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Research paper

Sleep disturbance-related neuroimaging features as potential biomarkers for the diagnosis of major depressive disorder: A multicenter study based on machine learning

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ABSTRACT

Background: Objective biomarkers are crucial for overcoming the clinical dilemma in major depressive disorder (MDD), and the individualized diagnosis is essential to facilitate the precise medicine for MDD.
Methods: Sleep disturbance-related magnetic resonance imaging (MRI) features was identified in the internal dataset (92 MDD patients) using the relevance vector regression algorithm, which was further verified in 460 MDD patients of an independent, multicenter dataset. Subsequently, using these MRI features, the eXtreme Gradient Boosting classification model was constructed in the current multicenter dataset (460 MDD patients and 470 normal controls). Meanwhile, the association between classification outputs and the severity of depressive symptoms was also investigated.
Results: In MDD patients, the combination of gray matter density and fractional amplitude of low-frequency fluctuation can accurately predict individual sleep disturbance score that was calculated by the sum of item 4 score, item 5 score, and item 6 score of the 17-Item Hamilton Rating Scale for Depression (HAMD-17) ($R^2 = 0.158$ in the internal dataset; $R^2 = 0.110$ in multicenter dataset). Furthermore, the classification model based on these MRI features distinguished MDD patients from normal controls with 86.3% accuracy (area under the curve = 0.937). Importantly, the classification outputs significantly correlated with HAMD-17 scores in MDD patients.
Limitation: Lacking some specialized tools to assess the personal sleep quality, *e.g.* Pittsburgh Sleep Quality Index.
Conclusion: Neuroimaging features can reflect accurately individual sleep disturbance manifestation and serve as potential diagnostic biomarkers of MDD.

1. Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder, with high morbidity and rates of suicide, and affect approximately 300 million persons worldwide (Malhi and Mann, 2018). Due to the underlying pathophysiology of MDD is complex and has not been clearly defined, the clinical diagnosis is obtained in according to the presence of some depressive symptoms (Brent, 1992). The

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Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Pacchiarotti et al., 2020) as a primary criterion is used to diagnose MDD through a structured interview, however, this construction of diagnostic framework is not based on any aetiology or pathophysiological changes, which may lead to the misdiagnosis of MDD (Baker, 2001). Most importantly, there is no any laboratory examinations [*e.g.* blood tests, magnetic resonance imaging (MRI) scans] to verify the truth of MDD diagnosis. Hence, the identification of objective biomarkers is crucial for the clinical practice of MDD.

In 1972, *Kupfer et al.* found the shortened rapid-eye-movement latency in MDD patients, which was the first evidence on the association of sleep disturbance with MDD (Kupfer and Foster, 1972). Sleep disturbance-mediated adverse changes in the central nervous system are closely related with the etiology and pathophysiology of MDD, *e.g.* inflammation, cholinergic system, and synaptic plasticity (Irwin and Opp, 2017; Mu and Huang, 2019; Riemann et al., 2020). Meanwhile, sleep disturbance as one of the core symptoms of MDD is recorded in the DSM-5 criteria, which is an important factor for the diagnosis and assessment of treatment outcome of MDD (Kennedy, 2008; Mendlewicz, 2009). Consequently, the recognition of sleep disturbance-related biomarkers may contribute to overcoming the clinical predicament of MDD.

MRI technology including structural and functional MRI, can directly observe the structural and functional changes of brain in sleep disturbance (Dang-Vu et al., 2010). Previous studies indicated that in individuals with chronic insomnia, gray matter deficits can be observed in multiple brain regions including orbitofrontal cortex, dorsolateral prefrontal cortex, and middle temporal gyrus (Altena et al., 2010; Joo et al., 2013). Likewise, aberrant spontaneous neuronal activity in the insular cortex, dorsal and ventral prefrontal cortex, precuneus, inferior parietal lobule, middle/inferior temporal gyrus, and occipital lobe were observed in individuals with insomnia by resting-state functional MRI (Li et al., 2016; Liu et al., 2016; Zhou et al., 2017). However, a recent meta-analysis indicated that although structural/functional brain abnormalities have been detected in sleep disturbance, there was no consistent results in these MRI-related brain changes across published studies, and highly heterogonous clinical populations might result in this situation (Tahmasian et al., 2018). Therefore, the use of a multicenter dataset may contribute to obtaining more reliable results on the latent brain alterations in sleep disturbance. Meanwhile, it is unclear whether sleep disturbance-related MRI features have the potential to acts as biomarkers for the diagnosis of MDD, particularly for the individualized diagnosis.

The aim of the present study is to identify potential sleep disturbance-related MRI indicators in MDD patients using a multivariate machine learning regression algorithm, relevance vector regression (RVR) (Tipping, 2001), at the individual level. RVR algorithm with excellent predictive efficacy and efficient parameter optimization, has been widely used for constructing the individualized prediction model in neuroimaging studies (Feng et al., 2019; Zhu et al., 2019) including our previous studies (Shi et al., 2020c; Wang et al., 2021). Additionally, based on these sleep disturbance-related MRI features, a classification model between MDD patients and normal controls (NCs) will be built using the eXtreme Gradient Boosting (XGBoost) method (Chen et al., 2016) that is an ensemble machine learning algorithm with the outstanding performance (Nakagawa et al., 2018; Sheridan et al., 2016; Shi et al., 2021b). Subsequently, the potential association of classification outputs with the severity of depressive symptoms is also investigated.

2. Methods and materials

2.1. Subjects

2.1.1. Internal dataset (discovery dataset)

The dataset included 92 MDD patients who were recruited from the Affiliated ZhongDa Hospital, Southeast University (Nanjing, China). All MDD patients met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4) criteria (Zimmerman et al., 2011), and the 17-Item Hamilton Rating Scale for Depression (HAMD-17) (Williams, 1988) was used to assess the depressive symptomatology. Meanwhile, each MDD patient obtained individual sleep disturbance score that was calculated by the sum of item 4 score, item 5 score, and item 6 score of HAMD-17 scale (Shi et al., 2020b; Whale et al., 2019), and MDD patients with definite sleep disturbance (sleep disturbance score > 0) were included in the present study. In additional, all patients underwent the multi-modal MRI scan (the acquisition protocol was shown in Supplementary Table 1). Clinical information of patients is summarized in Table 1, and details (*e.g.* inclusion and exclusion criteria) can be found in Supplementary Materials. The present study was approved by the ethics committee of the Affiliated ZhongDa Hospital, Southeast University (approval ID: 2019ZDSYLL055-P01), and all patients or their legal guardians signed informed consent. The present study were carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.1.2. Multicenter dataset (validation dataset)

The dataset included 460 MDD patients and 470 NCs, who were derived from the multicenter dataset of REST-meta-MDD consortium (Liang et al., 2020; Long et al., 2020; Yan et al., 2019). Details on REST-meta-MDD consortium dataset were shown in Supplemental Materials. As mentioned above, all MDD patients met the DSM-4 criteria (Zimmerman et al., 2011) and obtained HAMD-17 scores and sleep disturbance scores. MDD patients with sleep disturbance scores > 0 were analyzed in the present study and matched with NCs from the same study sites. Furthermore, each subject underwent the multi-modal MRI scan, and the acquisition protocol of each study site is outlined in Supplemental Table 1. Clinical features of all subjects are displayed in Table 1. Each study site obtained approval from the local ethics committees, and written consent forms from all subjects or their legal guardians.

2.2. MRI data acquisition and pre-processing

Detailed information about MRI data acquisition and pre-processing can be found in our previous studies (He et al., 2019; Liu et al., 2020a, 2020b; Shi et al., 2019, 2021a; Zhang et al., 2021) and Supplementary Materials.

For each subject, the average gray matter density (GMD) and mean fractional amplitude of low-frequency fluctuation (mfALFF) values of each brain region in the Brainnetome Atlas (Fan et al., 2016) that comprises 210 cortical and 36 subcortical subregions, were extracted (Supplementary Table 2). The average GMD and mfALFF values of these 246 brain regions were used as feature vectors for the subsequent analyses.

Table 1
Demographic and assessments information of subjects.

	Discovery dataset MDD (n = 92)	Validation dataset MDD (n = 460)	NC (n = 470)
Age (years)	37.94 ± 13.21	34.00 ± 10.85	33.99 ± 11.54
Gender (M/F)	33/59	170/290	200/270
Education (years)	9.96 ± 4.24	12.13 ± 3.74	13.33 ± 3.82
HAMD-17 scores	21.17 ± 5.44	22.12 ± 6.11	-
Sleep disturbance scores *	4.13 ± 1.45	4.07 ± 1.45	-

Data were presented as mean ± standard deviation.
* Sleep disturbance scores were computed by adding scores of items 4, 5, and 6 of the HAMD-17 scale.
MDD, major depressive disorder; NC, normal control; M, male; F, female; HAMD-17, the 17-Item Hamilton Rating Scale for Depression.

2.3. RVR analysis for the prediction model

In the discovery dataset, the association between sleep disturbance scores and the GMD and mfALFF values were investigated using a multivariate RVR method (Tipping, 2001) implemented in Pattern Recognition for Neuroimaging Toolbox (http://www.mlnl.cs.ucl.ac.uk/pronto/). The leave-one-out cross-validation (LOOCV) was conducted to assess the generalizability of the models (Cui and Gong, 2018; Feng et al., 2019), and Pearson correlation coefficient (R) and mean absolute error (MAE) between actual and predicted sleep disturbance scores were used to assess the prediction performance of the models (Feng et al., 2019; Gong et al., 2014). Subsequently, the permutation test was performed to determine the significance of R and MAE. Besides, the weight of each feature can quantify its contribution in the prediction model (Feng et al., 2019; Zhu et al., 2019), and a feature was retained if its absolute value of weight was in the top 10%, which can obtain the most predictive features (Shi et al., 2020c). Details of RVR method are shown in Supplementary Materials. Considering the combination of different types of imaging features may obtain better prediction performance, we constructed composite MRI features by using together the GMD and mfALFF features which were in the top 10% contribution in the respective RVR model (Shi et al., 2020c; Wang et al., 2021).

In addition, the optimal RVR prediction model, identified from the discovery dataset, was further verified independently to predict the sleep disturbance scores of MDD patients in the validation dataset. The LOOCV and the permutation test were also conducted as mentioned above.

Furthermore, to better annotate the distribution of imaging features, the standard 7-system template was used to yield seven large-scale functional networks through a whole-brain clustering analysis (Yeo et al., 2011). The Priori network modules were defined by assigning each network node obtained from the Brainnectome Atlas (Fan et al., 2016) to one of the seven large-scale functional modules, and the subcortical nodes to an independent module. Therefore, the primary modular partition defined by 246-node networks included the following eight brain networks: visual network (VN), sensorimotor network, dorsal attention network, ventral attention network, limbic network, frontoparietal network (FPN), default mode network (DMN), and subcortical system (SUB).

2.4. XGBoost analysis for the classification model

In the validation dataset, sleep disturbance-related imaging features were used for distinguishing MDD patients from NCs. The classification model was built using XGBoost algorithm (Chen et al., 2016) implemented in Python (ver3.7; www.python.org). XGBoost algorithm has the following attractive properties: (1) efficiently modeling for the nonlinear data and high dimensional data; (2) interpretability of the model due to it can calculate feature importance (Shi et al., 2021b). Hyper-parameters optimization of the XGBoost model was performed using the grid search combined with an empirical strategy. Details are displayed in Supplementary Materials.

The 10-fold cross-validation was used to evaluate the generalization of classification model (Dietterich, 1998), and the average accuracy, sensitivity, and specificity were used to quantify the classification performance of the model. Additionally, the receiver operating characteristic (ROC) curve was created to measure the classification ability of the model, and the area under the curve (AUC) was calculated to assess the performance of the classification model.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Pearson correlation analysis was performed to determine the relationship between the classification outputs and HAMD-17 scores in MDD patients in the validation dataset. $P < 0.05$ was considered as the statistical significance.

3. Results

3.1. RVR analysis

3.1.1. In the discovery dataset

The clinical features of the 92 MDD patients from the discovery dataset are displayed in Table 1. The application of RVR to the composite MRI features achieved better individualized prediction of sleep disturbance scores ($R^2 = 0.158$, $p < 0.001$, MAE = 1.124, $p < 0.001$; Fig. 1A, B, and C, Supplementary Figure 1A) than a single metric (GMD: $R^2 = 0.019$, MAE = 1.206; mfALFF: $R^2 = 0.071$, MAE = 1.460).

The composite MRI features of 25 GMD features and 25 mfALFF features contributed to RVR prediction, mainly localized in the SUB, FPN, and VN (Fig. 1D and E, Supplementary Table 3).

3.1.2. In the validation dataset

Table 1 shows the clinical features of the 460 MDD patients and 470 NCs from the validation dataset. The optimal RVR model with compound MRI features, determined from the discovery dataset, also exhibited better prediction performance for the individualized sleep disturbance scores of 460 MDD patients ($R^2 = 0.110$, $p < 0.001$, MAE = 1.150, $p < 0.001$; Fig. 2A, B, and C, Supplementary Figure 1B).

3.2. XGBoost analysis

To determine whether sleep disturbance-related MRI features can contribute to diagnosing MDD, an XGBoost classification model was built using 25 GMD features and 25 mfALFF features derived from the optimal RVR prediction model for distinguishing MDD patients from NCs in the multicenter dataset (Supplementary Table 4).

The classification accuracy of XGBoost model was 86.3% (sensitivity = 84.8%, specificity = 88.1%) and AUC value was 0.937 (Fig. 3A).

3.3. Association between XGBoost model classification probabilities and the assessment of severity of depression

In the validation dataset, the classification outputs were significantly correlated with HAMD-17 scores in MDD patients ($r = 0.292$, $p < 0.001$; Fig. 3B). Meanwhile, the significant correlation of the classification outputs with HAMD-17 scores was also found in MDD patients, with controlling age, gender, and years of education ($r = 0.287$, $p < 0.001$).

4. Discussion

In the present study, the sleep disturbance manifestation could be quantified in MDD patients at the individual level by the RVR method, which was found in our internal dataset, and the prediction model was further verified in an independent, multicenter dataset for assessing the reproducibility and generalizability. During the construction of models, we determined that the combined utilization of GMD and mfALFF features could predict sleep disturbance scores of individual MDD patients with greater performance than single GMD or mfALFF. In addition, the better diagnostic power of sleep disturbance-related MRI features was demonstrated in the multicenter, validation dataset. Importantly, the significant correlation of classification outputs with the assessments of depressive symptomatology was detected in MDD patients. Taken together, strong evidence from different datasets suggested that the potential MRI biomarkers (*i.e.* GMD and mfALFF) could accurately predict the individual sleep disturbance manifestation and display the higher accuracy for distinguishing MDD patients from NCs at the individual level.

With the RVR method, 50 sleep disturbance-related MRI features were identified in MDD patients at the individual level and that were

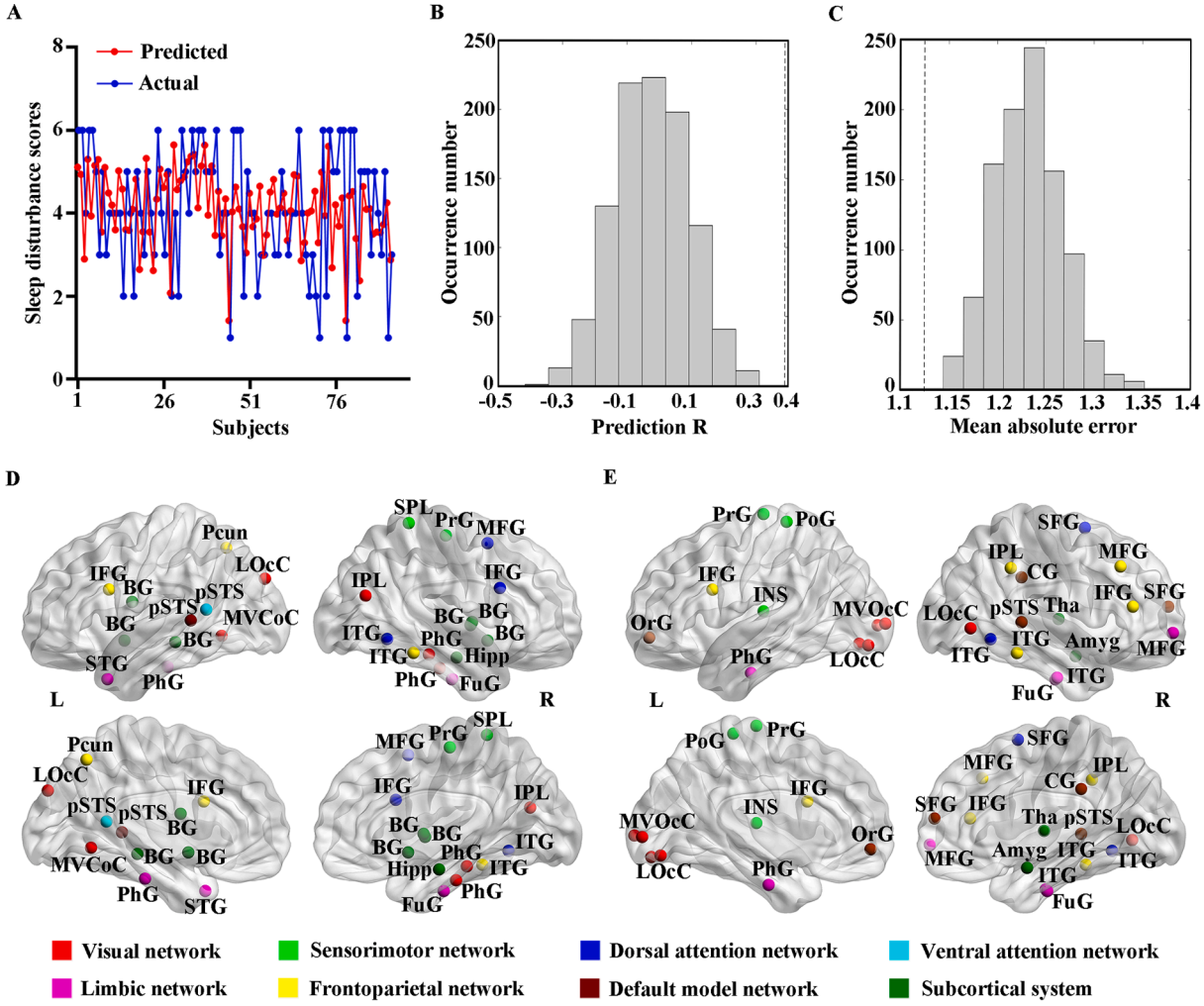

Fig. 1. Relevance vector regression analysis in the discovery dataset.
(A) Line plot showing consistency between actual and predicted sleep disturbance scores in 92 MDD patients. (B) and (C) Distribution of permutation of the prediction R and mean absolute error. The values obtained using real scores are indicated by the dashed line. (D) and (E) Visualizations of 25 GMD features and 25 mfALFF features of the optimal prediction model.
MDD, major depressive disorder; GMD, gray matter density; mfALFF, mean fractional amplitude of low-frequency fluctuation; SFG superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; OrG, orbital gyrus; PrG, precentral gyrus; STG, superior temporal gyrus; ITG, inferior temporal gyrus; FuG, fusiform gyrus; PhG, parahippocampal gyrus; pSTS, posterior superior temporal sulcus; SPL, superior parietal lobule; IPL, inferior parietal lobule; Pcun, precuneus; PoG, postcentral gyrus; INS, insular gyrus; CG, cingulate gyrus; MVOcC, medioventral occipital cortex; LOcC, lateral occipital cortex; Amyg, amygdala; Hipp, hippocampus; BG, basal ganglia; Tha, thalamus.

mainly distributed in the SUB (primarily focuses on basal ganglia), FPN, and VN. *Milak et al.* found that in drug-free MDD patients, sleep disturbance scores computed using the same method as our study, were correlated with abnormal metabolism in basal ganglia and limbic and paralimbic structures, which suggested that the alteration in brain activity of these areas may be involved in regulating the sleep state in depression (Milak et al., 2005). In fact, except regulating habit formation and reward/addictive behaviors, basal ganglia, especially striatum and globus pallidus, can also control the sleep and wakefulness by regulating adenosine and dopamine receptors (Castillo and Benarroch, 2020; Lazarus et al., 2013), therefore, the MRI-related features of these subcortical areas may be valuable biomarkers for reflecting the change of sleep. In addition, FPN, especially the inferior frontal gyrus, can participate in the regulation of behavioral arousal (Flamand et al., 2018), and *Pini et al.* demonstrated that increased FPN connectivity was associated with high sleep quality in mild cognitive impairment patients, which suggested that the change of FPN connectivity may provide compensatory mechanisms for withstanding nerve damage to improve sleep quality (Pini et al., 2020). Furthermore, previous study indicated that global functional connectivity density in the VN was significantly increased in patients with primary insomnia as compared with healthy controls, suggesting that aberrant brain functional alteration in the VN may be implicated in the neuropathological mechanism of sleep disturbance (Yu et al., 2018). Meanwhile, other brain networks, *e.g.* DMN, were also detected in the present sleep disturbance-related MRI features, and previous evidence showed that these networks displayed impaired function and abnormal activity in sleep disturbance (Marques et al., 2018; Wu et al., 2018). To conclude, the present findings supported these MRI-related features can be used as objective indicators for reflecting the potential brain alterations of sleep disturbance.

In addition, the combination of these 50 MRI-related features in a classification model could differentiate MDD patients from NCs accurately in a multicenter dataset, as a result, the present findings indicated that sleep disturbance-related MRI indicators may be potential biomarkers for the individualized diagnosis of MDD. Besides the emotion-related brain circuits based on the fronto-limbic system and DMN was the core brain change in MDD (Li et al., 2017; Zhong et al., 2016), abnormal neural activities in FPN and VN and the abnormal connectivity

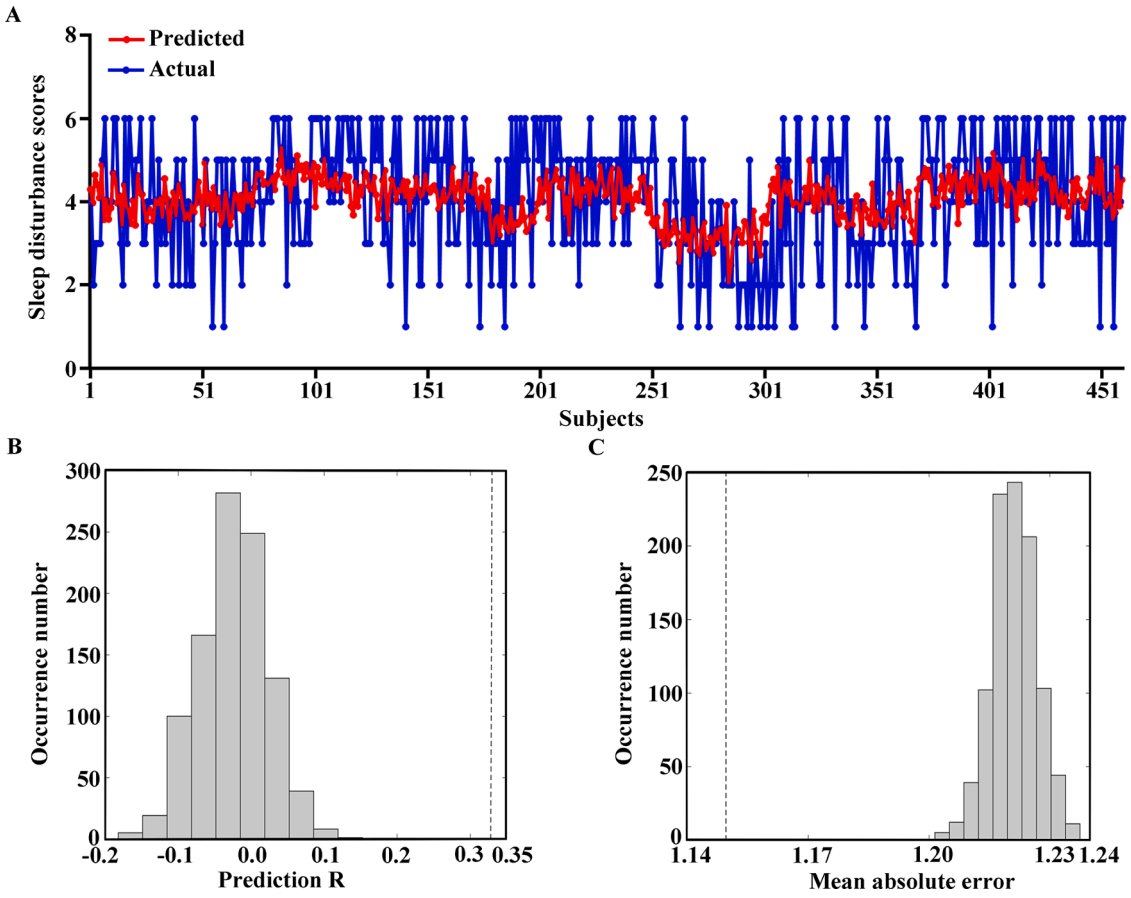

Fig. 2. Independent validation of the optimal relevance vector regression prediction model in the validation dataset.
(A) Line plot showing consistency between actual and predicted sleep disturbance scores in 460 patients with major depressive disorder. (B) Distribution of permutation of the prediction R. (C) Distribution of permutation of the mean absolute error. The values obtained using real scores are indicated by the dashed line.

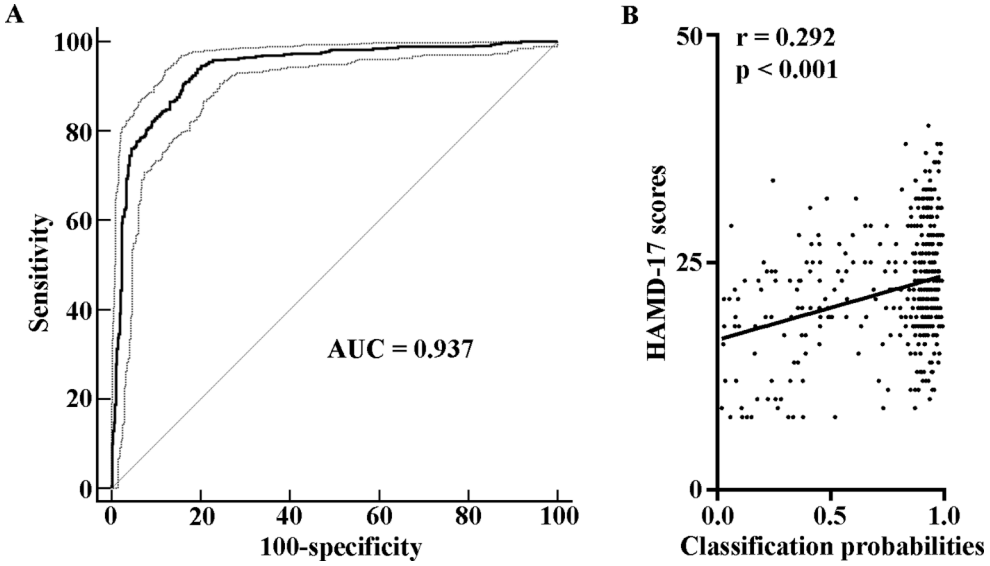

Fig. 3. XGBoost classification model in the validation dataset.
(A) Classification performance of the proposed 50 sleep disturbance-related imaging features between MDD patients and NCs. (B) Correlation between the XGBoost classification model classification probabilities and HAMD-17 scores in MDD patients.
XGBoost, eXtreme Gradient Boosting; MDD, major depressive disorder; NCs, normal controls; HAMD-17, the 17-Item Hamilton Rating Scale for Depression; AUC, area under the curve.

between FPN or VN and DMN were also important neural basis to process emotion (Jiang et al., 2020; Kaiser et al., 2015; Yu et al., 2016). Meanwhile, subcortical areas can execute numerous emotional function as well, and structural (*e.g.* gray matter volume) and functional (*e.g.* degree centrality, functional connectivity) abnormalities in the basal ganglia, amygdala, and thalamus have been reported in MDD patients (Gao et al., 2016; Long et al., 2020; Sacchet et al., 2015). Additionally, to evaluate the diagnostic utility of sleep disturbance-related MRI indicators in MDD, the present study further determined the association between these indicators and the assessment of depressive symptomatology. We found a significant correlation between the classification outputs and HAMD-17 scores, indicating that the probability of MDD

diagnosis depends on the severity of depressive symptoms. Therefore, the present findings illustrated a potential association between sleep disturbance-related brain MRI and the individualized clinical features of MDD.

In the present study, we firstly used the RVR and XGBoost algorithms to build a sleep disturbance prediction model and a sleep disturbance-related MDD classification model based on the multi-modal MRI data of multicenter datasets, respectively. In terms of the prediction model, the repetitively validation in different datasets strongly demonstrated that the sleep disturbance manifestation of MDD patients could be evaluated individualizedly, accurately, and conveniently in a clinical setting using objective MRI indicators. Meanwhile, the proposed prediction model identified some important sleep disturbance-related MRI features and these MRI features contributed to building a classification model with good diagnostic power and generalization between MDD patients and NCs in the multicenter dataset. Consequently, the present study provided not only novel insights into the neuroimaging study for assessing the individual sleep disturbance manifestation but also a promising clinical tool for identifying individuals with potential risk for MDD.

There were several limitations in the present study. (1) Our study lacks some specialized tools to assess the personal sleep quality, *e.g.* Pittsburgh Sleep Quality Index (Mollayeva et al., 2016), Insomnia Severity Index (Morin et al., 2011). In the future study, we will design targeted study to complete the related assessments of sleep disorder and evaluate the clinical value of the current sleep disturbance prediction model. Furthermore, the UK Biobank database (Ollier et al., 2005) will be also considered to assess the current model. (2) None of more clinical features, such as different neuropsychological assessments and central/peripheral molecular indexes [*e.g.* brain-derived neurotrophic factor (Shi et al., 2020a)], sleep-related biomarkers [*e.g.* serotonin (Al-Sharman et al., 2021), lysyl oxidase (Mesarwi et al., 2015)], is included in multicenter datasets, which limited our further investigation to assess the possible neurological basis of the sleep disturbance-related features and classification outputs. (3) Sleep disturbance is not the specific symptom of MDD, however, the number of MDD patients without sleep disturbance (sleep disturbance score = 0) is few in present datasets, which is not suited to analyze. (4) The values of coefficients were smaller both for the discovery dataset and the validation dataset although RVR models were built successfully. In the subsequent study, we will test the present findings in independent cohorts with high homogeneity, and particularly, the construction of models will consider the different effect of various sleep disorders (e.g. insomnia, circadian rhythm disorders, sleep-disordered breathing, hypersomnia, parasomnias, and restless legs syndrome) (M and Latreille, 2019).

Using different datasets, the present study demonstrated that the combined utilization of structural and functional MRI data could quantitatively predict sleep disturbance scores in individual patients with MDD. Meanwhile, in the multicenter dataset, the objective sleep disturbance-related MRI features could be further used as a diagnostic means for distinguishing MDD patients from NCs. Additionally, the neuroscientific interpretability of the classification outputs could facilitate the clinical application of the classification model in MDD.

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CRediT authorship contribution statement

Yachen Shi: Conceptualization, Data curation, Formal analysis, Software, Visualization, Writing – original draft. **Linhai Zhang:** Conceptualization, Data curation, Formal analysis, Software, Writing – original draft. **Cancan He:** Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft. **Yingying Yin:** Investigation, Methodology. **Ruize Song:** Investigation, Methodology. **Suzhen Chen:** Investigation, Methodology. **Dandan Fan:** Investigation, Methodology. **Deyu Zhou:** Conceptualization, Software, Supervision. **Yonggui Yuan:** Conceptualization, Data curation, Project administration, Supervision, Writing – review & editing. **Chunming Xie:** Conceptualization, Data curation, Project administration, Supervision, Writing – review & editing. **Zhijun Zhang:** Conceptualization, Data curation, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.027.

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