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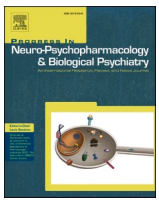

Functional connectome gradient predicts clinical symptoms of chronic insomnia disorder

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ABSTRACT

Insomnia is the second most prevalent psychiatric disorder worldwide, but the understanding of the pathophysiology of insomnia remains fragmented. In this study, we calculated the connectome gradient in 50 chronic insomnia disorder (CID) patients and 38 healthy controls (HC) to assess changes due to insomnia and utilized these gradients in a connectome-based predictive modeling (CPM) to predict clinical symptoms associated with insomnia. The results suggested that insomnia led to significant alterations in the functional gradients of some brain areas. Specifically, the gradient scores in the middle frontal gyrus, superior anterior cingulate gyrus, and right nucleus accumbens were significantly higher in the CID patients than in the HC group, whereas the scores in the middle occipital gyrus, right fusiform gyrus, and right postcentral gyrus were significantly lower than in the HC group. Further correlation analysis revealed that the right middle frontal gyrus is positively correlated with the self-rating anxiety scale ($r = 0.3702$). Additionally, the prediction model built with functional gradients could well predict the sleep quality ($r = 0.5858$), anxiety ($r = 0.6150$), and depression ($r = 0.4022$) levels of insomnia patients. This offers an objective depiction of the clinical diagnosis of insomnia, yielding a beneficial impact on the identification of effective biomarkers and the comprehension of insomnia.

1. Introduction

Insomnia is a common sleep disorder characterized by difficulty falling asleep, maintaining sleep, or waking up too early in the morning, often accompanied by significant daytime impairment. It affects millions of individuals globally(Morin et al., 2015), with approximately half experiencing a chronic form known as chronic insomnia disorder(CID) (Buysse, 2013). The escalation in the pace and stress of life has led to a continuous increase in insomnia prevalence. Research indicates that insomnia is linked not only to physical health issues like compromised immune system functioning and heightened cardiovascular disease risk, but also strongly correlated with mental health problems, specifically symptoms of depression and anxiety(Roth et al., 2006; Baglioni et al., 2010; Sarsour et al., 2010; Buysse, 2013; Gebara et al., 2018). Apart from difficulties in initiating and maintaining sleep(Sateia, 2014), insomnia also detrimentally affects various aspects of the patients' life and work, causing daytime fatigue, reduced concentration, emotional instability (Espie, 2002), and harm to physical and psychological well-being. Despite extensive research on insomnia, there remains a limited understanding of the neural mechanisms and intracerebral changes associated with the condition.

Resting-state functional magnetic resonance imaging (rs-fMRI) analysis has provided significant tools and methods for neuroscience research(Dresler et al., 2014). Many previous studies have focused on

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functional connectivity abnormalities associated with CID(Tagliazucchi and van Someren, 2017; Li et al., 2018a; Kim et al., 2021; Zou et al., 2021; Guo et al., 2023; Zheng et al., 2023), and our team's previous studies based on resting-state functional connectivity have also reported abnormal Coeruleus-Norepinephrine System functional connectivity in patients with insomnia with anxiety(Gong et al., 2021), as well as abnormal functional connectivity density in patients with depression (Gong et al., 2020). Although there have been many relevant studies, there is currently no consensus on the location and nature of the connectivity changes. For example, Some studies have concluded that functional connectivity is increased in patients with CID in the default mode network (DMN)(Li et al., 2017; Ma et al., 2018; Santarnecchi et al., 2018; Yan et al., 2018; Leerssen et al., 2019) and others have concluded the opposite(Nie et al., 2015; Zhou et al., 2016; Pang et al., 2017; Li et al., 2018b; Liu et al., 2018). This uncertainty may stem from various factors, including differences in specific insomnia populations studied, the equipment used for data acquisition, the level of participant cooperation during image acquisition, and the subsequent data analysis methods. Conventional research methods often fall short of fully capturing the impact of insomnia on brain function, necessitating the exploration of new and more comprehensive research approaches.

The hierarchical arrangement of the human brain serves as a foundational organizational framework, facilitating the encoding and integration of information across various cognitive processes, from sensory perception to higher-order cognition(Mesulam, 1998; Huntenburg et al., 2018). Both classical neuroanatomy and modern brain imaging techniques have provided consistent evidence supporting the presence of this hierarchical network architecture throughout neurodevelopment (van den Heuvel et al., 2016; Burt et al., 2018; Demirtaş et al., 2019). This architecture is believed to orchestrate the flow of sensory information through multiple cortical relays, ultimately converging in transmodal regions(Mesulam, 2012; Palomero-Gallagher and Zilles, 2019). Such a framework enhances the brain's ability to integrate abstract concepts, cognitive functions, and behavioral responses. There is now robust evidence supporting the existence of a global gradient in human cortical organization, extending from primary sensorimotor to transmodal regions. This gradient is evident in various aspects, including cortical morphology and gene expression(Margulies et al., 2016; Burt et al., 2018; Huntenburg et al., 2018). A collection of gradients captures intricate spatial relationships within connectivity patterns and facilitates the depiction of continuous and smooth transitions between functional networks. This approach moves beyond representing a single dimension or discrete parcellation, offering a more nuanced understanding of the complex interplay within the brain's functional organization(Huntenburg et al., 2018). In addition to describing gradients in the cerebral cortex, there are also gradients in specific organizations that are of interest, such as Song et al. investigated the hierarchical structure of the angular gyrus and how it is modulated by the underlying genetic architecture(Song et al., 2023). Wang et al. found three main patterns of functional connectivity gradients between the insula and different brain systems by studying the connectivity gradients between the insula and different brain systems(Wang et al., 2023). Shen et al. used the functional connectivity gradients to capture the different dimensions of the cingulate gyrus' hierarchical organization(Shen et al., 2023). Moreover, specific alterations in gradients associated with neurological and psychiatric disorders have been identified. For example, altered functional gradients due to cognitive vulnerability in depression(Wang et al., 2021) and the reduction in unimodal and transmodal network separation observed in autism(Hong et al., 2019). This approach offers a novel perspective, providing the potential for a more comprehensive and in-depth understanding of the impact of insomnia on brain function by studying the gradients of functional connectivity in insomnia patients. It aims to uncover the underlying mechanisms behind insomnia, paving the way for theoretical foundations to develop more effective treatment methods in the future.

The aim of this study was to uncover alterations in the brain associated with insomnia through gradient analysis. We will use diffusion embedding methods to identify functional connectome gradient from rs-fMRI(Vos de Wael et al., 2020) and reveal the reorganization of functional connectome gradient due to insomnia through gradient analysis. Furthermore, we attempted to build predictive models using a combination of machine learning and gradient scores. Considering the co-morbidity between insomnia and depression as well as anxiety(Roth et al., 2006; Baglioni et al., 2010; Sarsour et al., 2010; Buysse, 2013; Gebara et al., 2018), we attempted to build predictive models using these gradient scores as input features to predict clinical symptoms such as sleep quality, depression, and anxiety levels in insomnia patients (Shen et al., 2017). We hypothesized that CID would lead to alterations in the functional connectivity gradient, and that using the functional connectivity gradient as features could predict some of the clinical symptoms associated with insomnia.

2. Methods

2.1. Participants

In this study, 42 healthy controls (HC) and 62 subjects with chronic insomnia disorder (CID) were included. CID subjects met diagnostic criteria outlined in the International Classification of Sleep Disorders, Third Edition(Sateia, 2014), with PSQI scores >7(Buysse et al., 1989; Mollayeva et al., 2016), and were not on hypnotic medications, aged 18–65. HC had similar criteria but PSQI scores <6 and lacked sleep complaints. Exclusion criteria included neuropsychiatric disorders, chronic diseases, other sleep disorders, substance addiction, MRI contraindications, and cerebral lesions. Participants were recruited from Chengdu Second People's Hospital outpatients, underwent neuropsychological tests and MRI scans, and provided informed consent approved by the Institutional Review Board Ethics Committee (approval number: 2020021).

2.2. Clinical symptom evaluation

1. Pittsburg Sleep Quality Index (PSQI)(Buysse et al., 1989): Developed by Prof. Buysse and colleagues at the University of Pittsburgh, the PSQI assesses sleep quality through 19 items across seven dimensions: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. Higher scores indicate poorer sleep quality.
2. Self-rating depression scale (SDS)(Zung, 1965): Created by psychologist Zung, the SDS measures depression levels with 20 items assessing depressive symptoms experienced in the past week. Respondents rate their feelings, and the total score determines depression severity.
3. 3. Self-Rating Anxiety Scale(SAS)(Zung, 1971): Also developed by Zung, the SAS evaluates anxiety levels through 20 items assessing anxiety symptoms over the past week. Respondents choose answers based on their feelings, and the total score indicates anxiety severity.

2.3. Image acquisition

Images in the dataset were acquired at the Chengdu Second People's Hospital using a GE 3.0-Tesla scanner (GE Healthcare Discovery Pioneer, General Electric, Milwaukee, WI). In addition to the fs-MRI data required for subsequent analysis, T2-FLAIR images of each participant were acquired to detect clinically asymptomatic lesions. Structural images were acquired using a high-resolution scrambled-phase gradient echo sequence with the following parameters: repetition time/echo time (TR/TE) of 7.06/3.04 ms; flip angle (FA), 12°; acquisition matrices, 256 × 256; field of view, 240 × 240 mm; thickness, 1.0 mm; gap, 0 mm, number of slices, 192; and number of excitations, 1.0. An 8-min gradient echo-planar imaging pulse sequence was used to obtain functional images with the following parameters: repetition time (TR), 2000 ms; echo

time (TE), 30 ms; FA, 90°; acquisition matrix 64 × 64; thickness, 3.5 mm; number of slices, 33; and number of time points, 240. All subjects were asked to close their eyes, relax, and remain still during the scanning process. After the scan, all subjects confirmed that they were awake during the scan.

2.4. Image preprocessing

The tool used for pre-processing the image data was DPABI 6.0 (Data Processing & Analysis of Brain Imaging; http://rfmri.org/dpabi), implemented using MATLAB 9.0 software (TheMathWorks, Inc., Natick, MA) (Yan et al., 2016). The rs-fMRI data preprocessing steps were as follows:(1) removing the first 10 time points; (2) head motion correction by realigning the first volume; (3) alignment to the EPI template, resampling to 3 × 3 × 3 mm^3, and smoothing with 6 mm half-height wide Gaussian kernels; (4) Friston 24-parameter modeling of the head motion, mean white, cerebrospinal fluid, and global signals included in the nuisance regression; (5) filtering with a bandpass of 0.01–0.1 Hz; To minimize the impact of head movement, participants with movements exceeding 2 mm or 2° were excluded.

2.5. Functional connectome gradient analysis

Using the preprocessed rs-fMRI images, we calculated the whole-brain functional connectivity gradient for each participant. Specifically, first, we calculated the Pearson correlation coefficients of the time series between voxels on the gray matter skeleton, i.e., we obtained the functional connectivity matrix of the brain. This was then transformed from nonlinear to linear using the Fisher z-transform with the following equation:

$$z = \frac{1}{2} ln\left(\frac{1+r}{1-r}\right) \tag{1}$$

with r representing the original Pearson correlation functional connectivity matrix. Then operate on the Fisher z-transformed connectivity matrix, sparing it so that only 10 % of the connectivity data is retained and the rest is set to zero. And computed the cosine similarity matrix in accordance with existing studies(Margulies et al., 2016). This matrix is downscaled using the diffusion map embedding method to obtain multiple components that are representative of functional organizational properties. This algorithm introduces a new operator P_α which is defined as follows:

$$P_\alpha = D_\alpha^{-1} W_\alpha \tag{2}$$

Where W_α is established by normalizing the affinity matrix based on diffusion parameters. $D_\alpha$is the degree matrix derived from W_α. α is the anisotropic diffusion parameter used by the diffusion operator, this parameter controls the effect of the density of the sampling point on the flow shape. Taking values in the range 0 to 1. We set α to 0.5 with reference to previous studies(Hong et al., 2019; Vos de Wael et al., 2020), it approximates the Fokker-Planck diffusion.

The principal component resulting from this analysis captures the main axis of macroscale functional organization of the cerebral cortex, and additional orthogonal components capture additional functional organizational properties(Margulies et al., 2016; Bethlehem et al., 2020).

To ensure that gradients were mapped consistently across individuals, we used the Procrustes rotation method to align each individual's original gradient distribution pattern to a group-level template. Specifically, we first constructed a group-level gradient template using the average functional connectivity matrix obtained for all patients and normal controls computationally and then aligned each subject's gradient to this template. Finally, we ranked the gradients identified in the aligned gradient distribution templates in descending order based on the average connection variance in the functional connectome occupied by each gradient. The gradient computation and gradient alignment processes described above, were completed using Brainspace, a data analysis platform(https://github.com/mica-mni/brainspace).

Since the main and second gradients explained most of the variance in the data(Bethlehem et al., 2020; Margulies et al., 2016), in this study, the first two gradients were compared between the two groups of subjects, and a two-sample *t*-test was used to identify between-group differences in the first two gradients between CID and HC by using age, gender, and years of education as covariates. Multiple comparisons were also corrected for multiple comparisons using the false discovery rate (FDR) method, with the significance level set at $p < 0.05$. Correlation analyses were subsequently conducted to explore whether the functional gradient difference area was associated with insomnia and its comorbid mental symptoms.

2.6. Prediction analyses

The flow of prediction is shown in Fig. 1, an connectome-based predictive modeling (CPM) model was trained to predict Clinical Symptoms of Insomnia Patients based on functional connectivity gradients for each subject(Shen et al., 2017; Cui and Gong, 2018), The relevance vector regression (RVR) code used is based on Cui et al. The source code can be found at the following link (https://github.com/ZaixuCui/Pattern_Regression_Clean/tree/master/RVR). Specifically, we performed the following analyses:

1. Save the principal components of each subject's functional gradient, calculate their Pearson correlation with PSQI scores, and extract columns corresponding to features with a significance level ($p < 0.05$) based on ascending order of *p*-values.
2. To avoid over-fitting issues in training set, a 10-fold cross validation was performed: the dataset was randomly divided into 10 subsets, with one subset used for training and the remaining as the test set. This procedure was repeated ten times to obtain predicted PSQI scores for all participants. The correlation between actual and predicted scores was calculated to assess predictive performance. To determine the significance of the predictive model, 5000 permutation tests were performed, disrupting all PSQI scores across all participants and obtaining the distribution of permutation correlations between actual and predicted scores.
3. To compute the contributions of each network in the prediction process, the extracted features were mapped to eight networks, including visual network (VIS), motor network (MOT), dordal attention network (DAN), ventral attention network(VAN), limbic network (LMB), frontoparietal network (FPN), DMN, and a cerebellar network (CR)(Yeo et al., 2011). The sum of feature weights in each network was calculated to determine their contributions.
4. To further evaluate whether the Individual gradients of functional connectivity could predict depression and anxiety severity in subjects, the same procedures as predicting PSQI scores were performed to predict the SDS and SAS scores.
5. To test the robustness of the RVR model based on functional connectome gradient, the data were randomly split into training and test sets in proportions of 1:1, 2:1, 3:1, and 4:1, and the predictive model was trained and tested iteratively.

3. Results

3.1. Demographic and clinical features

After image preprocessing, 12 CID and 4 HC were excluded for head movements of >2 mm or 2°. As shown in Table 1, There were no significant differences in age, gender, and education level between the remaining 50 participants with CID and the 38 HC participants. The mean duration of the disease in the CID group was 7.42 years. The CID

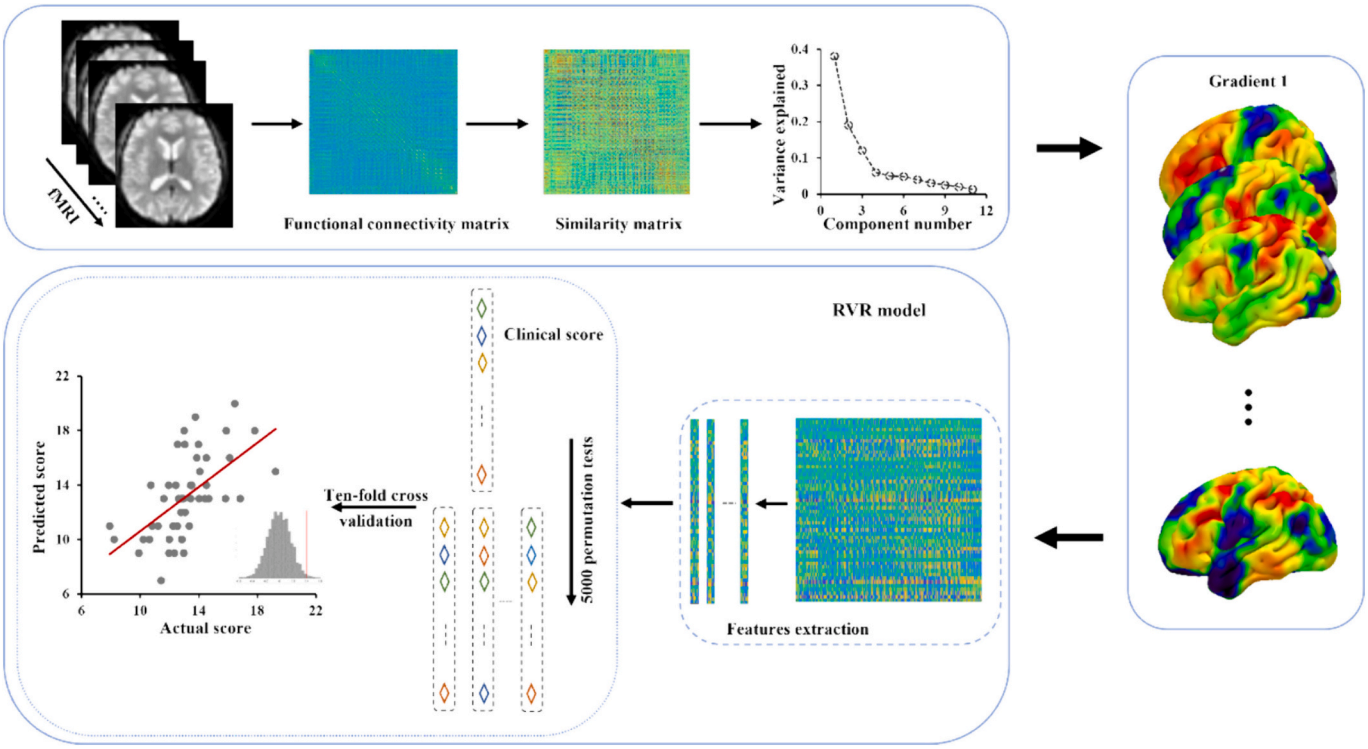

Fig. 1. Schematic representation of methodology.

Table 1
Demographic and behavioral characteristics of participants.

Variables	CID($n = 50$)	HC($n = 38$)	p-Value
Age(years)	34.52 ± 11.22	35.11 ± 8.82	0.877
Gender(male/female)	20/30	9/29	0.107[a]
Education(years)	15.59 ± 2.47	14.71 ± 3.7	0.146
Duration(years)	7.42 ± 6.45	–	–
PSQI	13.02 ± 3.19	3.39 ± 1.65	<0.001
SDS	50.24 ± 11.43	38.49 ± 10.5	<0.001
SAS	48.14 ± 12.04	34.7 ± 8.31	<0.001

Abbreviations: CID, chronic insomnia disorder; HC, health control; PSQI, Pittsburgh Sleep Quality Index; SAS, Zung's Self-Rating Anxiety Scale; SDS, Zung's self-Rating Depression Scale.

[a] The *p* value was obtained by chi-square test; other *p* values were obtained by a two-way *t*-test.

group scored higher than the HC group in terms of sleep, anxiety, and depression, which implies poorer quality of sleep, and more severe depression and anxiety.

3.2. Functional connectome gradient results.

Using the diffusion map embedding method, we obtained functional gradient scores for all subjects, which represent the spatial similarity of functional connectivity. We focused on the first two gradients with the highest variance in the representation. The two-sample T results corrected for FDR showed that the main gradient distribution was found to be abnormal between the two groups, and the second gradient showed no between-group differences. The differences between the two groups for the main functional gradient are shown in Fig. 2, Specific areas of significant difference are shown in Table 2. The gradient scores in the middle frontal gyrus, superior anterior cingulate gyrus, and right nucleus accumbens were significantly higher in the CID patients than in the HC group, whereas the scores in the middle occipital gyrus, right fusiform gyrus, and right postcentral gyrus were significantly lower than in the HC group.

Correlation analyses were used to explore whether there was an association between gradient difference regions and insomnia-related scale scores, and the results showed that Frontal_Mid_2_R was positively correlated with SAS scores ($r = 0.3702, p = 0.0081$)(Fig. 3), no significant correlation was observed in other regions.

3.3. Functional connectome gradient predicts clinical symptoms

Based on the functional connectivity, a functional connectome gradient was calculated for each subject, which represents the spatial similarity of functional connectivity. The main gradient was used to predict the clinical presentation of the patients, and the predictions are shown in Fig. 4, the small plot in the bottom right corner shows the distribution of the permutated correlations between actual and predicted scores, based on 5000 permutation tests. The position of the real correlation coefficient before permutation in the distribution was recorded. The *permutation p* value was defined as the [1-(location/5000)]. The smaller the *permutation p* value, the more significant the difference between the observed data and the hypothesis model. Using *permutation p* <0.05 as a threshold for significance, less than the level of significance indicates that the observed differences are not due to random factors. It was found that a gradient calculated based on functional connectivity successfully predicted PSQI scores $(r = 0.5858; p = 7.8477 \times 10^{-6}; MAE, 1.9013; permutation\ p = 2.0 \times 10^{-4})$, SDS scores $(r = 0.4022; p = 0.0034; MAE, 8.1195; permutation\ p = 0.007)$, SAS scores $(r = 0.6150; p = 2.0632 \times 10^{-6}; MAE, 9.3949; permutation\ p = 0.001)$. Table 3 presents the prediction outcomes assessed using R2, adjusted R2, RMSE, and MAE. The projections on the brain of the features that contributed to the creation of the predictive model are shown in Fig. 5. The top ten features that contribute most to predicting PSQI scores belong to the DAN and FPN. The top ten features that contribute most to predicting the SDS score belong to VAN, VIS, FPN, DAN and DMN. The top ten features contributing most to the predicted SAS score belong to FPN and VIS networks. in order to test the robustness of the model, we randomly divided the data into training and

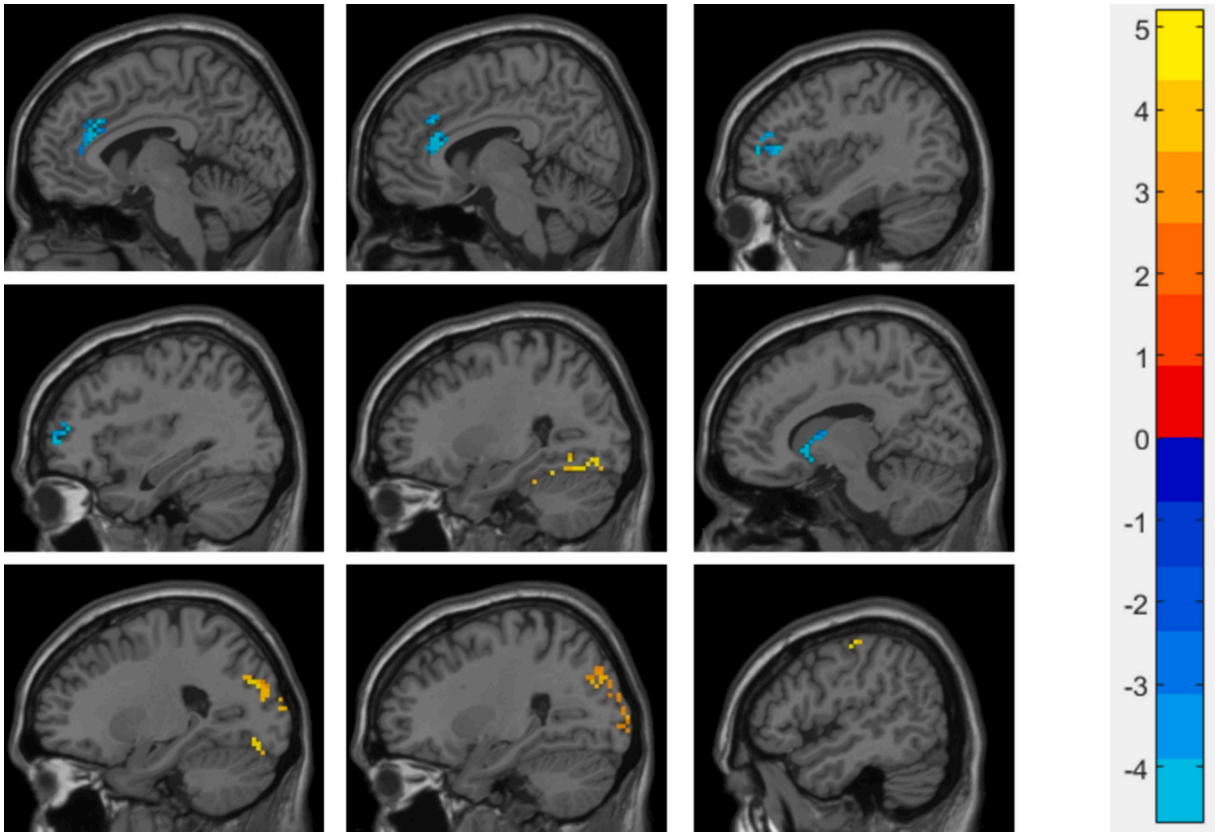

Fig. 2. Between-group differences in the spatial distribution of functional gradients ($p_{corrected} < 0.05$).Top Left: ACC_sup_L, Top Middle: ACC_sup_R, Top Right: Frontal_Mid_2_L,Middle Left: Frontal_Mid_2_R, Middle: Fusiform_R, Middle Right: N_Acc_R, Bottom Left: Occipttal_Mid_L, Bottom Middle: Occipttal_Mid_R,Bottom Right: Postcentral_R.

Table 2
Functional gradient score differences between CID and HC groups.

AAL3 atlas	Region	MNI Coordinates			t values	Cluster size (voxels)
		x	y	z		
CID > HC						
Frontal_Mid_2_R	Right, Middle frontal gyrus	39	54	12	−3.74	34
Frontal_Mid_2_L	Left, Middle frontal gyrus	−39	48	12	−3.75	28
ACC_sup_R	Right, Anterior cingulate cortex	6	30	15	−4.10	26
ACC_sup_L	Left, Anterior cingulate cortex	−6	33	24	−4.69	24
N_Acc_R	Right, Nucleus Accumbens	15	12	−9	−4.54	20
CID < HC						
Occipital_Mid_L	Left, Middle occipital gyrus	−48	−75	6	4.67	210
Occipital_Mid_R	Right, Middle occipital gyrus	45	−78	15	5.22	134
Fusiform_R	Right, Fusiform gyrus	27	−66	−15	3.86	39
Postcentral_R	Right, Postcentral gyrus	48	−21	60	3.87	23

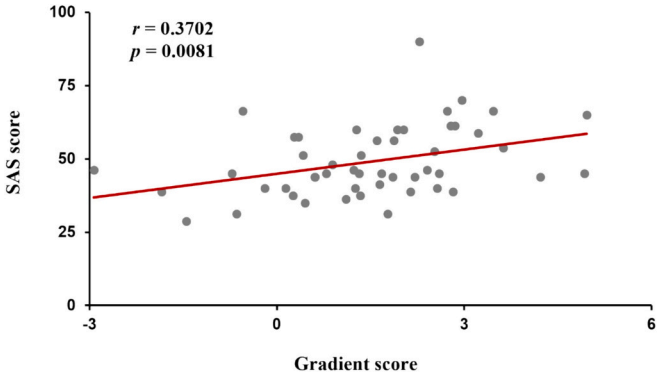

Fig. 3. Correlation analysis between Frontal_Mid_2_R gradient score and Self-Rating Anxiety Scale (SAS)scale.

test sets in the ratio of 1:1, 2:1, 3:1 and 4:1. repeated training and testing of the predictive model, which still successfully predicted the scores of each scale (for details, please see Fig. S1-S4 in Supporting Information).

4. Discussion

Combined functional connectome gradient with multivariate pattern analysis techniques, we were able to further explore the effects of insomnia disorders on cognitive and functional processes in the brain. In the current study, we investigated abnormalities within the primary functional gradients among individuals with CID and HC, aiming to uncover potential biomarkers based on functional gradients for predicting clinical scale scores in insomnia patients. This exploration aimed

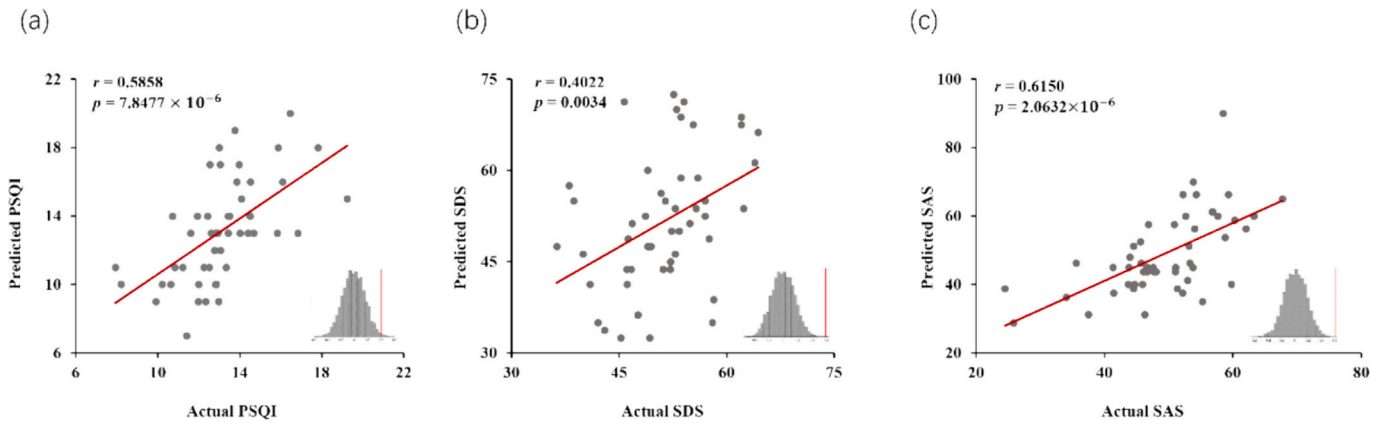

Fig. 4. Predictive Analysis of Various Scale Scores Utilizing Functional Connectome Gradient Values. Sub-figures (a)-(c) illustrate the predictive outcomes for the Pittsburgh Sleep Quality Index (PSQI), the Self-Rating Depression Scale (SDS), and the Self-Rating Anxiety Scale (SAS), respectively.

Table 3
Assessment of predictive outcomes of clinical scales.

CIDQ	R^2	Adjust-R^2	RMSE	MAE
PSQI	0.3438	0.3301	2.4071	1.9013
SDS	0.1617	0.1443	10.3440	8.1195
SAS	0.3782	0.3653	7.2623	9.3949

Abbreviations: CIDQ, chronic insomnia disorder questionnaire; RMSE, root mean square error; MAE, mean absolute error.

to illuminate potential alterations in brain organization linked to chronic sleep disturbances. The findings indicated that insomnia precipitated significant alterations in the functional gradients of certain brain regions. Specifically, gradient scores in the middle frontal gyrus, superior anterior cingulate gyrus, and right nucleus accumbens were markedly higher in CID patients compared to the HC group. Conversely, scores in the middle occipital gyrus, right fusiform gyrus, and right postcentral gyrus were notably lower in the CID group than in the HC group. Moreover, predictive models based on connectivity gradients demonstrated efficacy in forecasting sleep scores in insomnia patients, along with scale scores related to insomnia, such as depression and anxiety. These results suggested that abnormalities in functional connectivity gradient networks may represent one of the neuropathological mechanisms underlying abnormal brain function in patients with CID. Characteristics of brain functional gradients could potentially serve as objective biomarkers for assessing clinical symptoms in insomnia patients.

4.1. Reorganization of functional connectome gradients in CID

Our findings revealed significant differences in gradient scores between CID patients and the HC group across several key brain regions. Specifically, CID patients exhibited higher gradient scores in the middle frontal gyrus, right nucleus accumbens, and superior anterior cingulate gyrus, indicative of altered cortical connectivity and integration processes. In a previous study, Kajimura et al. (1999) proposed three types of inactivation in non-rapid eye movement sleep, in which the middle frontal gyrus is inactivated throughout, independent of sleep stage (Kajimura et al., 1999). The activity of the frontal middle gyrus during sleep may be related to the processing of sensory information and body movements, and the activity of the frontal middle gyrus may be diminished by the weakening of the brain's response to external stimuli during sleep, which contributes to the brain's entry into a state of rest and recovery(Dang-Vu et al., 2010). Previous studies on insomnia disorders have found that the neuronal assemblage of the nucleus accumbens, as well as the integrity of the anterior cingulate cortex, are key to the mechanisms of co-morbidity between insomnia disorders and persistent pain(Sardi et al., 2024). In addition to serving as an important nucleus for behavioral regulation of reward, motivation, and learning, the nucleus accumbens is also involved in mediating sleep-wakefulness

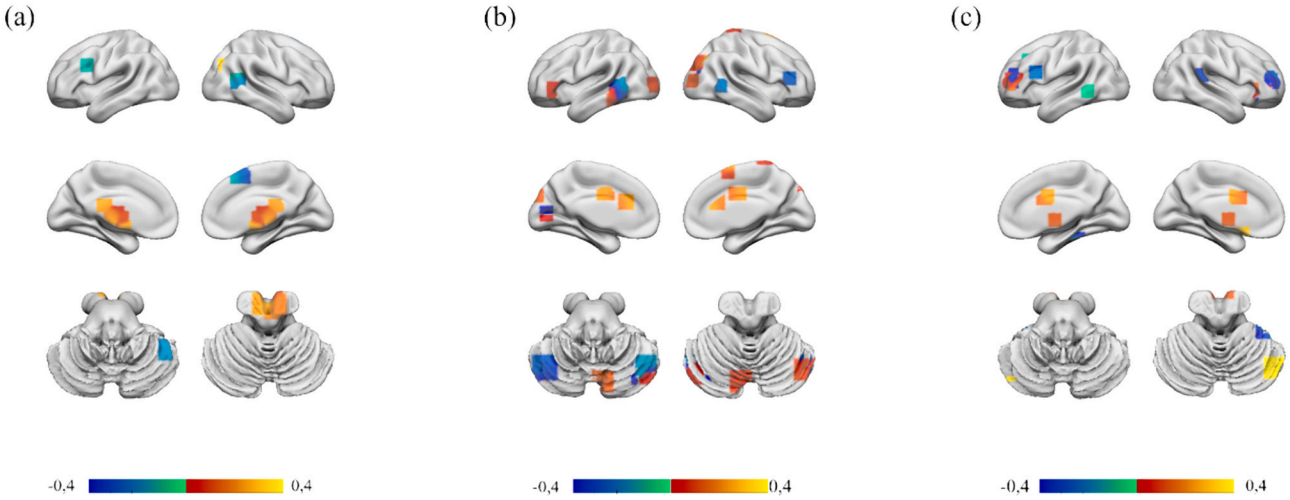

Fig. 5. Projections on the brain of features that contribute to predictive modeling, Sub-figures (a)-(c) delineate the respective feature contributions in predicting scores for the Pittsburgh Sleep Quality Index (PSQI), Self-Rating Depression Scale (SDS), and Self-Rating Anxiety Scale (SAS).

cycles and pain behaviors through the preoptic area and the ventral tegmental area(Sun et al., 2023). The anterior cingulate cortex is involved in a variety of higher-order brain functions such as attention allocation(Pardo et al., 1990), emotion(Jackson et al., 2006), reward-based decision making(Bush et al., 2002). The activation of cortical astrocytes within it is thought to play a key role in neuropathic pain and may have a significant impact on sleep disorders in patients (Yamashita et al., 2014). A previous study using PET-CT demonstrated higher glucose metabolism in the anterior cingulate gyrus at sleep onset in patients with insomnia disorder compared to HC(Nofzinger et al., 2004). Analysis of functional connectivity suggests that increased connectivity in the anterior cingulate cortex is associated with sleep quality (Cheng et al., 2018; Guo et al., 2023). We hypothesized that increased gradient scores in the anterior cingulate gyrus are associated with high arousal emotional activity in patients with insomnia disorder.

Conversely, lower gradient scores were observed in the middle occipital gyrus, right fusiform gyrus, and right postcentral gyrus in CID patients, suggesting potential disruptions in sensory processing and motor integration. The fusiform gyrus showed strong positive correlations with sleep quality(Dai et al., 2014), it is associated with visual tasks such as face recognition and object recognition. During sleep, activity in the fusiform gyrus may be associated with visual experiences and dreams (Siclari et al. 2017). The postcentral gyrus is responsible for processing and interpreting bodily sensory information and activity may be diminished during sleep, and this diminution may contribute to reduced perception of external stimuli, Chen et al. found a significant increase in regional homogeneity in the right postcentral gyrus after sleep deprivation at the neural level(Chen et al., 2023). The abnormal activation of the occipital gyrus observed in patients with insomnia disorder is consistent with the heightened arousal theory, which may be driven by hyperactivity in the patient's visual brain regions (Nofzinger et al., 2004). The occipital lobe is a visual cortical center, and increased connectivity within visual and other sensory regions may contribute to ongoing sensory processing of environmental stimuli, ultimately impeding the ability to initiate or maintain sleep.

The synergistic action of different tissues in the brain is essential for maintaining basic body perception and for keeping sleep relatively stable. However, insomnia may lead to imbalances in brain function, which may be reflected in functional connectome gradients. Our study revealed spatial variations in brain functional connectivity in patients with insomnia by comparing functional connectome gradients in CID and HC. This finding is supported to some extent by previous studies and further emphasizes the potential impact of insomnia on brain function.

4.2. Correlation of gradient differences and scale scores

The results of the current study show that after correction for multiple comparisons, there were still changes in gradients in several brain regions. However, after correlation analysis with scale scores, we found that only one region, Frontal_Mid_2_R, was positively correlated with anxiety symptoms, whereas the other regions appeared to be unrelated to insomnia and co-morbid symptom scales. Such results deserve further discussion and interpretation.

First, one must note that gradient analysis and scale scores are two different assessment methods, and certain brain regions show changes in gradient analysis but not correlations in scale scores, possibly because scale scores do not fully reflect the complexity of brain function(Buckner et al., 2008; Biswal et al., 2010; Margulies et al., 2016). Second, gradient changes may affect other brain regions or the nervous system, thus indirectly affecting patients with insomnia rather than directly correlating with clinical symptoms(Bullmore and Sporns, 2009; Kelly et al., 2012; Medaglia, 2017). Such indirect effects may need to be validated by further functional connectivity analyses. Finally, we also need to consider the effects of sample size and statistical effects(Ioannidis, 2005; Poldrack et al., 2017). It is possible that correlations between other gradient changes and anxiety symptoms were not detected due to small sample size or insufficient statistical validity.

In conclusion, this result reflects the complex relationship between brain structure and function, and further research is needed to deepen the understanding. It also emphasizes the importance of integrating multiple factors in neuroscience research to better explain and understand insomnia symptoms.

4.3. Functional connectome gradients may help predict clinical symptoms in patients with CID

The difference in gradients between the CID and HC groups may indicate that the gradient axis captures insomnia-induced functional changes. Insights emerging from mapping intrinsic brain connectivity networks provide a potentially mechanistic framework for an understanding of aspects of human behavior(Mo et al., 2024; Zhang et al., 2024). In the modeling process, different networks contributed differently in different prediction processes. FPN, as the core network of the triple network model, is responsible for performing extroverted tasks such as control(Cheng, 2022b; Marek and Dosenbach, 2018; Wang et al., 2018) and attention allocation (Liu et al., 2022), and has major contributions in the prediction process of all three scale scores. DAN, a core functional network in the brain, plays an important role in perceptual tasks, especially in tasks that require attentional shifting and spatial orienting tasks(Corbetta and Shulman, 2002), and the stabilization and concentration of attention are closely related to mood states and sleep quality. Depressed patients often have difficulty concentrating, and decreased sleep quality may lead to diminished attention and cognitive functioning. Therefore, the activity level of the DAN may reflect an individual's cognitive state and emotional stability, thus playing an important role in the prediction of depression and sleep quality. VIS, which contributes greatly to the prediction process of anxiety and depression, is one of the core networks in the brain responsible for visual information processing, which involves visual functions such as visual perception, visuospatial analysis, and target recognition (Kitada et al., 2010). The DMN and the VAN are predominantly involved in the prediction process of SDS, with the DMN being involved in mainly inward-oriented activities, such as introspection, self-assessment, and memorization (Perkins et al., 2015; Cheng et al., 2022a; Pang et al., 2022). The VAN is mainly involved in attentional orientation and emotional processing in the external environment and is closely related to an individual's affective response to external stimuli and emotion regulation(Vossel et al., 2014). Gradient characterization is based on the static functional connectivity of the brain, the main gradient, although not representative of all the variance in the data, performed well in predicting scale scores. Perhaps it's because certain features of particular gradient axes may be informative for brain changes in patients with insomnia. Our results suggest that the treatment of patients with insomnia only or insomnia with depression or anxiety should be considered separately, given the different neurobiological effects of different insomnia co-morbidities.

4.4. Limitations

Several limitations should be noted in this study. The small sample size may have missed other brain function gradient changes and their correlations with clinical symptoms in insomnia patients. Although we used robust validation techniques like ten-fold cross-validation and 5000 permutation tests, we did not use an external dataset for validation. External validation is crucial for assessing a model's generalizability and real-world applicability. Without it, we cannot conclusively determine the model's performance on new data.

Future research will expand its scope by incorporating larger and more diverse datasets. And conduct more detailed gradient analyses of CID, focusing specifically on changes in gradients such as those in the cingulate gyrus(Shen et al., 2023) and insula(Wang et al., 2023).

5. Conclusion

This study established a link between functional connectivity gradient and insomnia, demonstrating that insomnia disrupts functional connectome gradients. Combining these gradients with machine learning effectively predicted clinical symptoms' severity, such as sleep quality, anxiety, and depression. This suggests functional gradient are related to insomnia's underlying mechanisms and its mental comorbidities. By not relying on behavioral data or direct sleep observation, this method offers a unique opportunity for individual-level clinical prediction. It provides researchers and clinicians with a comprehensive view of a person's condition and could potentially integrate with genomics, polysomnography, and other methods to develop comprehensive biomarkers, aiding in more precise treatment and intervention strategies.

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Ethical Statement

This research was examined and approved by the Institutional Review Board Ethics Committee of Chengdu Second People's Hospital (ethics approval number: 2020021). Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Jiahui Wu: Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation. **Zhen Yuan:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jiang Zhang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Zhiwei Zhang:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Tianwei Qin:** Writing – original draft, Visualization, Formal analysis. **Xiaoxuan Li:** Writing – original draft, Data curation. **Hanbin Deng:** Writing – review & editing, Methodology, Conceptualization. **Liang Gong:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

Data availability

Analytic code and data for this work are available upon request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2024.111120.

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