivity of emotion regulation networks

Hang Wu, Rui Liu, Jingjing Zhou, Lei Feng, Yun Wang, Xiongying Chen, Zhifang Zhang, Jian Cui, Yuan Zhou, and Gang Wang

The prediction of antidepressant response is critical for psychiatrists to select the initial antidepressant drug for patients with major depressive disorders (MDD). The implicated brain networks supporting emotion regulation (ER) are critical in the pathophysiology of MDD and the prediction of antidepressant response. Therefore, the primary aim of the current study was to identify the neuroimaging biomarkers for the prediction of remission in patients with MDD based on the resting-state functional connectivity (rsFC) of the ER networks. A total of 81 unmedicated adult MDD patients were investigated and they underwent resting-state functional magnetic resonance imaging (fMRI) scans. The patients were treated with escitalopram for 12 weeks. The 17-item Hamilton depression rating scale was used for assessing remission. The 36 seed regions from predefined ER networks were selected and the rsFC matrix was calculated for each participant. The support vector machine algorithm was employed to construct prediction model, which separated the patients with remission from those with non-remission. And leave-one-out cross-validation and the area under the curve (AUC) of the receiver operating characteristic were used for evaluating the performance of the model. The accuracy of the prediction model was 82.08% (sensitivity = 71.43%, specificity = 89.74%, AUC = 0.86). The rsFC between the left medial superior frontal gyrus and the right inferior frontal gyrus as well as the precuneus were the features with the highest discrimination ability in predicting remission from escitalopram among the MDD patients. Results from our study demonstrated that rsFC of the ER brain networks are potential predictors for the response of antidepressant drugs. The trial name: appropriate technology study of MDD diagnosis and treatment based on objective indicators and measurement. URL: http://www.chictr.org.cn/showproj.aspx?proj=21377. Registration number: ChiCTR-OOC-17012566.

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INTRODUCTION

The main characteristics of major depressive disorder (MDD) are depressed mood and anhedonia [1]. As of 2010, it is the second leading factor in influencing years lived with disability among various diseases [2]. Antidepressant medication, such as selective serotonin reuptake inhibitor (SSRI), is the first-line treatment for MDD patients [3]. However, antidepressants are not effective for all MDD patients. In clinical practice, remission is considered the desired outcome, which indicates patients are symptom-free and recovered for the moment [4]. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that the overall remission rate was 28% after the first level of treatment [5]. A naturalistic prospective study reported that the remission rate was 43.3% after the acute antidepressant treatment phase, which is usually set to 12 weeks after initiation of treatment [6]. Inadequate antidepressant treatment might prolong the suffering of the patients, and increase the waste of medical resources. Prediction of the patient’s response to drugs based on baseline data might help psychiatrists determine whether a specific drug is suitable for the patient. With the low predictive value of clinical and sociodemographic variables, substantial attention has been directed at identifying neuroimaging biomarkers that predict response of antidepressant drugs in MDD patients [7–9].

Multiple neuroimaging studies have reported that structural and functional imaging is a potential antidepressant treatment response predictor [10–22] (Table S1). For example, gray matter volume was used to predict clinical remission after 8-week treatment of fluoxetine among 18 MDD patients [11]. The accuracy reported was 88.9%, and the right rostral anterior cingulate cortex, left posterior cingulate cortex, left middle frontal gyrus, and right occipital cortex was identified as predictors of clinical remission. Another study reported 75% accuracy using diffusion MRI to identify the neuroimaging biomarkers which might help in predicting if patients respond to 2 weeks of antidepressant treatment among 85 MDD patients and found that the most sensitive biomarkers for identifying SSRI-improvers were the right

1The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital & the Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China. 2CAS Key Laboratory of Behavioral Science, Institute of Psychology, Beijing, China. 3Department of Psychology, University of Chinese Academy of Sciences, Beijing, China. 4These authors contributed equally: Hang Wu, Rui Liu, Jingjing Zhou. 5email: zhouyuan@psych.ac.cn; gangwangdoc@ccmu.edu.cn

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hippocampus, left amygdala, right parahippocampal gyrus, right anterior cingulate gyrus, left dorsolateral part of superior frontal gyrus, and left inferior temporal gyrus [22].

More studies apply resting-state functional connectivity (rsFC) to predict antidepressant treatment among MDD patients. An ensemble learning model based on rsFC was designed to predict response to 2 weeks of antidepressants in 98 MDD patients [20]. The obtained accuracy was 80.6% and the bilateral hippocampus, left orbital part superior frontal gyrus, left paracingulate gyrus, right posterior cingulate gyrus, right amygdala, and left paracingulate gyri were identified as important predictors. In a research study using an index characterizing the reconfiguration of dynamic brain networks, the anterior cingulate cortex (ACC) was reported as a predictor to separate responders from non-responders after antidepressant treatment with escitalopram (≤8 weeks) in a multicenter sample with 106 first-episode MDD patients [21]. An accuracy of 70–89% was achieved by using fMRI to predict whether MDD patients were in remission after 12 weeks of antidepressant treatment [14, 15, 18]. It was found consistently that the prefrontal cortex and the cingulate cortex were important for the prediction of antidepressant efficacy. This suggested that baseline brain image can be used for predicting the response of patients after taking antidepressants, which is of great value in the clinical management of patients with depression. However, there are still some limitations in these studies. First, the follow-up time of studies with a large sample size is relatively short, usually, 2 weeks or 8 weeks [16, 21, 22], which is insufficient to determine whether patients can achieve remission [6]. Second, the sample size of studies with a long follow-up time (12 weeks) is often small [14, 18], which is a major defect for the machine learning model [23].

Although the data used in the above-mentioned studies were obtained from different neuroimaging modalities, it is worthy to be noted that the brain regions that were reported as the main contributors to the prediction of treatment response locate in large-scale brain networks underlying emotion generation, and one network implicated in both emotion regulatory processes and emotional reactivity.

Depression has been related to abnormal communication between large-scale brain networks, which can be expressed by rsFC [25]. The predictive effect of this abnormal communication pattern on efficacy prediction has been confirmed by literature studies [16, 20, 21]. The relevant networks of ER were disturbed in MDD patients and the rsFC of related regions were correlated with the severity of depression [26]. Therefore, focusing on the ER networks will help to determine whether it occupies a core position in efficacy prediction, not just overlap in different studies. This can lead to the identification of a unified biomarker for the diagnosis and prognosis of depression. Meanwhile, focusing on the rsFC of the ER networks, the features can be limited to a very small range and thus enable the application of multivariate methods, such as recursive feature elimination [27] and least absolute shrinkage and selection operator [28], which can retain the interaction information of features as much as possible, and enable better prediction performance compared with the method of deleting features by univariate statistics [29].

While the majority of previous studies exploring biomarkers for antidepressant response prediction used a small sample size for monotherapy [11, 17, 30] or mixed antidepressant treatments [12, 19, 20], which might affect the performance of the prediction model, a larger sample size of patients with MDD was recruited in the present study. All patients were unmedicated before recruitment and then were treated with escitalopram for 12 weeks. We postulated that rsFC between ER networks would be useful in predicting whether a MDD patient will obtain remission after 12 weeks of treatment with antidepressants.

**METHODS**

**Participants**

A total of 81 MDD patients were recruited from the Outpatient Department of Beijing Anding Hospital, Capital Medical University, between June 2018 and December 2019. A part of the data (n = 40) were used previously and thus clinical assessments, inclusion/exclusion criteria, and diagnostic procedures are provided in the previous study [31]. In short, the patients were diagnosed by experienced psychiatrists with the Mini International Neurological Interview.
deviations of the mean value [31, 41]. Finally, of maximum rotation or if their mean FD exceeded three standard mm²; number of slices planar imaging (GRE-EPI) pulse sequence with the following parameters: resting-state fMRI images were acquired using a gradient-recall echo-

due to severe motion and a total of 67 MDD patients were included which more than 2.5 mm maximum translation in any direction of baseline.

scanning. All the patients underwent resting-state fMRI scanning at and relax their minds, but not fall asleep during resting-state fMRI posterior; 200 volumes. Patients were instructed to keep their eyes closed, and the sample size of the non-remission group was larger than that of remission group. The labels corresponding to each patient were randomly disrupted and permutation tests were calculated through cross-validation; (4) steps 3 were repeated until the number of remaining features is equal to the minimum number of features we set. To choose the most discriminative features and obtain stable features, we tested the 100 combinations of the hyperparameter C ranging from [0.1, 0.2, 0.3, ..., 1] and the minimum number of features n ranging from [10, 20, 30, ..., 100] during SVM–RFECV feature selection. The selected features were then used to train the linear SVM model, and the hyperparameter C of this model was adjusted by grid search in a 10-fold cross-validation process. A total of 30 values were extracted equidistantly from the range of 0.01 to 10. Finally, to improve the accuracy and robustness of the feature selection, Leave-One-Out Cross-Validation (LOOCV) and the area under the curve (AUC) of the Receiver Operating Characteristic (ROC), accuracy, sensitivity, and specificity were used to evaluate the performance of the prediction model. In each LOOCV loop, one subject was set aside to be used as the test set, and the remaining subjects were used as the training set. After 67 loops, each subject had been used as the test set. Moreover, to confirm the important rsFC features in the prediction model, the frequency of each feature was calculated across all the loops, with high frequency indicating higher importance in the ability of remission prediction. The labels corresponding to each patient were randomly disrupted and permutation tests were implemented 1000 times to test the generalization ability of the model. Since the sample size of the non-remission group was larger than that of remission group, this may cause the model prefer to predict patients as non-remission. Therefore, we conducted a bootstrap (randomly selected 20 samples from each of the two groups) 1000 times to test whether the accuracy, sensitivity, and specificity remain stable in a balanced sample set. We also analyzed whether the accuracy of the model could be improved after considering the baseline HAMD-17 item scores. All machine learning analyses were performed using Python and Scikit-learn [42]. Statistical analysis We conducted statistical analyses in Statistical Product Service Solutions (SPSS) version 23.0. First, one-sample Kolmogorov–Smirnov test was conducted to estimate the normal distribution of the continuous variables. Two sample t-test or Mann–Whitney U test each was used for analyzing the difference between the remission group and non-remission group for demographic and clinical variables conforming to normal distribution or not. Categorical variables were compared using Chi-square tests. A p-value of less than 0.05 was considered to be statistically significant. All tests were two-tailed.

RESULTS Demographic and clinical scales Table 1 presented the demographic and clinical characteristics of the MDD patients with remission and non-remission, and the

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remission rate was 41% (28 in remission of 67 patients). Univariate analyses showed that there were no significant differences in age, education level, gender composition, baseline HAMD-17 score, onset frequency of depression, and dosage of escitalopram between the remission patients and the non-remission patients (all \( p > 0.05 \)). Compared with non-remission patients, the remission patients had significantly lower 12-week HAMD-17 scores and a higher percentage of HAMD-17 score reduction (%HAMD-17 = (HAMD-17 scores at baseline - HAMD-17 score at 12 weeks)/HAMD-17 scores at baseline) (all \( p < 0.05 \)). The results of the normality test are demonstrated in Table S3.

**Prediction model**

The hyperparameter \( C = 0.1 \) and the minimum number of features \( n = 40 \) were selected in the SVM–RFECV. In every loop of LOOCV, \( C \) was chosen for the best performance of the model, with the average value being 1.3. The prediction accuracy and performance of SVM are presented in Fig. 2. The AUC of the prediction model was 0.86 (sensitivity = 71.43%, specificity = 89.74%). The accuracy of the prediction model was 82.08% (\( p < 0.001 \) based on permutation tests). Bootstrap results demonstrated that in balanced small samples, the performance of the model was stable and the mean and standard deviation of accuracy, sensitivity, and specificity were 0.69 ± 0.05, 0.66 ± 0.08, and 0.71 ± 0.07. The addition of the HAMD-17 item scores into the original feature set did not contribute to the improvement of the prediction performance as none of the clinical items was selected for the feature subset.

**Consensus features**

A total of 176 rsFC features were selected at least once in 67 loops. Among them, the rsFC between the left medial superior frontal gyrus (mSFG, BA8) and the right inferior frontal gyrus (IFG, BA47) and the rsFC between the left mSFG (BA8) and the right precuneus (BA19) were selected in every loop. A total of 21 edges were selected in at least 90% of the cycles (frequency \( \geq 61 \)), indicating these features have a high prediction ability of the treatment response (Fig. 3). The majority of the edges were the rsFC between different ER networks and mainly belonged to the rsFC between ER network 1 and other ER networks, especially with the subcortical ER network (i.e., ER network 3) and the intermediatory network (i.e., ER network 4) (Table 2).

**DISCUSSION**

The predictive potential of rsFC in ER networks at baseline was investigated in patients after a 12-week escitalopram treatment in this study. The accuracy of the prediction model was 82.08%, which points that rsFC may be a clinically applicable predictor, for individual discrimination between patients likely to remit from depressive episodic and patients who are not, after a 12-week escitalopram treatment regime. Specifically, results showed that
the rsFC in brain networks supporting ER predicts clinical remission following antidepressant treatment. Additionally, the rsFC between the left mSFG and the right inferior frontal gyrus as well as the precuneus were the features with the highest discriminative ability in predicting remission from escitalopram among MDD patients.

The current study focused on the rsFC in the ER networks, which is different from previous studies exploring biomarkers for antidepressant effect prediction. The majority of previous studies [16, 17, 19, 43] focused on feature investigation at a whole brain level based on univariate statistics, which may be affected by the noise signals and ignore the features that may not be statistically significant but may contain important information when interacting with other features [44, 45]. In addition, by focusing on specific networks, the features to be filtered were limited to a very small range, thus RFECV could be used for filtering, which can keep the interaction information of features as much as possible compared with the method of deleting features by univariate statistics [29]. The prediction performance of the proposed model (AUC = 0.86, sensitivity = 71.43%, specificity = 89.74%) obtained in the current study was higher compared with other literature studies [17, 18, 21, 30]. At the same time, another group explored the relationship between the dynamic functional connectivity (dFC) based on the ER networks and the efficacy of antidepressants. They demonstrated that the predicted reduction rate of HAMD scores based on the strength of baseline dFC was significantly correlated with the actual reduction rate of HAMD scores. This finding also illustrated the role of ER networks in predicting the efficacy of antidepressants [46]. The above finding and our study suggest a direction in which future studies could focus, namely on the features with potential prediction efficacy found by previous studies, rather than screening features in the whole brain range by univariate statistics.

Out of the total 630 features that were investigated, only 21 were selected as the most predictive and stable features, which further supports the assumption of Yamashita [47] that mental illness is due to the dysfunction of a part of the rsFC of the brain, rather than the whole brain. The most important features reported in this study were the rsFC between the ER network 1 and other ER networks, especially with the subcortical ER network (ER network 3) and the intermediary network (ER network 4). ER network 1 is responsible for voluntary emotion regulation. ER network 3 is associated with emotion perception and generation, and ER network 4 plays an intermediary role in re-appraisal and integrates information from the prefrontal networks (ER network 1 and 2) as well as the subcortical network (ER network 3) to generate emotional responses and regulate these response processes as well as emotional reactivity [24]. Our finding suggests that functional interaction between the regions responsible for a higher level of ER and the regions involved in the lower levels of regulation is vital for the prediction of treatment outcomes in MDD. The rsFC between the left mSFG and the right IFG and between the left mSFG and the precuneus were considered as the features with the highest discrimination ability in this model because they were selected in every loop of LOOCV. The left mSFG, a part of dorsomedial prefrontal cortex (dmPFC), is involved in voluntary emotion regulation with other regions in ER network 1 [24]. In previous studies, a region near the left mSFG in our study, which is often called ACC, was also suggested to be critical in the prediction of treatment efficacy [21, 48, 49].

This study also has some limitations. First, despite the high accuracy achieved in the current study, whether the model can still achieve high accuracy on a dataset with a larger sample size or from multiple sites remains to be verified. However, combined with previous studies, we have reason to believe that this large-scale brain network contains rich efficacy prediction information [46]. Second, the patients in this study used only escitalopram as antidepressants, which ensure the homogeneity of our sample, but in the real world, the patients used far more kinds of drugs, which makes it more difficult for the model to accurately predict. Third, the current study only focused on the functional profile of the ER networks (i.e., rsFC). Previous studies have suggested that structural features of brain regions in the ER networks also possess the predictive ability of treatment responses. Structural and functional features can be integrated with future studies to assess whether a better prediction performance can be achieved. Fourth, the spheres drawn by the peak coordinates as ROI were chosen but not the clusters, which may lead to loss of information in the brain regions. Finally, behavior measurements on ER are lacking in this study. The dysfunction of emotion processing and regulation is one of the prominent features in the pathophysiology of MDD [26, 50]. Thus, it is unknown whether the addition of these behavior measurements into the original feature set can further improve prediction performance. However, the addition of HAMD-17 item scores into the original feature set, which may reflect problems in ER, did not improve the prediction performance, as none of the clinical items were selected in the feature subset.

**Fig. 3 Important features in the prediction model.** There were 21 edges, which were selected in at least 90% of the loops (frequency ≥ 61). The red, orange, green, and blue nodes corresponded to the first, second, third, and fourth ER network, respectively. A The consensus features were showed in chord picture. B The consensus features were showed in brain map. Abbreviations: please see also Table 2.
CONCLUSIONS
In conclusion, by focusing on the rsFC in the emotion regulation networks, we demonstrated that using features from this rsFC can predict the performance of remission in patients with MDD. These findings suggested that the rsFC of emotion regulation networks has the potential to be used as a biomarker for predicting the treatment response of MDD patients to escitalopram. Future studies can test the generalization ability of this prediction model using larger sample sizes and/or in multi-center datasets and explore whether the relevant rsFC will be changed with the progress of treatment.

CODE AVAILABILITY
The code that support the findings of this study are available from the corresponding authors upon reasonable request.

REFERENCES
1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). 5th ed. Arlington: American Psychiatric Association, 2013.
2. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–96.
3. Xiao H, Yuan M, Li H, Li S, Du Y, Wang M, et al. Functional connectivity of the hippocampus in predicting early antidepressant efficacy in patients with major depressive disorder. J Affect Disord. 2019;243:503
4. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry. 2006;163:1905–17.
5. Goldstein-Piekarski AN, Staveland BR, Ball TM, Yesavage J, Korgaonkar MS, Williams LM. Intrinsinc functional connectivity predicts remission on antidepressants: a randomized controlled trial to identify clinically applicable imaging biomarkers. Transl Psychiatry. 2018;8:57.
17. Godlewkska BR, Browning M, Norbury R, Igoumenou A, Cowen PJ, Harmer CJ. Predicting treatment response in depression: The role of anterior cingulate cortex. Int J Neuropsychopharmacol. 2018;21:988–96.

18. Karim HT, Wang M, Andreescu C, Tudorascu D, Butters MA, Karp JP, et al. Acute trajectories of neural activation predict remission to pharmacotherapy in late-life depression. Neuroimage. Clin. 2018;19:831–9.

19. Kragoulian MS, Goldstein-Piekarski AN, Fortino A, Williams LM. Intrinsic connectomes are a predictive biomarker of remission in major depressive disorder. Mol Psychiatry. 2020;25:1537–49.

20. Pei C, Sun Y, Zhu J, Wang X, Zhang Y, Zhang S, et al. Ensemble learning for early-response prediction of antidepressant treatment in Major Depressive Disorder. J Magn Reson Imaging. 2020;52:161–71.

21. Tian S, Sun Y, Zhao S, Zhang S, Mo Z, Liu X, et al. Predicting escitalopram monotherapy response in depression: The role of anterior cingulate cortex. Hum Brain Mapp. 2020;41:1249–60.

22. Xue L, Pei C, Wang X, Wang H, Tian S, Yao Z, et al. Predicting neuroimaging biomarkers for antidepressant selection in early treatment of depression. J Magn Reson Imaging. 2021. https://doi.org/10.1002/jmri.27577.

23. Gao S, Calhoun VD, Sui J. Machine learning in major depression: From classification to treatment outcome prediction. CNS Neurosci Ther. 2018;24:1037–52.

24. Morawetz C, Riedel MC, Salo T, Berboth S, Eickhoff SB, Laird AR, et al. Multiple large-scale neural networks underlying emotion regulation. Neurosci Biobehav Rev. 2020;116:382–95.

25. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. JAMA Psychiatry. 2015;72:603–11.

26. Ebneabassi A, Mahdirpour M, Nejati V, Li M, Liebe T, Colic L, et al. Emotion processing and regulation in major depressive disorder: A 7T resting-state fMRI study. Hum Brain Mapp. 2021;42:797–810.

27. Guyon I, Weston J, Barnhill S. Gene selection for cancer classification using support vector machines. Mach Learn. 2002;34.

28. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Softw. 2010;33:1–22.

29. Li J, Cheng K, Wang S, Morstatter F, Trevino RP, Tang J, et al. Feature selection: A data perspective. ACM Comput Surv. 2018;50:1–45.

30. Meyer BM, Rabl U, Huerem J, Bartova L, Kalcher K, Provenzano J, et al. Prefrontal networks dynamically related to recovery from major depressive disorder: A longitudinal pharmacological fMRI study. Transl Psychiatry. 2019;9:564.

31. Cui J, Wang Y, Liu R, Chen X, Zhang F, Feng Y, et al. Effects of escitalopram therapy on resting-state functional connectivity of subsystems of the default mode network in unmedicated patients with major depressive disorder. Transl Psychiatry. 2021;11:634.

32. Sheehan DV, Lecrubier Y, Sheehan KH, Janavs J, Amorim P, Janavs J, et al. The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22–33.

33. Kato M, Hori H, Inoue T, Iga J, Iwata M, Inagaki T, et al. Discontinuation of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment: The VAST-D randomized clinical trial. JAMA. 2017;318:132–45.

34. Williams LM, Rush AJ, Kolosh SH, Wisniewski SR, Cooper NJ, Nemeroff CB, et al. International study to predict optimized treatment for depression (iSPOT-D), a randomized clinical trial: Rationale and protocol. Trials. 2011;12:4.

35. Yan C-G, Wang X-D, Zuo X-N, Zang Y-F. DPABI: Data processing & analysis for resting-state brain imaging. Neuroinformatics. 2016;14:339–51.

36. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med. 1996;35:346–55.

37. Yan C-G, Chen X, Li L, Castellanos FX, Bai T-J, Bo Q-J, et al. Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. Proc Natl Acad Sci USA. 2019;116:9078–83.

38. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject movement. Neuroimage. 2012;59:142–54.

39. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Steps toward optimizing motion artifact removal in functional connectivity MRI: a reply to Carp. Neuroimage. 2013;76:439–41.

40. Zhang S, Cui J, Zhang Z, Wang Y, Liu R, Chen X, et al. Functional connectivity of amygdala subregions predicts vulnerability to depression following the COVID-19 pandemic. J Affect Disord. 2022;297:421–9.

41. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: Machine Learning in Python. J Mach Learn Res. 2011;12:2802–30.