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Research paper

Frontoparietal network homogeneity as a biomarker for mania and remitted bipolar disorder and a predictor of early treatment response in bipolar mania patient

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ABSTRACT

Objective: Previous studies have revealed the frontoparietal network (FPN) plays a key role in the imaging pathophysiology of bipolar disorder (BD). However, network homogeneity (NH) in the FPN among bipolar mania (BipM), remitted bipolar disorder (rBD), and healthy controls (HCs) remains unknown. The present study aimed to explore whether NH within the FPN can be used as an imaging biomarker to differentiate BipM from rBD and to predict treatment efficacy for patients with BipM.

Methods: Sixty-six patients with BD (38 BipM and 28 rBD) and 60 HCs participated in resting-state functional magnetic resonance imaging and neuropsychological tests. Independent component analysis and NH analysis were applied to analyze the imaging data.

Results: Relative to HCs, BipM patients displayed increased NH in the left middle frontal gyrus (MFG), and rBD patients displayed increased NH in the right inferior parietal lobule (IPL). Compared to rBD patients, BipM patients displayed reduced NH in the right IPL. Furthermore, support vector machine results exhibited that NH values in the right IPL could distinguish BipM patients from rBD patients with 69.70 %, 57.89 %, and 91.67 % for accuracy, sensitivity, and specificity, respectively, and support vector regression results exhibited a significant association between predicted and actual symptomatic improvement based on the reduction ratio of the Young Mania Rating Scale total scores (r = 0.466, p < 0.01).

Conclusion: The study demonstrated distinct NH values in the FPN could serve as a valuable neuroimaging biomarker capable of differentiating patients with BipM and rBD, and NH values of the left MFG as a potential predictor of early treatment response in patients with BipM.

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1. Introduction

Bipolar disorder (BD) is a common psychiatric disease with high disability, suicide, and recurrence rates, which leads to a decrease in patients' quality of life and social function (Bauer, 2022). Its main characteristics are cyclically switching from depression to mania or hypomania, and periods of remission state. Remitted BD (rBD) is often mistaken for major depressive disorder (MDD) due to similar clinical traits, such as depressive symptoms and ruminations (He et al., 2016), while bipolar mania (BipM) is easily misdiagnosed as schizophrenia in part due to the fact that they share common genetic and neurobiological traits, as well as overlapping phenomenology such as psychotic symptoms, including delusions and/or hallucinations (Rogers, 2023). At present, the diagnosis of BD mainly depends on the interview between doctors and patients, which is subjective to a certain extent, leading to many missed or misdiagnosed cases in clinical practice (Schiweck et al., 2021). These misdiagnoses can lead to problematic consequences for patients and their families and increase the burden to society as adequate treatment is ensured only by correct clinical identification of many missed or misdiagnosed cases in clinical practice (Schiweck et al., 2017). These studies show that moods are easily shiftable in people with BD. However, it is unknown what causes bipolar patients to switch between the possible states of the disorder, such as mania, depression, and remission. Furthermore, the pathological imaging mechanism of BD is still unclear and there is no predictor of manic or depressive episode in rBD patients.

Resting-state fMRI (rs-fMRI) can detect spontaneous neuronal activity non-invasively, therefore, it is widely used to study the pathogenesis, therapeutic effect, and prognosis evaluation of neuropsychiatric disorders (Gao et al., 2022b, 2023; Guo et al., 2022; Lin et al., 2022). In particular, the network analysis proved to be particularly suitable for studying the biological basis of psychopathology (Fornito et al., 2017; Zhang et al., 2021c). A large number of studies have shown that multiple brain regions in patients with BD have local functional abnormalities (Sk et al., 2018; Vargas et al., 2013; Wang et al., 2016), including changes in the function and morphology of the prefrontal cortex, and the anterior cingulate cortex. Although rBD patients showed normal scores in emotional, cognitive, and motor aspects, there are still differences between structural MRI and functional MRI in rBD patients. In the task state MRI study, the activation of dorsolateral prefrontal cortex on the left side of rBD was found to be significantly and positively correlated with the score of the global functional assessment scale (Yoshimura et al., 2014). Rs-fMRI also found high connectivity between the right dorsal caudate putamen and ventrolateral prefrontal cortex in rBD patients, which was significantly related to the level of high-sensitivity C-reactive protein (Tseng et al., 2021), and structural MRI showed that the volume of dorsolateral prefrontal cortex in patients with BD was significantly reduced (Adler et al., 2007). Furthermore, in a cross-sectional study, the number of BipM was higher, which was related to a smaller volume of gray matter in the prefrontal brain regions (Chen et al., 2018), and the longitudinal study of BD patients followed up for 6 years found that the volume of frontal cortex in manic episode group was significantly reduced. However, there was no volume change in the non-manic episode group (Abé et al., 2015). This study suggested that the decrease in the volume of the frontal lobe area can be attributed to the incidence of manic episodes. It has also been reported that the local shape of the basal ganglia in rBD patients is significantly related to the longer duration of the disorder, the increased number of manic episodes, and the treatment with antipsychotic drugs (Liberg et al., 2015). These changes can predict the psychomotor disturbances of rBD, and these abnormalities may also be a factor in manic episodes. However, these abnormal brain regions are located in the FPN. Therefore, the study of the FPN in BipM and rBD patients with rs-fMRI is conducive to exploring the pathological imaging mechanism of BD and may lead to finding potential imaging biomarkers to predict transition into mania.

Network homogeneity (NH) is a voxel-wise analysis to examine the correlation of a given voxel with all other voxels within a particular network, such as the FPN. The mean correlation coefficient of the time series of a voxel with the time series of other voxels in the network is defined as NH of this voxel. Compared with traditional FC analysis, NH provides an unbiased investigation to evaluate homogeneity of a particular network without the requirement to know previously where the network might be. Here, homogeneity is defined as similarity of the time series of a given voxel to those of other voxels of the particular network. NH has been well applied to analyze imaging data associated with schizophrenia, MDD, and epilepsy (Gao et al., 2018; Guo et al., 2014; Zhou et al., 2020). The application of multivariable pattern recognition technologies, for example, support vector machine (SVM), may aid in facilitating diagnosis based on neuroanatomical biomarkers (Zhang et al., 2023). SVM is a particular type of supervised machine learning approach, where data points can be classified in high-dimensional space by maximizing the edges between classes. The first-rank arithmetic is progressed via a “training” stage and training data is applied to exploit arithmetic that can distinguish between the previously defined groups via the operational staff. A “test” stage, that the arithmetic is applied to blindly forecast the group in which observed values are made. SVM analysis has been widely utilized to distinguish patients with schizophrenia, epilepsy, and MDD from healthy controls (Gao et al., 2021, 2022a, 2022b). However, whether abnormal NH may be used as underlying brain imaging biomarkers to discern BipM from rBD through SVM analysis remains unclear.

In this study, we aimed to use the NH method to detect the FPN in BD patients. We hypothesized that both BipM and rBD patients would show disrupted NH, as well as different NH patterns between BipM patients and rBD patients, which might be served as underlying imaging biomarkers to discern BipM patients from rBD. We also hypothesized that disrupted NH could be correlated to clinical characteristics, such as the patients’ duration of illness and symptomatic severity, and disrupted NH would be capable of predicting treatment efficacy in the patients with BipM.

2. Methods

2.1. Subjects

Fourty-one patients with bipolar mania (BipM) and 33 patients with remitted bipolar disorder (rBD) aged 18–45 years were enrolled from the outpatient unit and ward of the Department of Psychiatry of Renmin Hospital of Wuhan University, from July 2022 to January 2023. Patients were independently diagnosed by three psychiatrists, based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Kessing et al., 2021). Inclusion criteria for all patients were as follows: (1) the patients fulfilled diagnosis of either mania or remission; (2) rBD patients were either currently unmedicated or judged to be clinically safe for a washout of currently ineffective medications under the supervision of the study psychiatrist. No patients were taken off medications that were working effectively for the purpose of enrolment in this study. Patients were medication-free prior to MRI scanning for at least 14 days, and off neuroleptics for at least 3 weeks. BipM patient was inpatients who had just been stable after taking medicines (lithium carbonate, valproate and quetiapine) and can cooperate with MRI; (3) the age lies between 18 and 45; (4) no history of using electroconvulsive treatment; (5) right-handed; (6) there is no family history of bipolar disorder, meaning that neither first-degree nor second-degree relatives have been affected by the condition. Healthy controls were enrolled from the community and university by advertisement. The education level and age of patients and healthy controls were matched. Potential healthy controls were ruled out if they had any neurological disorders,
psychosis symptoms, or substance abuse. Potential controls were also ruled out on the condition that their first-degree relatives had a history of mental illness. The exclusion criteria for all participants were: (1) meeting DSM-5 diagnostic criteria of other psychiatric disorders; (2) past or present physical illness; (3) pregnancy; (4) cerebral structure abnormalities following initial MRI scanning; (5) contraindications for MRI scan. All subjects were right-handed and Han Chinese with >9 years of education.

The study was approved by the Medical Research Ethics Committee of Renmin Hospital of Wuhan University (WDRY2022-K195) and was executed consistent with the Helsinki Declaration. All subjects offered their written informed consent. Moreover, this study was registered in the China Clinical Trial Registration Center (https://www.chictr.org.cn/index.aspx) (ChiCTR220064938).

2.2. Neuropsychological assessment

The Hamilton Depression Scale-17 (HRSD-17) was used to assess severity of depressive symptoms (Sun et al., 2017); Hamilton Anxiety Scale (HAMA) was applied to assess anxiety state for all participants (Dai et al., 2022), and the Chinese version of Perceived Deficits Questionnaire (PDQ) was applied to assess cognitive performance (Shi et al., 2017). The Young Mania Rating Scale (YMRS) was used to assess symptomatic severity in the patients at baseline and after 8 weeks of treatment (Patel et al., 2007). In this study, all the subjects were evaluated by two trained psychiatry doctoral students in the same environment with a full set of neuropsychological tests.

2.3. Image acquisition and data preprocessing

All individuals, were scanned by two technicians with professional licenses in the MRI scanning facility on an Achieva 3T-MRI scanner (GE, SIGNA Architect). Individuals were asked to lie down and close their eyes but remained awake throughout the scan. See Supplementary material for detailed scanning parameters and preprocessing procedures.

2.4. Frontoparietal network identification

Spatial independent component analysis (ICA) uses the group ICA tool to identify the FPN components in the template from the Group-ICATv4.0a toolbox for BD patients and HCs. The FPN mask included the bilateral inferior orbit-frontal gyrus, inferior oper-frontal gyrus, middle frontal gyrus, inferior parietal lobule and middle cingulate gyrus (Fig. 1S). Detailed description of analysis and statistical procedures of ICA can be found in the Supplementary material.

2.5. NH analysis

An in-house MATLAB2013b script was used to calculate NH. FPN masks were used to establish correlation coefficient values when comparing a given voxel to all other voxels, after which z-transformation was performed to convert these coefficients into z values with the goal of normalizing the resultant data. These values were then used to facilitate NH mapping, with transformed z-maps then being used for group comparisons. During the NH analysis, age, gender, and years of education were entered as covariates in the group comparisons. The framewise displacement value for each participant was also used as a covariate in the group comparisons due to the fact that head micro-motion might affect brain signals from volume to volume.

2.6. Statistical analysis

We performed one-way analysis of variance (ANOVA) to analyze the group differences in age, years of education across the three groups by using SPSS22.0 and two-sample t-test was employed to analyze the differences in illness duration, YMRS, HRSD-17, HAMA, PDQ scores between the two different groups of BD patients. The chi-square test was employed to analyze gender distributions between groups. Paired t-test was used to analyze the differences in YMRS at baseline and after 8 weeks of treatment. Analysis of covariance (ANCOVA) was executed to compare differences across the three groups on voxel-based NH maps with age, gender, years of education, and framewise displacement as covariates. Then, post hoc t-tests were executed to compare NH differences between groups. Gaussian random field theory (GRF) was employed to correct multiple comparisons through using REST_V1.8 at p < 0.01 (voxel significance: p < 0.01, cluster significance: p < 0.01).

2.7. Correlation analysis

Once apparent group differences were found, we defined the resultant brain regions as regions of interest (ROIs) and extracted their mean z values to detect the correlations between abnormal NH and clinical features (YMRS, HRSD-17, HAMA, PDQ scores, and illness duration) in BD patients. The results were corrected through the Benjamini-Hochberg correction method at p < 0.05.

2.8. Support vector machine analyses

Support Vector Machine (SVM) is a popular machine learning method for classification. Using a Library for SVM V3.1 (LIBSVM V3.1) software package in MATLAB2013b (MathWorks, USA), the SVM approach was applied to test the feasibility and effectiveness of abnormal NH values distinguishing BipM patients from rBD patients, BipM patients from HCs, and rBD patients from HCs. In the study, the method of “leave - one - out - test” was applied to validate the results. SVM analysis was employed to test the capacity for the extracted NH in abnormal brain regions (BipM vs rBD) to discriminate BipM patients from the rBD, (BipM vs HCs) to discriminate BipM patients from HCs, and (rBD vs HCs) to discriminate rBD patients from HCs, through applying the LIBSVM V3.1 software package. Detailed description of SVM procedures in Supplementary material.

2.9. Support vector regression (SVR) analysis

LIBSVM was applied to examine whether NH values could be used to predict treatment efficacy (Chang and Lin, 2011). A SVR method was used to predict treatment efficacy measured by reduction ratio (RR) of YMRS total scores. The RR of the YMRS total scores was calculated using the following formula: \( RR = \frac{(YMRS_{total,0} - YMRS_{total,bw})}{YMRS_{total,0}} \). YMRS_{total,0} is the YMRS Total Scores at baseline, and YMRS_{total,bw} refers to the YMRS total scores after 8 weeks of treatment. See Supplementary material for detailed description of analysis of SVR procedures.

3. Results

3.1. Demographic and clinical characteristics

Ten BipM patients were excluded due to following factors: two due to excessive head movement; 2, misdagnosis found during follow-up; 2, comorbid sex identity disorder; 2, brain organic diseases; 2, unable to persist in scanning. Two further rBD patients were ruled out due to the fact that they were finally diagnosed as major depressive disorder after follow-up. Four HCs were excluded because their head motion was >2 mm in x, y, or z direction, and they did not consent to rescanning. Finally, a total of 38 BipM patients, 28 rBD patients and 60 HCs were enrolled in the analysis (Fig. 1). No statistically significant differences were revealed in education level and age across three groups, and there was no apparent difference in illness duration and PDQ scores between BipM patients and rBD patients. However, the three groups displayed significant differences in gender, and the two groups between BD showed significant statistical differences in YMRS, HRSD-17, and HAMA.
After 8 weeks of treatment, the patients exhibited significant improvement in the YMRS total scores and the total scores relative to the baseline scores (p < 0.01) (Table 1).

### 3.2. Group differences in NH

We first investigated the NH in the FPN across the groups. ANCOVA displayed significant NH differences in the right inferior orbit-frontal gyrus and inferior temporal gyrus, left inferior oper-frontal gyrus and middle frontal gyrus, and bilateral inferior parietal lobule and middle cingulate gyrus across groups (Fig. 1S). Relative to HCs, BipM patients displayed significant NH increase in the left middle frontal gyrus (MFG), while rBD patients displayed significantly higher NH increase in the right inferior parietal lobule (IPL). Compared with rBD patients, BipM...
patients showed significantly lower NH in the right IPL (Table 2 and Fig. 2).

### 3.3. Correlation results

Then, the increased NH in the right IPL (rBD vs HCs) was positively associated with the illness duration in the rBD patients (Fig. 3). No correlations were found between decreased NH in any resultant clusters and scales scores.

### 3.4. SVM results

Finally, we use SVM to analyze the NH value of the difference between groups. The NH in the left MFG (BipM vs HCs) displayed an accuracy of 69.70 %, a sensitivity of 68.42 %, and a specificity of 80.00 % (Fig. 4A). The NH in the right IPL (rBD vs HCs) displayed an accuracy of 73.86 %, a sensitivity of 71.43 %, and a specificity of 95.00 % (Fig. 4B). Discrimination of BipM vs rBD displayed an accuracy of 77.55 %, a sensitivity of 57.89 %, and a specificity of 91.67 % (Fig. 4C). The detailed description of the SVM results is provided in Table 3.

### 3.5. SVR results

The NH values in the left MFG at baseline could be used to predict early treatment response of the patients with BipM. The SVR results showed positive correlations between the actual and predicted RRs in the total score of YMRS ($r = 0.466$, $p < 0.01$, Fig. 5).

### 4. Discussion

Using the NH approach, we provided an unbiased survey of the FPN in BipM, rBD patients, and HCs to explore the pathological neuro-imaging mechanism of BD patients and find potential biomarkers to differentiate BipM, rBD and HCs. Our principal finding was that, compared with the HCs, BipM patients displayed increased NH in the left middle frontal gyrus (MFG), and rBD patients displayed increased NH in the right inferior parietal lobule (IPL). Compared with rBD patients, BipM patients displayed reduced NH in the right IPL. Furthermore, a positive correlation was observed between the increased NH values in the right IPL (rBD vs HCs) and illness duration in rBD patients. In addition, support vector machine results supported that the observed decreased NH in the right IPL could be used as a candidate biomarker to predict rBD patients switching to BipM patients, and the increased NH values of the left MFG as a potential predictor of early treatment response in patients with BipM.

Increased self-awareness, impaired cognition, and emotional instability were reported as the core psychopathology of BD patients, characterized by increased self-awareness, reduced attention to environmental phenomena, and high and low emotions (Chakrabarty et al., 2022; Huang et al., 2022). The enhanced self-awareness is attributed to the negative emotions towards oneself and the cognitive processing towards oneself. The MFG is considered to be the key region of the FPN, which can directly affect the cognitive function of the human body and indirectly affect the limbic system to impair the emotional regulation of the human body (Lorenz et al., 2018). Therefore, we speculate that the increased NH in the left MFG may affect the function
of this region and disrupt the coordination between the frontal lobe, parietal lobe and limbic system. This may affect the emotional and cognitive deficits observed in BD patients (LeDoux, 2000). In addition, the MFG shows high connection strength, which can distinguish patients experiencing a manic episode from schizophrenia patients (Zhang et al., 2021b). Another study found that the functional connection between the frontal lobe and lingual gyrus was related to the expression of HRF and DRD2 genotype (Yan et al., 2022). These results indicated that the MFG is involved in the pathological neuroimaging mechanism of manic episodes in patients. Consistent with these findings, the NH value of the left MFG in this study can be used as a candidate marker with relatively high sensitivity and specificity to distinguish BipM patients from HCs. Furthermore, support vector regression results in the study exhibited a significant association between predicted and actual symptomatic improvement based on the reduction ratio of the YMRS total scores in patients with BipM. It indicated that NH values of the left MFG may predict early treatment response in patients with BipM.

The parietal lobe is involved in the comprehensive sense of local body. The IPL is a core part of the parietal lobe, which is considered to be the basis of the higher-order process of sensory input, multisensory and sensorimotor integration, spatial attention, intention, and the joint representation of external space and body (Revah et al., 2022).
can be attributed to different analytical methods used in the study. It is used as a candidate biomarker to predict switching to mania in rBD used SVM to analyze the NH value of this abnormal IPL and found that prediction for treatment response (Ji et al., 2019; Jiang et al., 2020). We structures, which can be observed to provide diagnosis and prognosis wide network of frontal, temporal, parietal, occipital, and subcortical DMN networks (Gong et al., 2021). In addition, IPL is a key node in a brain network analysis observed low connectivity between the FPN and inconsistent, which may be caused by different analysis methods, sample size, and from a single center, was used in the study. Secondly, this study focused on the FPN, which can clarify the pathophysiological contribution of this network. However, relevant findings in other brain regions may have been ignored. Thirdly, although patients with rBD have not taken medication for two weeks, patients with BipM were all taking medication. It is difficult to rule out the interference of medication. In addition, patients with BipM take different mood stabilizers, which will also have an impact on predicting the curative effect despite our covariate treatment of different drugs. We will try our best to eliminate these differences in future research. Finally, the gender ratio may have a certain effect in the study (Jiang et al., 2021; Popel et al., 2021). Although we used covariant processing in the analysis of data, it is better for us to collect gender matched subjects in future research.

5. Conclusion

The current study's results showed abnormal NH values in the FPN in patients with BD. These abnormalities can be used as candidate biomarkers to distinguish BipM/rBD patients from healthy controls, and predict the switching of rBD mania to BipM patients. Therefore, the results highlight the importance of the FPN in the pathophysiology of BD. Furthermore, these aberrant NH values could serve as potential neuroimaging biomarkers for predicting early treatment response in patients with BipM.

CRediT authorship contribution statement

Authors Yujun Gao: Conceptualization, Methodology, Investigation, Statistical Analysis, Writing - Original Draft.
Author Xin Guo: Data Curation, diagnosing and treatment, Investigation, Statistical Analysis.
Author Sanwang Wang and Zhengyuan Huang: Data collecting, Visualization, Investigation and follow up.
Author Yi Zhong: Software, Visualization.
Author Chao Weng: Visualization, Statistical Analysis.

Table 3

Differentiate two patient groups and HCs by using the NH values of a single region with the SVM method.

<table>
<thead>
<tr>
<th>Cluster location</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BipM VS HCs Left MFG</td>
<td>77.55 % (76/98)</td>
<td>57.89 % (22/38)</td>
<td>91.67 % (55/60)</td>
</tr>
<tr>
<td>BipM VS HCs Right IPL</td>
<td>73.86 % (65/88)</td>
<td>71.43 % (20/28)</td>
<td>95.00 % (57/60)</td>
</tr>
<tr>
<td>BipM VS rBD Left MFG</td>
<td>69.70 % (46/66)</td>
<td>68.42 % (26/38)</td>
<td>80.00 % (32/40)</td>
</tr>
</tbody>
</table>

SVM = support vector machines; BipM = bipolar mania; rBD = remitted bipolar disorder; HCs = healthy controls; NH = network homogeneity.

Considering that clinical characteristics such as illness duration and scale score are related to abnormal nodal strength and nodal efficiency in the FPN (Wang et al., 2020), we predict that the homogeneity of abnormal FPN is related to the clinical variables of BD patients. However, our study showed that abnormal FPN homogeneity was not related to clinical variables, which was unexpected. These inconsistent findings can be attributed to different analytical methods used in the study. It is also possible that these abnormal NH values are independent of the specific markers of these symptoms and are not affected by these factors. In addition, our study found that the increased right IPL homogeneity in rBD patients was positively correlated with the illness duration. NH is a voxel measurement which can be used to evaluate the correlation between voxels and all other voxels in the FPN. When damaged to a certain extent, its brain function has a certain degree of compensation. It shows that the compensatory increase of right IPL impairment in rBD patients is related to the duration of the disease.

This study should note several limitations. Firstly, a relatively small sample size, and from a single center, was used in the study. Secondly, we used covariant processing in the analysis of data, it is difficult to rule out the interference of medication. In addition, patients with BipM take different mood stabilizers, which will also have an impact on predicting the curative effect despite our covariate treatment of different drugs. We will try our best to eliminate these differences in future research. Finally, the gender ratio may have a certain effect in the study (Jiang et al., 2021; Popel et al., 2021). Although we used covariant processing in the analysis of data, it is better for us to collect gender matched subjects in future research.

Fig. 5. Visualization of the SVR results in the patients with BipM. Left: 3D view of the regressed performance with the best parameters \((c = 0.04, g = 4, \text{and MSE} = 0.32672)\). Right: a positive correlation was observed between actual and predicted individual ratio of changes in the YMRS total scores. Diagonal line suggests the association between actual and predicted individual ratio of changes in the YMRS total scores in the patients; SVR = support vector regression; BipM = bipolar mania; YMRS = Young Mania Rating Scale; MSE = mean squared error.
Author Haibo Wang: MRI scanning.
Author Yunfei Zha: MRI checking.
Author Han Zhang: Visualization, Investigation.
Author Gaohua Wang: Data Curation, diagnosing and treatment.
Author Jie Sun, Lin Lu, and Gaohua Wang (Corresponding Author): Conceptualization, Funding Acquisition, Resources, Supervision, Writing - Review & Editing.
All the authors agree with the contribution and author ranking of the paper.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.07.033.

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