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ORIGINAL ARTICLE

Study Protocol for Characteristics of Neurovascular Discoupling of Cognitive Impairment in Insomnia Based on Multimodal MRI

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Abstract

Insomnia disorder (ID) may develop into mild cognitive impairment (MCI) or even dementia. However, there is a lack of reliable objective methods for the identification of MCI in ID patients. Neurovascular coupling (NVC) dysfunction may be a potential biological marker of MCI in ID patients, but its characteristics in ID have not been fully explored. Therefore, exploring the imaging features of NVC dysfunction in patients with ID based on functional magnetic resonance imaging (fMRI) and combining clinical information and neuropsychological features to develop a machine learning-based algorithm may help to detect MCI in ID. In this study, ID patients aged 30-60 and healthy controls (HC) will be recruited and divided into ID with MCI (ID-MCI), simple ID, and HC groups based on neuropsychological evaluation. Resting-state magnetic resonance imaging (rs-fMRI) will be used to explore the characteristics of NVC dysfunction in patients with ID-MCI based on blood oxygen-level dependent (BOLD) and arterial spin labeling (ASL) methods. Then, the selected features and related clinical features will be set into the classifier model using privileged information. Finally, the optimal model will be trained and the classification performance will be obtained using the testing data. This study will reveal the imaging characteristics of NVC dysfunction in patients with ID-MCI based on fMRI, and provide a machine learning model for the diagnosis of MCI in patients with ID and has potential clinical significance for timely intervention and treatment to delay the development of MCI.

Trial registration: This study has already been registered at Clinical Trials. gov (ID: NCT05659511). Registration date: January 2nd, 2023.

Keywords: Insomnia disorder, Mild cognitive impairment, fMRI, Neurovascular coupling, Machine learning

1. Background

Insomnia disorder (ID) is the most common type of sleep disorder. A survey by the Chinese Sleep Research Society reveals that the incidence of insomnia among Chinese adults is as high as 38.2 % [1,2]. ID is a significant contributor to cognitive impairment and is significantly associated with a high risk of 27% cognitive disorders, which include mild cognitive impairment (MCI) and dementia [2]. MCI is an early stage of cognitive dysfunction that is not severe enough to affect daily life, but it has a high likelihood of progression to dementia, which occurs in 5% to 17% of people with MCI each year[3]. MCI and ID can be causally related to each other, and ID can cause MCI or act as a manifestation of MCI[4]. If not controlled, a vicious circle will be formed[5]. MCI caused by ID has the potential to maintain stability, not deteriorate, or even reverse to normal cognitive state in the early stage [6,7]. Therefore, MCI in the early stage of ID can be used as the time window for the prevention and treatment of dementia. Timely diagnosis and early intervention are very important for improving and restoring the

cognitive function of patients.

At present, the diagnosis of MCI is mainly based on clinical symptoms and cognitive scale assessment, and patients have detectable declines in memory, language, and other cognitive functions. The Montreal Cognitive Assessment (MoCA) is a common assessment tool for rapid screening of MCI at present, but it requires a high educational level[8], is suitable for junior high school graduates, and is highly subjective and prone to bias[9]. Neuroimaging biomarkers have relatively objective predictions for cognition[10], functional magnetic resonance imaging (fMRI) has been widely used in the detection of brain structure-function, which can objectively and quantitatively and non-invasively reflect the cognitive decline related to sleep disorders under physiological conditions. Therefore, the combination of the two may have greater advantages in predicting changes in cognitive function[11]. However, the mechanism of ID induced MCI is complex, and there is currently a lack of early objective biomarkers for biological imaging.

Neurovascular coupling (NVC) dysfunction may be a key mechanism of cognitive impairment. NVC is a functional complex of neurons, blood-brain barrier, microglia and extracellular matrix that maintains the integrity of brain function [12]. Neurotransmitters and inflammatory factors induced by inflammation and hypoxia are messengers of NVC functional complex [13]. It is shown that during normal sleep-wake cycles, the neuronal activity was consistent with the change of cerebral blood flow (CBF)[14]. ID promotes inflammatory cells to release inflammatory factors through a variety of pathways[15,16], resulting in vascular endothelial injury, vascular endothelial dysfunction[17,18], and ultimately cerebral hemodynamic disorders and brain microstructure damage[19]. At the same time, it was found that CBF significantly reduced in the bilateral parahippocampal gyrus, fusiform gyrus[20], thalamus[21], right prefrontal lobe and posterior parietal lobe after acute sleep deprivation [22]. In studies on acute sleep restriction (4 hours of sleep per night), significant reductions in frontal parietal CBF were found [23], while neuronal activity increased significantly in brain regions associated with emotion and memory, such as the amygdala and hippocampus [24]. These studies hinted that sleep disorders may lead to NVC dysfunction. However, limited studies were conducted on the imaging features and diagnostic efficacy of NVC in patients with ID.

Research has shown that combining neuronal activity with CBF can help identify MCI[25]. In neuroimaging, compared with single imaging, multimodal MRI can analyze the coupling state of neural activity and CBF [26,27]. It is worth noting that our research group conducted a preliminary exploration of MCI caused by early NVC disorders and developed relevant techniques to describe the NVC dysfunction [28]. MR based NVC is a new approach among many current multimodal fusion analysis methods to describe the interactions of CBF that support brain function. Therefore, based on this technology, we will explore the key imaging indicators and brain regions of ID-related MCI to more objectively diagnose MCI in patients with ID.

At present, machine learning (ML) can fully assist diagnosis and screen for key features by effectively integrating imaging indicators and other clinical indicators. Some scholars have applied ML to other diseases related to ID. Yang et al. used resting state functional magnetic resonance imaging (rs-fMRI) and ML to identify chronic ID by logistic regression, and the results showed that Amplitude of low frequency fluctuation (ALFF) and functional connection (FC) features had good performance in the diagnosis of chronic ID using logistic regression [29]. Xu et al. proposed a ML to predict the anxiety of ID patients by using imaging features through Support Vector Machine [30]. These studies suggest that ML is effective in the diagnosis of ID-related diseases. However, there is still a lack of research on which ML algorithm and parameters can be used to screen critical NVC characteristics and effectively diagnose ID patients with MCI. Therefore, another purpose of this paper is to explore the imaging characteristics of NVC dysfunction in ID patients by combining fMRI and arterial spin labeling (ASL), to reveal the mechanism of NVC dysfunction in ID-induced MCI through multimodal MRI, and to build an optimal ML for predicting MCI in ID.

We hypothesiz that patients with ID will exhibit specific NVC changes and that abnormalities in NVC will predict MCI in patients with ID. We will first collect multimodal MRI indicators and

multidimensional cognitive scale features, as well as neuropsychological and related clinical indicator features, from healthy controls (HC), simple ID patients (ID), and ID patients with MCI (ID-MCI); Secondly, two-sample t test will be used to analyze the NVC MRI features of subjects in the ID group and ID-MCI group. This feature will further be used to reveal the NVC of ID-MCI patients compared to ID patients, and will be used for subsequent ML analysis. Thirdly, a prediction model for MCI symptoms will be established using ML algorithms based on imaging and clinical indicators related to cognitive impairment. Finally, the independent dataset will be used for external validation of the predictive model.

2 Methods

2.1 Participants

Diagnosis of ID will be based on the criteria of the Chinese Adult Insomnia Diagnosis and Treatment Guidelines 2017 and confirmed by the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI)[31]. All patients with ID will be recruited through the outpatient department of Neurology Sleep Center of the Second Affiliated Hospital of the Air Force Medical University. Participants with ID will be divided into ID and ID-MCI based on Montreal Cognitive Assessment (MoCA) (https://mocacognition.com/permission/ Authorized for use in this study). MCI is diagnosed by a MoCA score of < 26[32]. After the study procedure has been fully explained in detail and written informed consent has been obtained, subjects who match the following criteria will be included in the ID group: (1) age ranges from 30-60 years old; (2) PSQI > 5 and ISI ≥ 8; (3) right-hand dominance; (4) a minimum of secondary school education. Subjects who meet both the ID and MCI inclusion criteria will be rated as having ID-MCI. Meanwhile, matched HC subjects will be recruited through the Physical Examination Center of the Second Affiliated Hospital of the Air Force Medical University. HC subjects and ID patients will be excluded as follows: (1) years of education < 7 (2) dementia (MoCA < 18); (3) severe brain diseases, such as cerebral infarction, encephalomalacia, significant brain atrophy, craniocerebral trauma, and inflammatory lesions of the central nervous system (these diseases can be excluded by routine MR Scanning); (4) MR Contraindications; (5) Have taken psychoactive and steroid hormone medications in the past 3 months; (6) Unideal images; (7) recent experience of night shift, swing shift, or other shift work. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Air Force Medical University (202211-16).

2.2 Clinical and Neuropsychological Assessments

All participants will undergo the following neuropsychological assessments: cognitive status will be assessed by MoCA, the episodic memory of verbal information will be assessed with California Verbal Learning Test (CVLT), and the Self-rating Depression Scale (SDS) and the Self-rating Anxiety Scale (SAS) will be performed to measure the severity of self-reported symptoms of depression and anxiety. Clinical information such as age, sex, occupation, smoking, drinking, tea and coffee habits, education level, duration of disease, and past medical history will be also collected.

The ID status will be mainly assessed by PSQI and ISI. PSQI is used to evaluate the sleep condition of the subjects in the past month. PSQI includes 19 self-tested questions, which are composed of 7 parts, namely subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, sleep medication use, and daytime dysfunction. The total score ranges from 0-21 points, and the higher the score is, the worse the sleep quality is[33]. ISI is a reliable and effective tool for quantifying the severity of ID. The ISI includes seven items that assess the severity of sleep onset and sleep maintenance difficulties (including nighttime and early morning awakenings), satisfaction with current sleep patterns, disruption to daily functioning, appreciability of impairment due to sleep problems, and distress or worry caused by sleep problems on a 0-28 scale, with higher scores indicating more severe ID[34].

2.3 MRI

All participants will be scanned using a 3.0-T MRI system (MR750; GE Healthcare, Milwaukee, WI, USA), using an 8-channel head coil array with foam pads to secure the head and limit head movement, and earplugs and sponge pads to reduce mechanical noise. Conventional sequential and rs-fMRI scans will be performed for each participant. Intracranial lesions will be detected by conventional sequences such as T1-weighted

images, T2-weighted images, and fluid-attenuated inversion recovery images will be excluded. Meanwhile, rs-fMRI and ASL scans will be performed to detect changes in neuronal activity and CBF. During the scan, participants will be asked to close their eyes and relax, but remain awake. All MR images of each participant will be assessed by two experienced radiologists (with more than 5 years of experience) to ensure that there is no severe brain disease.

2.3.1 rs-fMRI

The rs-fMRI sequence will be acquired using a gradient-recalled echo-planar imaging (GRE-EPI) sequence with the following parameters: repetition time (TR) =2000ms, echo time (TE) =30ms, flip angle (FA) =90°, slice number=36, inter slice gaps=1, field of view (FOV) =220x220, matrix=64x64, slice thickness=3mm. The whole process will take 7 min 30 s.

2.3.2 ASL

ASL will be used to obtain the resting perfusion image, according to the following parameters: TR=5046ms, TE =11.088ms, slice number =50, FOV=240x240, matrix=128x128, slice thickness =3mm, FA =111°, number of excitation (NEX)=3. The whole scan will cost 4 min 53 s.

2.3.3 sMRI

3D brain volume imaging (3D-T1BRAVO) will employ sagittal scanning to obtain high-resolution T1WI images for image segmentation and registration to standard brain anatomy templates with TR=8.16ms, TE=3.18ms, TI=450ms, FA=12°, FOV=256x256, matrix =256x256, slice thickness =1mm, slice number =188, The scan will last for 4 min 43 s.

2.3.4 MRI Image Processing

2.3.4.1 rs-fMRI data

The rs-fMRI imaging data will be preprocessed in Data Processing Assistant for Resting-State fMRI (DPABI, http://www.restfmri.net/forum/DPARSF) and the SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) software package in MATLAB R2016b (Mathworks, Natick, USA) platform. After converting DICOM format to 3D NIFTI format which is more suitable for processing, the first 5 time points will be discarded. The remaining rs-fMRI datasets will be then corrected for intra-volume acquisition time delay and inter-volume head motion. Any images with head motion of 3.0-mm translation or 3.0° rotation in any direction will be excluded. In addition, the functional images will be co-registered to the structural images and normalized from individual spaces to standard Montreal Neurological Institute (MNI) space by the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) registration method. Then, the standardized map will be spatially smoothed with a 6-mm full-width at half-maximum Gaussian kernel to reduce the error and increase the signal-to-noise ratio. To reduce the effects of low-frequency drift and high-frequency noise, the data will be further detrended and temporally band-pass filtered (0.01–0.08 Hz). The whole process also includes eliminating covariance by regression and reducing the influence of head movement, white matter (WM), and cerebrospinal fluid signals (CFS)[35]. ALFF and other functional indicators will also be estimated simultaneously in the DPARSFA software.

2.3.4.2 ASL data

The CBF images will originate from the ASL image obtained by scanning using of an automatic image post-processing tool in the GE MRI 750 system. Data will be preprocessed using SPM12, in which the normalized parameters from the 3D-T1BRAVO image combined with the ASL image of the individual space to the standard MNI space will be estimated, and then these parameters will be normalized to the CBF image of the individual data. The data will be normalized to reduce individual differences to obtain relative CBF values. Then, each subject's CBF image will be spatially smoothed with a Gaussian kernel of 6x6x6 mm full-width at half-maximum to reduce inter-individual differences and increase the signal-to-noise ratio (SNR).

3 Statistical Analysis

3.1 Demographic and Clinical Information

Statistical analysis of the demographic and clinical data between the groups will be performed using SPSS 25.0. For the analysis of quantitative data such as age, years of education, SAS, SDS, MoCA score and CVLT score, ANOVA will be used if they are normally distributed with homogeneous variance,

otherwise, Kruskal-Wallis H test will be used. Chi-square test ($\chi 2$) will be used to analyze categorical data, such as sex, smoking, drinking, and tea drinking habits. After multiple comparisons, differences with $P < 0.05$ will be considered statistically significant.

3.2 MRI Image

A one-way ANOVA will be performed to identify the differences among the ID-MCI, ID, and HC groups. The resultant F value map will be then thresholded using $P < 0.05$. Subsequently, the regions that showed significant differences will be extracted as regions of interest (ROI) for FC analysis, and Pearson correlation coefficients will be calculated between the mean time series of each ROI and the time series of each voxel in the rest of the brain. To improve normality for analyses, correlation coefficients will be converted to z-values using Fisher r-to-z transformation. The mean ALFF, ReHo, DC, CBF, and FC values will be used for a posthoc analysis. Statistical comparisons of the above index values between each two groups will be performed using a two-tailed t-test with two-sample values at a threshold of $P < 0.05$. The resulting brain regions from rs-fMRI and CBF will be later used as ROIs points for NVC analysis using the MICA toolkit, with FDR correction and considered statistically significant at $P < 0.05$.

4 Feature Selection and Cross-Validation

For feature selection, it is necessary to maximize the information and reduce the interference effects of various noise sources in data processing. Based on the results of NVC dysfunction, a preliminary model will be established by using a multi-factor regression method considering neuropsychological and clinical information. In most cases, the number of features is far greater than the number of subjects available, and removing irrelevant or redundant features reduces computational load and speeds up the learning process. Therefore, dimensionality reduction will be carried out by principal component analysis (PCA), that is, PCA will be carried out to extract the most representative feature dimensions to simplify the model. In order to improve the classification performance, data fusion of different types of modes will be comprehensively used for the upcoming classification task. Due to different types, it is necessary to conduct standardization, carry out ML on the fused data, and select the features with greater weight for modeling. Cross-validation will be then carried out, The sample data will be randomly divided into two parts (such as 70% training set and 30% test set), and the training set will be used to train the model and verify the model and parameters on the test set. This process will be repeated multiple times (until the entire data is covered) with different random partitioning to generate an average performance measure[36]. The results will be then compared and the parameters will be adjusted to ensure that each algorithm achieves the optimal solution to select the best one. This process will be operated on MVPA based MATLAB R2016b (64bit) as a platform.

Statistical Testing

The effect of ML will be judged by a permutation test, and the classification accuracy rate of each time will be significantly inferred by multiple comparison correction methods. That is, class labels will be arranged 1000 times (ID-MCI patients and HC labels will be randomly assigned to training subjects) and repeated throughout the cross-validation process. The mean and standard deviation (SD) of the classification accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) of each model will be computed in repeated re-divided dataset randomly. For further model assessment, a permutation test will be performed to assess the statistical significance of the classification accuracy. The permutation test will be repeated 1,000 times. During each time, the classifier reallocated labels of ID-MCI patients and HC to the training data randomly and repeated the whole classification process. The P value will be acquired after the entire permutation has been finished, and the result will be considered significant if the accuracy of all permutations is less than 5% ($P < 0.05$)[37].

5 Outcome Measure

5.1 Main Outcome Measure

Correlation between imaging features of NVC dysfunction in ID-MCI and cognitive function.

5.2 Secondary Outcome Measure

An automated and individualized accurate diagnosis model with ID-MCI with the best sensitivity, specificity, and accuracy will be

initially constructed on the basis of combining clinical information and neuroimaging features.

6. Discussion

This study will use fMRI technology to study the NVC features of cognitive impairment in patients with ID, and the correlation between ID related cognitive impairment and NVC features will be analyzed. Then, combining clinical information, a diagnostic model will be established using ML to identify early cognitive impairment of ID and evaluate its predictive performance.

ID causes abnormalities in neural activity or CBF signals, and the changes in the two affect each other. The change of CBF affects the metabolic microenvironment of neurons, and the activity of neurons also achieves the role of CBF regulation through the regulation of vascular smooth muscle. Normal brain function depends on sustained and sufficient CBF supply, and additional neuronal demands for nutrients during periods of intensive neuronal activity are matched by increased CBF from the NVC. A study that uses mice to explore how arousal state impacts cerebral hemodynamics and NVC has shown that the correlation between neural activity and CBF is highest during non-rapid eye movement slow wave sleep and lowest during awake state[38,39]. Moreover, human sleep slow waves are also associated with hemodynamic changes in the brain, especially the brainstem and thalamus [40], which are the main brain areas involved in the "hyperarousal theory". Some scholars have proposed that NVC dysfunction is one of the causes of cognitive impairment[39,41], which may be due to the cascade reaction caused by NVC dysfunction, leading to Amyloid-β protein clearance is impaired, ultimately leading to the Alzheimer's disease[41], and sleep plays a crucial role in its pathophysiology. This clearance process may occur during non-rapid eye movement slow wave sleep[42]. In summary, ID can further lead to cognitive impairment by affecting NVC dysfunction.

The "hyperarousal theory" is the most widely accepted explanation for the underlying mechanism of ID. It points out that excitement manifests as activation of the body, cognition, and cortex. Cortical arousal subjectively manifests as an increase in cognitive activity, and the occurrence of chronic ID is accompanied by an increase in autonomic nervous system activity [43]. Since Nofzinger et al. reported functional neuroimaging evidence of hyperarousal using [18F]fluorodeoxyglucose positron emission tomography[44], several rs-fMRI studies have been conducted to elucidate the neurobiological mechanism of the "hyperarousal theory" of ID. These studies found abnormal resting-state functional indicators in multiple brain regions, especially FC, including the prefrontal, parietal, insular, amygdala, thalamic, visual cortex[45], and salience network[46], among others, which also had abnormal CBF[20-22]. Csipo et al has demonstrated that 24 h of ID leads to altered CBF and hemodynamic components of cortical NVC responses together with impairments in cognitive performance, mainly in the prefrontal cortex [47], which may be the key brain area for future studies.

There have been many studies on ID in fMRI, but most of them focus on exploring a single aspect. We will reveal which combination is the ML model with the largest area under the ROC curve by combining imaging features of multiple functional indicators in CBF and fMRI, information from MoCA, PSQI, ISI, SAS, and SDS scales, as well as lifestyle information such as tea, alcohol, coffee, exercise, and work conditions. We will calculate its corresponding sensitivity, specificity and accuracy, and select the best MCI diagnostic model and parameter settings to determine whether the multi-mode measurement method is more accurate and reliable than the scale or a single model, so as to help identify MCI patients. In this regard, we assume that the multimodal approach improves the classification accuracy of MCI patients. If our hypothesis is validated, it will provide further evidence for the study of ID related cognitive impairment. Therefore, this upcoming study will be based on ML algorithms to help detect MCI in ID. Specifically, we will gradually explore the optimal ML model for diagnosing MCI in ID patients through various ML methods[48], and identify neuroimaging biomarkers for MCI patients with ID. These biomarkers can help identify individuals with a higher risk of cognitive decline in early ID patients, and help to timely develop treatment or intervention plans, delaying the development of brain atrophy and dementia.

However, ID is influenced by a variety of factors including tea, alcohol, coffee, depression, illness,

physical activity, nature of work, shift[49,50], and even socioeconomic status and community environment[51], and the results may be distorted by certain factors due to the inability to categorize patients with ID in more detail. In addition, the multi-modal model tends to ignore the correlation between the attributes of the data set in the characteristic selection, which is biased in the attribute division. The limitation of sample size and the verification of independent data sets are also major challenges to improve the accuracy of the diagnostic model.

Conclusion

Proper brain function depends on NVC: neural activity rapidly increases local CBF to meet moment-to-moment changes in regional brain energy demand[52]. NVC can simultaneously reflect changes in neural activity and CBF compared with a single indicator. In this study, we propose the NVC indicators for exploring MCI in ID patients based on MRI, and will screen the best diagnostic ML model for MCI in patients with ID. It is helpful to diagnose MCI in ID patients and find the neuroimaging biomarkers in ID-MCI patients. We anticipate that this model can supplement or be combined with models for predicting MCI to predict MCI in patients with ID. It can promote timely intervention for serious diseases such as dementia. The diagnostic model will continue to be optimized for accurate prospective assessment of more ID patients with early cognitive impairment through NVC dysregulation.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing of interest

Financial Disclosure. The authors declare no competing financial interests.

Non-financial Disclosure. The authors declare no potential conflicts of interest.

Consent for Publication

Not applicable.

Ethics Approval Statement

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Air Force Medical University (202211-16).

Abbreviations: ID, Insomnia disorder; MCI, mild cognitive impairment; MoCA: Montreal Cognitive Assessment; NVC: Neurovascular coupling; CBF: cerebral blood flow; fMRI: functional magnetic resonance imaging; ML: machine learning; rs-fMRI, resting state functional magnetic resonance imaging; ALFF, Amplitude of low frequency fluctuation; FC: functional connection; HC: healthy controls; ID-MCI: ID patients with MCI; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; CVLT: California Verbal Learning Test; SDS: Self-rating Depression Scale; SAS: Self-rating Anxiety Scale; 3D-T1BRAVO: 3D brain volume imaging; MNI: Montreal Neurological Institute; DARTEL: Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra ; WM : white matter; CSF: cerebrospinal fluid signals; ROI: regions of interest; PCA: principal component analysis; SD: standard deviation.

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