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ORIGINAL RESEARCH

Functional Brain Activity Alterations in Type 1 Narcolepsy Patients with Anxiety and Depression: A 7-Tesla Resting State-Functional Magnetic Resonance Imaging Study

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Purpose: This study aimed to investigate abnormal changes in brain region functional activity in type 1 narcolepsy (NT1) patients comorbid with anxiety and depression.

Methods: Twenty NT1 patients and 20 healthy controls (HCs) underwent subjective/objective sleep assessments (polysomnography, SAS, SDS) and 7T rs-fMRI to analyze regional homogeneity (ReHo) and fractional amplitude of low-frequency fluctuations (fALFF).

Results: Compared with the HCs group, NT1 patients had higher SAS and SDS scores. Analysis of the correlation between sleep parameters and brain activity in NT1 patients showed that increased ReHo values in the right insula and right cerebellum were negatively correlated with the TST ($r = -0.463$, $p = 0.040$) and excessive day time sleepiness ($r = -0.486$, $p = 0.041$). The fALFF of the left lingual gyrus positively correlated with sleep efficiency ($r = 0.582$, $p = 0.007$). Additionally, altered brain activity in NT1 patients was associated with emotional disorders. ReHo and fALFF values of the right insula showed a positive correlation with SAS scores (ReHo: $r = 0.583$, $p = 0.011$; fALFF: $r = 0.557$, $p = 0.016$), and the fALFF value of the left postcentral region also correlated positively with SAS scores ($r = 0.597$, $p = 0.009$). Moreover, the ReHo values of the left and postcentral lingua were positively correlated with the SDS scores (left lingua: $r = 0.478$, $p = 0.045$; postcentral lingua: $r = 0.499$, $p = 0.035$). The fALFF values of the left occipital inferior and postcentral regions also exhibited positive correlations with the SDS scores (left occipital inferior: $r = 0.541$, $p = 0.020$; postcentral regions: $r = 0.550$, $p = 0.018$).

Conclusion: Abnormalities of rs-fMRI activities in NT1 patients, particularly those in the insula, calcarine, lingual gyrus, and postcentral regions, were closely associated with sleep disturbance and emotional disorders. These findings provide a better understanding the pathophysiology of NT1 with emotional disorders. Future longitudinal studies with independent cohorts are needed to explore the underlying neural mechanisms for neuropsychiatric comorbidities in NT1.

Keywords: narcolepsy, sleep, anxiety, depression, brain functional activity

Introduction

Narcolepsy is a rare but lifelong chronic and disabling neurological sleep disorder characterized by excessive daytime sleepiness and cataplexy in the majority of individuals.[1,2] Narcolepsy is estimated to affect 25–50 people per 100, 000 in various nations worldwide, with a higher prevalence in males.[3,4] Most patients develop symptoms at the age of 5–40 years, with two peaks at ages 15 and 35 years.[3,5] This disease is classified into two subtypes based on whether patients have cataplexy, a sudden brief episode of partial or complete paralysis triggered by strong emotions.[1,4] Cataplexy is

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experienced by patients with type 1 narcolepsy (NT1) but does not occur in type 2 narcolepsy. NT1, also called "narcolepsy-cataplexy", is caused by damage of the hypothalamus, resulting in decreased production of hypocretin/orexin.[6] Type 2 narcolepsy does not have hypocretin/orexin deficiency and its cause remains unknown.[6,7] In addition, NT1 patients exhibit many accompanying sleep-wake symptoms due to abnormal rapid eye movement (REM) sleep, including sleep paralysis, hypnagogic hallucinations, frequent dreams, and disrupted nighttime sleep.

A prominent manifestation of narcolepsy is its association with several comorbidities such as overweight, autonomic disturbance, metabolic diseases, cardiac problems, and psychiatric disorders. Notably, psychiatric comorbidities such as anxiety and depression are more prevalent in narcoleptic patients than in the general population. The coexistence of anxiety disorders in narcolepsy ranges from 21% to 53%, and the time course of the different types of anxiety disorders may vary in patients with narcolepsy.[8–11] Depression is one of the most commonly reported symptoms of narcolepsy patients. The occurrence of depression in narcolepsy ranges from 27.4% to 56.9%, and is more prone to suicidal tendencies.[9,12,13] Moreover, patients of NT1 also presented moderate-to-severe hopelessness and higher scores for suicidal thoughts, which were closely associated with anxiety and depression.[14] Notably, the comorbidities of psychiatric disorders were higher in children and younger patients than in older patients.[1,2] The use of medication for the treatment of psychiatric disorders is higher in patients.[1,2] Thus, narcolepsy, in combination with psychiatric disorders, presents a challenge both clinically and in the families of patients. However, the mechanisms underlying these psychiatric disorders remain unclear.

Due to the rapid advancement of neuroimaging techniques, magnetic resonance imaging (MRI) has become an essential method for neuroimaging evaluation, playing a growing role in the research of neuropsychiatric illnesses.[15] Using functional brain imaging, previous studies have found several abnormal brain network activities in NT1. These studies showed that changes of brain network activities were only restricted in the hypocretin/orexin neurons containing hypothalamus, but also a wide array of brain regions. These regions include the sleep/wakefulness related brainstem, midbrain, and thalamus; attention and cognition related hippocampus, amygdala, and prefrontal cortex; emotional processing related with limbic system.[16–18] Despite growing evidence revealed changes of brain functional activities in NT1 patients, few studies have examined these changes with the comorbid anxiety and depression. Meanwhile, the utilization of ultra-high field (UHF) MRI enhances spatial resolution. Consequently, this study posits the hypothesis that the examination of brain functional activities through UHF-MRI may yield more significant insights into NT1 associated with emotional disorders.

Thus, the present study investigated changes in brain functional activity in NT1 patients with comorbid anxiety and depression using 7-tesla (7T) rs-fMRI. In this preliminary exploratory study of 7T resting-state fMRI in NT1, we employed two fundamental and robust metrics: regional homogeneity (ReHo) and fractional amplitude of low-frequency fluctuations (fALFF). They were well established for investigating localized functional alterations and exhibit a complementary relationship. In addition, correlation analysis was performed to examine the relationships between functional abnormalities of specific brain regions and sleep disorders, anxiety, and depression symptoms.

Materials and Methods

Participants

This study enrolled 20 patients diagnosed with NT1 from the Sleep Psychology Center at Chongqing Fifth People's Hospital, serving as the study group. The inclusion criteria for NT1 were in accordance with the International Classification of Sleep Disorders-3rd edition (ICSD-3). These criteria include (a) excessive daytime sleepiness lasting more than ≥3 months; (b) cataplexy with a multiple sleep latency test (MSLT) latency of ≤8 minutes and ≥2 sleep-onset rapid eye movement periods (SOREMPs). These symptoms and test results were all assessed and diagnosed by clinicians to ensure the accuracy and reliability of the diagnosis. Among the enrolled patients, 17 were initially diagnosed with NT1 and therefore had no prior medication history. The rest 3 patients had prior exposure to medications. Twenty HCs were recruited for the study. All participants were assessed using the Narcolepsy Severity Scale (NSS),[19] Insomnia Severity Index (ISI),[20] Self-rating Anxiety Scale (SAS),[21] and the Self-rating Depression Scale (SDS).[22] Written informed consent was obtained from the legal guardians of all minor participants with NT1, and assent was also secured from the minors

themselves, in accordance with the approval of the Ethics Committee of the Fifth People's Hospital of Chongqing (Approval No. 2024CQSDURMYYEC-008). The study adhered to the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all participants.

Subjective Sleep Measurements

To evaluate the subjective aspects of sleep and related symptoms, we used several standardized scales. NSS was used to assess the severity of narcolepsy symptoms, with higher scores indicating greater severity (mild: NSS ≤ 10; moderate: 11 < NSS < 16; severe: NSS ≥ 16). ISI was used to evaluate the severity of insomnia and its impact on daily life, with scores ranging from 0 to 28, with higher scores indicating more severe insomnia.

The SAS and SDS were administered to measure the frequency of anxiety and depressive symptoms, respectively, with each item scored from 0 to 4. Higher scores reflected more severe anxiety and depression.

Objective Sleep Measurements

For objective sleep assessments, the patients underwent polysomnography (PSG) at the sleep center. The analysis was conducted by certified technicians following the standards of the American Academy of Sleep Medicine (AASM) standards. The key parameters measured included the total sleep time (TST), sleep efficiency (SE), sleep latency (SL), REM sleep latency, and sleep stage percentages (N1%, N2%, SWS%, and REM%). Furthermore, the MSLT was conducted to assess daytime sleepiness through a series of 20-minute nap opportunities during the day. The average sleep latency and occurrence of REM sleep were recorded. Patients with NT1 typically exhibit a short latency and two or more SOREMPs.

Image Acquisition

All imaging data were collected using a 7T MRI scanner (MAGNETOM Terra, Siemens Healthineers, Erlangen, Germany) equipped with a 1Tx and 32Rx Nova Head Coil (Nova Medical, Wilmington, MA, USA). Participants were instructed to remain relaxed and awake with their eyes closed during the scan. Foam pads were used to minimize the head movement and scanner noise. Initially, a Fluid Attenuated Inversion Recovery (FLAIR) sequence scan was conducted to exclude the presence of any potential intracranial lesions, with the following imaging parameters: repetition time (TR) = 9000 ms, inversion time (TI) = 2600 ms, echo time (TE) = 96 ms, flip angle (FA) = 120°, slice thickness = 3 mm, voxel size = 0.7 × 0.7 × 3 mm^3, and scan time = 3 min 9 s. Subsequently, a T1-weighted Magnetization Prepared with 2 Rapid Acquisition Gradient Echoes (T1-MP2RAGE) sequence was collected using the parameters listed below: TR = 4300 ms, TE = 2.3 ms, slice thickness = 0.65 mm, TI1 = 1000 ms, TI2 = 3200 ms, FA1 = 4°, FA2 = 4°, bandwidth = 200 hz/pixel, acceleration factor = 3, voxel size = 0.65 × 0.65 × 0.65 mm^3, and scan time = 10 min 16s. Finally, resting-state fMRI (rs-fMRI) data were obtained using an echo-planar imaging (EPI) sequence with the following parameters: TR = 2000 ms, TE = 21.0 ms, slice thickness = 1.5 mm, FA = 90°, bandwidth = 1698 hz/pixel, acceleration factor = 2, voxel size = 1.5 × 1.5 × 1.5 mm^3, slices = 90, measurements = 240, and scan time = 8 min 16s.

Image Postprocessing

The rs-fMRI data were preprocessed with DPABI_V8.0 (http://rfmri.org/dpabi) using MATLAB 2022b (MathWorks). For each participant, the preprocessing steps included the following: (a) removal of the first 10 volumes; (b) correction for slice timing; (c) correction of head motion (participants with a maximum translation in any direction >1.5 mm and a maximum rotation >1.5°were excluded); (d) regression of nuisance covariates, which encompassed the Friston 24 motion parameters, global mean signal, white matter (WM) signal, and cerebrospinal fluid (CSF) signal; and (e) spatial normalization to the Montreal Neurological Institute (MNI) space using the DARTEL method (resampling voxel size was 1.5 × 1.5 × 1.5 mm^3). To avoid the artifacts of head motion, participants with a maximum translation in any direction >1.5 mm and a maximum rotation >1.5° were excluded for further data analysis.

Calculation of ReHo and fLAFF

ReHo and fALFF values were estimated using DPABI software. For the ReHo estimation, time-series data were initially filtered using a bandpass filter ranging from 0.01 0.1 hz. The ReHo value for each voxel was subsequently determined as the Kendall concordance coefficient (KCC) of the time series for a given voxel and its 26 nearest neighbors.[23] The resulting ReHo map was normalized to the global mean ReHo value, and all ReHo maps were spatially smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 3 mm. To calculate the fALFF, spatial smoothing was performed with a 3 mm FWHM Gaussian kernel. The power spectrum of each voxel was computed, followed by the squaring of the power spectrum for each frequency. The average power within the frequency range of 0.01–0.1 hz was calculated to derive the ALFF value. The fALFF value was subsequently obtained by summing the squared power spectrum across the specified frequency range and dividing this sum by the total sum of the squared power spectrum across the entire frequency band.[24] Finally, the individual ReHo and fALFF maps were standardized into z-score maps by subtracting the mean and dividing it by the standard deviation of the entire map. Statistical analysis of ReHo and fALFF values was performed using DPABI software, with a two-sample *t*-test conducted to examine voxel-wise differences between the NT1 and HC groups. Multiple comparison corrections were applied using the Gaussian random field correction (GRF) method (voxel-level $P < 0.001$ and cluster-level $P < 0.05$).

Statistical Analysis

The Shapiro–Wilk test was conducted using SPSS version 21 to assess the normality and homoscedasticity of all variables. Normally distributed data were compared between the two groups for age and scores on NSS, SDS, SAS, and ISI using independent sample t-tests. The chi-square test was used to compare sex data, with the significance level set at $P < 0.05$, and results were described using the mean ± standard deviation (SD). Additionally, we employed the SPM12 toolbox in MATLAB for the statistical analysis of imaging data, using age, sex, and head motion values as covariates. Two-sample t-tests were used to compare the differences in the ReHo and fALFF values between the two groups. Considering that the present study is a preliminary exploratory investigation with a small sample size, the selection of correction method aims to yield more meaningful results while satisfying the requirements for multiple comparison correction and thereby guiding subsequent research and potential treatment approaches. Thus, corrections were made using cluster-level Gaussian random field (GRF) correction, achieving a corrected significance level of $P < 0.05$. In SPSS, correlation analysis was applied to compare the significantly changed brain regions in the NT1 group MRI (rs-fMRI) with sleep monitoring data, and partial correlation analysis was applied to compare the scores on the subjective assessment scales, including ISI, SDS, SAS, and NSS scores. Age and years of education were adjusted for as covariates.

Results

General Data, Sleep and Emotional Symptoms in NT1 Patients

Demographic assessment reveals that individuals with NT1 and HCs were comparable in gender distribution, age, and education background. Notably, patients in the NT1 group had a higher BMI (Table 1) than those in the HCs, consistent with previously published reports.[25] The narcolepsy severity scale (NSS) score of NT1 group was 32.3 ± 8.54, pointing to a severe condition of NT1 (mild: $NSS \leq 10$; moderate: $11 < NSS < 16$; severe: $NSS \geq 16$). In addition, NT1 patients not only experienced cataplexy but also experienced excessive daytime sleepiness (EDS), hallucinations, sleep paralysis, and disrupted nocturnal sleep (DNS).

In the subjective sleep assessment, the NT1 group exhibited more severe insomnia, as measured using the insomnia severity index (ISI). For objective sleep parameters measured using polysomnography (PSG), NT1 patients (Table 2) showed a longer mean total sleep time (TST) than HCs did. The sleep efficiency of NT1 patients was markedly lower than that of the HCs. In addition, the NT1 group had a significantly higher percentage of N1 sleep and a lower percentage of N2 sleep, suggesting a disrupted sleep architecture in NT1.

The mean sleep latency (SL) and mean REM sleep latency (RSL) are important parameters in the multiple sleep latency test (MSLT) for the diagnosis of NT1. The NT1 patients exhibited a mean SL of 3.52 ± 1.98 minutes, within the normal range of SL (<8 minutes). However, the mean RSL of NT1 patients was 4.34 ± 2.95 minutes, which was

Table 1 Demographics Assessment Results of NT1 Patients and HCs

	NT1 (n=20)	HC (n=20)	t/Z value	*P* value
Sex, male (n%)	13 (65)	12 (60)	0.11	0.74
Age	22.95±9.03	22.85±6.34	0.04	0.97
Education	12 (9.25,16)	15 (11,16)	13.04	0.17
BMI	24.31±3.45	22.00±2.88	0.27	0.02*
Duration	8.45±5.30	–	–	–
NSS	32.30±8.54	–	–	–
NSS - EDS	17.85±2.41	–	–	–
NSS - cataplexy	7.75±3.06	–	–	–
NSS - hallucinations	3(0, 5.00)	–	–	–
NSS - sleep paralysis	3(0, 5.75)	–	–	–
NSS - DNS	1(0, 2.00)	–	–	–

Note: *, P<0.05.
Abbreviations: NT1, narcolepsy type 1; HCs, healthy controls; BMI, body mass index; NSS, the Narcolepsy Severity Scale; EDS, excessive daytime sleepiness; DNS, disrupted nighttime sleep.

Table 2 Comparison of Sleep Indicators Between NT1 Patients and HCs

Sleep Indicator	NT1 (n=20)	HC (n=20)	t/Z value	*P* value
ISI	10.9±6.42	3.50±2.74	4.74	0.00**
TST (min)	473.95±65.28	441.85±25.58	2.05	0.05*
Sleep efficiency (%)	82.55±7.84	94.60±2.79	−6.48	0.00**
SL (min)	8.73±9.81	12.55±8.22	−1.34	0.19
REM SL (min)	105.05±91.14	109.93±45.11	−0.21	0.83
N1 (%)	20.10±13.21	12.87±5.22	2.28	0.03*
N2 (%)	39.31±12.42	54.75±5.33	−5.11	0.00**
N3 (%)	21.50±13.08	15.55±1.91	2.01	0.05
REM (%)	19.08±7.42	16.83±4.63	1.15	0.26
AHI	2.27±4.84	2.41±1.64	−0.13	0.90
SOREMPs	3(2.00,4.00)			
Mean SL (min)	3.52±1.98			
Mean REM SL (min)	4.34±2.95			

Notes: * P<0.05; ** P<0.01.
Abbreviations: NT1, narcolepsy type 1; HC, healthy controls; ISI, insomnia severity index; TST, total sleep time; SL, sleep latency; REM SL, rapid eye movement (REM) sleep latency; N1, non-rapid eye movement sleep stage 1; N2, non-rapid eye movement sleep stage 2; N3, non-rapid eye movement sleep stage 3; AHI, apnea-hypopnea index; SOREMPs, sleep-onset REM periods (REM sleep stage ≤ 15 min from sleep onset during daytime naps).

significantly lower than the normal threshold of 15 minutes. Consistent with previous findings,[1,2] these data suggested that NT1 patients had slightly shorter NREM sleep and REM onset latencies.

Partial Correlation Analysis Between Sleep Parameters and Anxiety/Depression in NT1 Patients

The SAS and SDS scales were used to assess anxiety and depression levels in NT1 patients and HCs. Compared with the HC group, NT1 patients exhibited significantly increased SAS and SDS scores (Figure 1). Next, a partial correlation analysis was employed to investigate the association between objective sleep parameters and anxiety and depression in NT1 patients. TST and sleep efficiency were negatively correlated with SAS scores (Figure 2a–c, TST: $r = -0.479$, $P = 0.044$; sleep efficiency, $r = -0.505$, $P = 0.033$). These findings indicated that reduced sleep duration and efficiency are associated with increased anxiety.

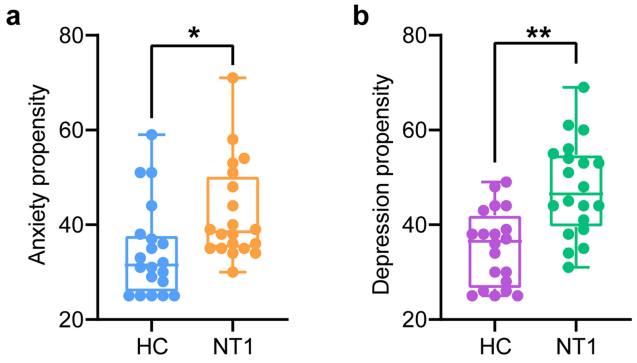

Figure 1 Comparison of anxiety and depression in NT1 patients and HC. (**a**) Anxiety probability between HCs and NT1 patients measured using SDS. (**b**) Depression probability between HCs and NT1 patients measured using SAS. Error bars represent standard deviation. * P<0.05; ** P<0.01.

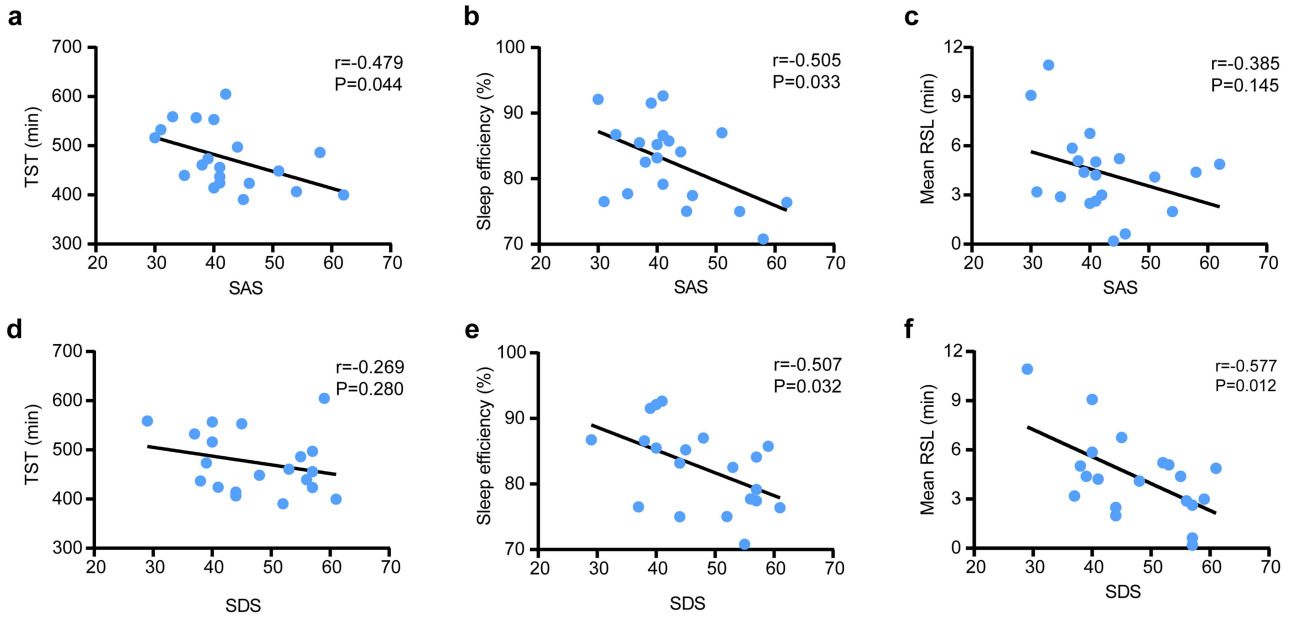

Figure 2 Partial correlation analysis between sleep and anxiety/depression symptoms in NT1 patients. (**a–c**) Correlation of TST (**a**), sleep efficiency (**b**), or mean RSL (**c**) with SAS in NT1 patients. (**d–f**) Correlation of TST (**d**), sleep efficiency (**e**), or mean RSL (**f**) with SDS in NT1 patients.

The correlation between TST and SDS scores was not significant (Figure 2d, r = −0.269, P = 0.280). However, sleep efficiency demonstrated a significant negative correlation with SDS scores (Figure 2e, r = −0.507, P = 0.032), suggesting that poor sleep efficiency may lead to depressive symptoms. In addition, a negative correlation was observed between mean RSL and SDS scores (Figure 2f, r = −0.577, P = 0.012), indicating that shorter REM latency was significantly associated with higher levels of depression.

Brain Regions with Significant Differences Between NT1 Patients and HCs

To explore the brain networks associated with sleep disturbances and emotional abnormalities in NT1, we employed high-resolution 7T MRI technology. Resting-state functional MRI (rs-fMRI) was used to compare the patients with NT1 and HCs. Brain functional activity was measured using ReHo and fALFF. ReHo assesses the temporal synchrony of neural activity among neighboring voxels, thereby reflecting local functional consistency and identifying regions with disrupted intrinsic coordination. fALFF quantifies the amplitude of low-frequency oscillations, capturing abnormal local spontaneous neuronal activity. Compared with HCs, significant differences in ReHo and fALFF values were observed in NT1 patients. NT1 patients exhibited elevated ReHo values in the left thalamus, left putamen, right medial cingulate

region, right fusiform gyrus, lingual gyrus, calcarine cortex, left inferior occipital gyrus, left superior temporal gyrus, bilateral insula, postcentral gyri, precentral gyri, paracentral lobules, and right supplementary motor area (Table 3 and Figure 3). Concurrently, increased fALFF values in NT1 patients were observed in the left cuneus, right fusiform gyrus, bilateral insula, left lingual gyrus, left inferior occipital gyrus, postcentral gyri, left supplementary motor area, and right calcarine cortex (Table 3 and Figure 4). The altered network activities in several brain regions suggest the presence of complex neurobiological substrates underlying NT1.

Partial Correlation Analysis Between Brain Activity and Sleep Parameters in NT1 Patients

The correlation between altered rs-fMRI activity and sleep symptoms in NT1 patients was analyzed. Analysis results showed that A negative correlation was observed between the ReHo value in the right insula and TST (Figure 5a, r = −0.463, P = 0.040), indicating that a longer TST was associated with a lower ReHo value in the right insula. In contrast, the ReHo value of the left calcarine was positively correlated with sleep efficiency (Figure 5b, r = 0.510, P = 0.021). In addition, the ReHo values in the right cerebellum were negatively correlated with the excessive day time sleepiness (EDS) in NSS (Figure 5c, r = −0.486, p = 0.041). The fALFF of the right insula was negatively correlated with TST

Table 3 Brain Regions with Significant Differences in ReHo or fALFF Values Between Patients in NT1 and HCs

Brain Regions	AAL Partitions	MNI Spatial Coordinates (mm)			Cluster Size	T value
		X	Y	Z		
ReHo						
Diencephalon	Thalamus L	−13.50	−18.00	7.50	146	5.81
Basal ganglia	Putamen L	−21.00	4.50	−6.00	75	5.68
Limbic lobe R	Cingulum Mid R	10.50	−9.00	45.00	77	5.86
Occipital lobe	Calcarine	−7.50	−61.50	9.00	1080	8.96
Occipital lobe	Lingual L	−7.50	−61.50	9.00	799	8.96
Occipital lobe	Occipital Inf L	−31.50	−85.50	−15.00	96	6.25
Temporal lobe	Temporal Sup L	−40.50	−31.50	7.50	205	6.15
Temporal lobe	Fusiform R	39.00	−43.50	−22.50	61	5.38
Temporal lobe	Insula L	−33.00	−28.50	19.50	99	6.05
Temporal lobe	Insula R	33.00	−24.00	13.50	63	7.27
Frontal lobe	Postcentral L	−63.00	−6.00	24.00	215	5.98
Frontal lobe	Postcentral R	63.00	−3.00	24.00	104	6.25
Frontal lobe	Precentral R	34.50	−24.00	57.00	159	6.23
Frontal lobe	Precentral L	−27.00	−27.00	52.50	68	5.82
Cerebrum	Paracentral lobule	−3.00	−27.00	57.00	549	7.46
fALFF						
Temporal lobe	Fusiform R	30.00	−52.50	−18.00	69	5.85
Occipital lobe	Occipital Inf L	−34.50	−87.00	−7.50	60	6.54
Occipital lobe	Lingual L	−24.00	−45.00	−9.00	24	6.41
Occipital lobe	Lingual L2	−13.50	−45.00	−4.50	33	7.81
Occipital lobe	Calcarine R	16.50	−48.00	−1.50	83	6.45
Temporal lobe	Temporal Sup L	−55.50	−13.50	6.00	78	6.33
Temporal lobe	Insula R2	36.00	−30.00	18.00	34	7.08
Frontal lobe	Postcentral R	64.50	−4.50	24.00	39	6.17
Frontal lobe	Postcentral L1	−49.50	−9.00	27.00	63	5.95
Frontal lobe	Postcentral R2	55.50	−7.50	37.50	50	5.87

Note: P<0.05, cluster-level FDR correction.
Abbreviations: NT1, narcolepsy type 1; HC, healthy controls; L, left; R, right; AAL, Automated anatomical labelling; MNI, Montreal Neurological Institute; x, y, z, coordinates of the main peak in the MNI space; ReHo, regional Homogeneity; fALFF, fractional Amplitude of Low-Frequency Fluctuations.

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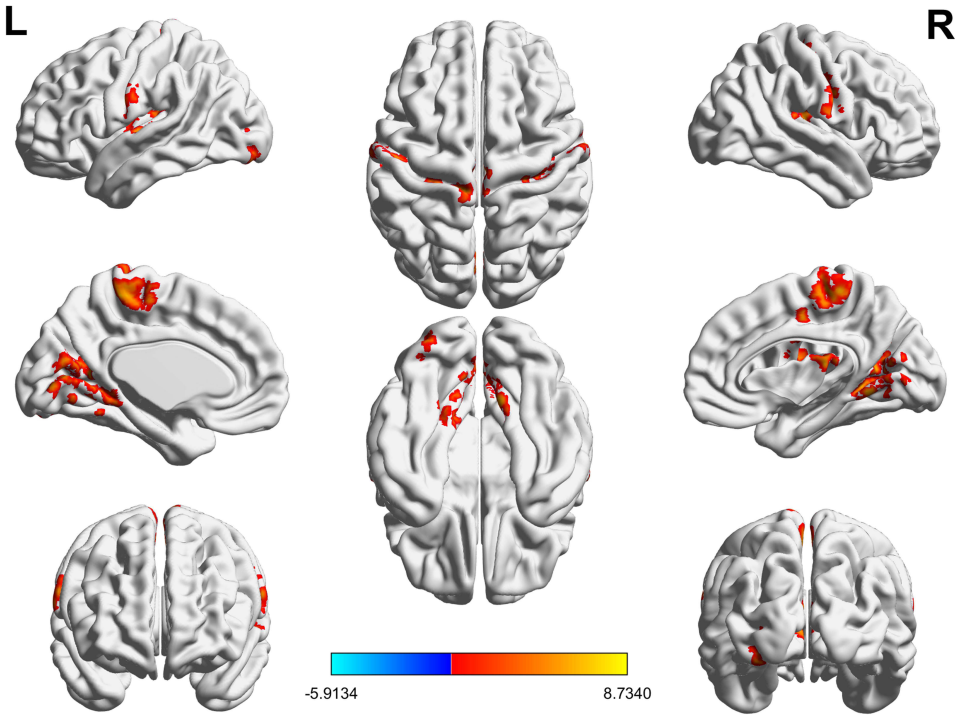

Figure 3 Highlighted brain regions with significant ReHo value differences between NT1 patients and HCs. The regions include the left thalamus, the right medial cingulate area, the lentiform nucleus, the right fusiform gyrus, the lingual gyrus, the cuneus, the left inferior occipital gyrus, the left superior temporal gyrus, bilateral insula, bilateral postcentral gyrus, bilateral precentral gyrus, bilateral precentral region, and the right supplementary motor area. Warm colors indicate that NT1 patients have higher ReHo values than HC, while cool colors indicate that NT1 patients have lower ReHo values than HC. Voxel-level $P < 0.001$, cluster level $P < 0.05$, two-tailed, corrected by GRF.

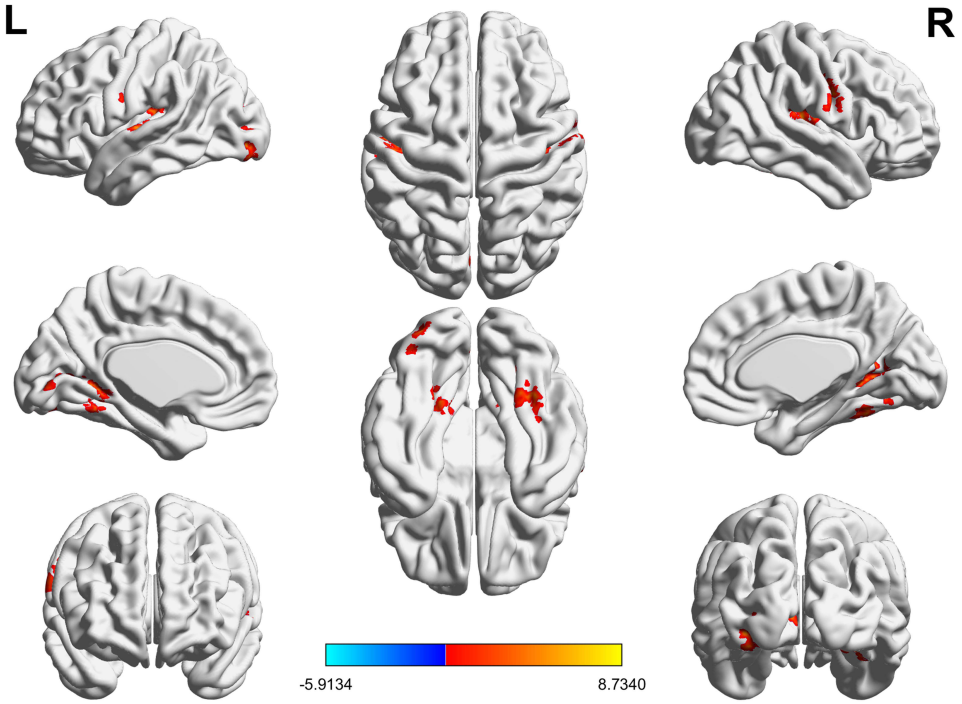

Figure 4 Highlighted brain regions with significant fALFF value differences between NT1 patients and HCs. The regions include the left cuneus, the right inferior temporal gyrus, the bilateral insula, the left lingual gyrus, the left inferior occipital gyrus, the bilateral postcentral gyrus, the left supplementary motor area, and the right calcarine fissure. Warm colors indicate that NT1 patients have higher fALFF values than HC, while cool colors indicate that NT1 patients have lower fALFF values than HC. Voxel-level $P < 0.001$, cluster level $P < 0.05$, two-tailed, corrected by GRF.

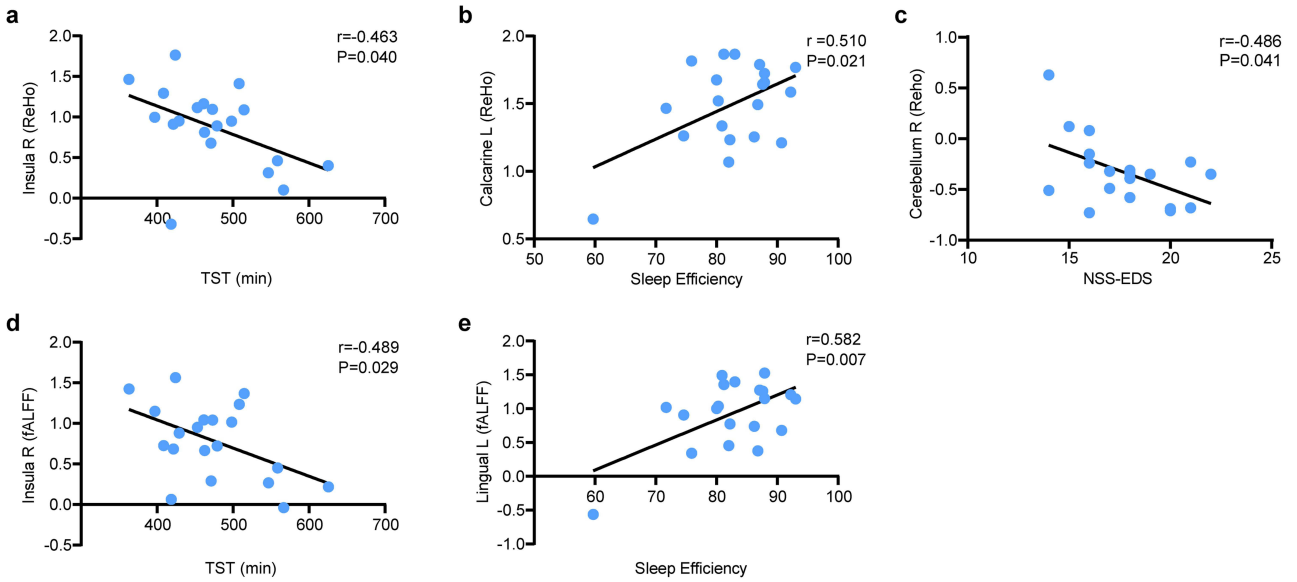

Figure 5 Partial correlation analysis between brain regional metrics and sleep parameters in NT1 patients. (**a**) Correlation between the ReHo value in the right insula and TST. (**b**) Correlation between the ReHo value in the left calcarine and sleep efficiency. (**c**) Correlation between the ReHo value in the left cerebellum and NSS-EDS. (**d**) Correlation between the fALFF of the right insula and TST. (**e**) Correlation between the fALFF of the left lingual and sleep efficiency.

(Figure 5d, r = −0.489, P = 0.029), but the fALFF of the left lingual gyrus was positively correlated with sleep efficiency (Figure 5e, r = 0.582, P = 0.007). These results suggest that abnormal activities of the right insula, left calcarine, and left lingual gyrus are associated with for the sleep symptoms of NT1 patients.

Partial Correlation Analysis Between Brain Activity and Emotional Disabilities in NT1 Patients

We also analyzed the associations between brain activity metrics and self-reported anxiety and depression levels. The ReHo value of the right insula was positively correlated with SAS scores (Figure 6a, r = 0.583, P = 0.011). Likewise, the fALFF of the right insula was positively correlated with SAS scores (Figure 6b, r = 0.557, P = 0.016). In addition, the fALFF of the left postcentral region also correlated positively with SAS scores (Figure 6c, r = 0.597, P = 0.009). These findings suggest that abnormal activity in the right insula and left postcentral region were correlated with the anxiety in NT1 patients.

The ReHo values of the left lingual (Figure 6d, r = 0.499, P = 0.035) and left postcentral regions (Figure 6e, r = 0.478, P = 0.045) were positively correlated with SDS scores. In addition, the fALFF values of the left occipital inferior (Figure 6f, r = 0.541, P = 0.02) and left postcentral regions (Figure 6g, r = 0.550, P = 0.018) were positively correlated with the SDS scores. These results indicate that altered functional activities in the left lingual, left postcentral, left occipital inferior, and left postcentral regions are closely associated with depression in NT1 patients.

Discussion

The Relationship Between Sleep Architecture and Anxiety and Depressive Symptoms in NT1 Patients

NT1 is a chronic neurological disorder characterized by cataplexy, hypnagogic hallucinations, excessive daytime sleepiness, paralysis, and disrupted nocturnal sleep. NT1 was also associated with a significant prevalence of psychiatric symptoms, particularly anxiety and depression, even hopelessness and suicidal thoughts.[8] In the present study, the SAS and SDS scores of NT1 subjects were significantly higher than those of HCs, indicating psychiatric symptoms in NT subjects. Moreover, we observed significant correlations between these psychiatric symptoms and sleep disorders in participants with NT1. The total sleep time and sleep efficiency were negatively correlated with the severity of anxiety

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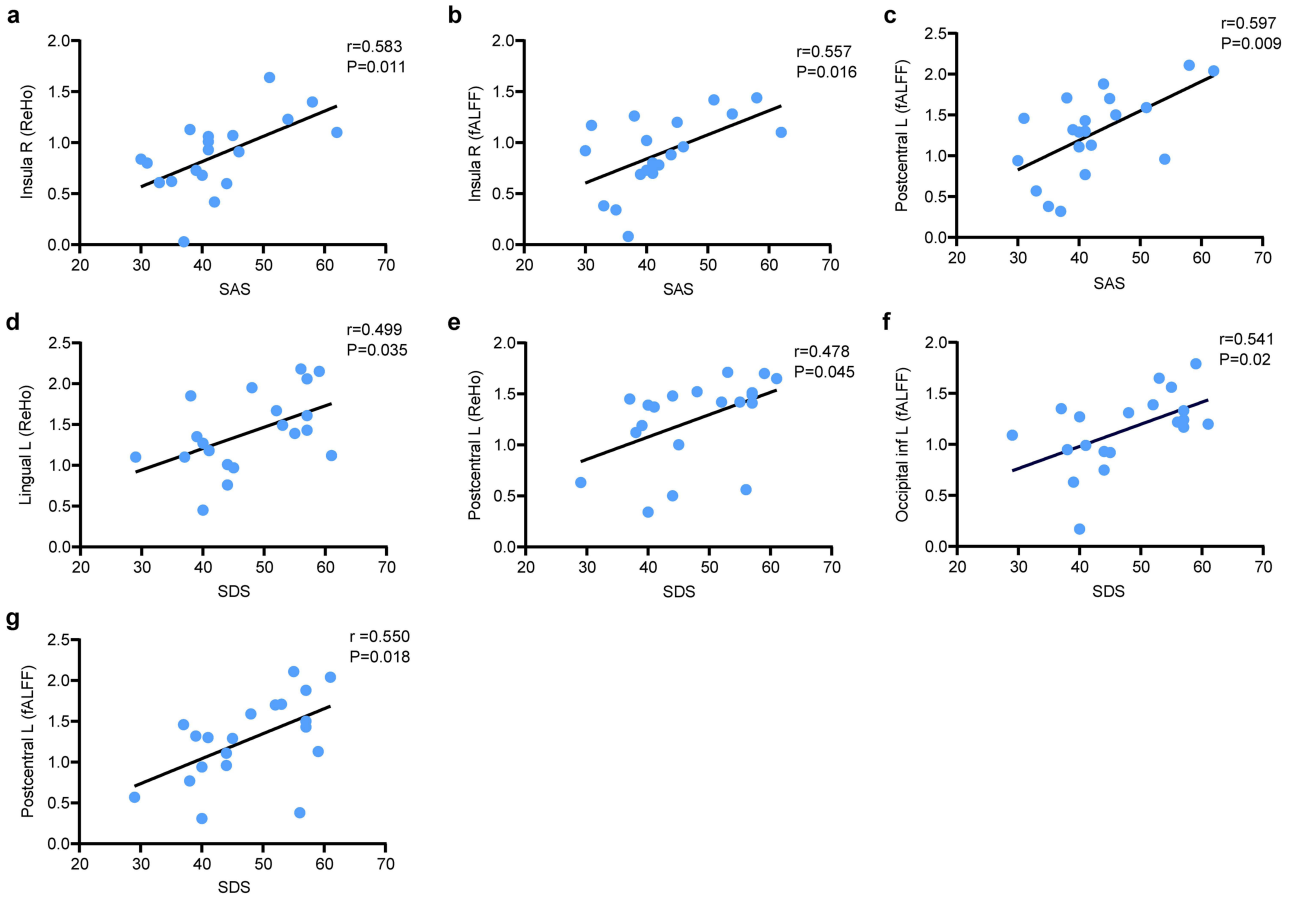

Figure 6 Significant associations between ReHo and fALFF values in specific brain regions and emotional symptoms in NT1 patients. (**a**) Correlation between ReHo value of right insula and SAS scores. (**b**) Correlation between fALFF value of right insula and SAS scores. (**c**) Correlation between fALFF value of left postcentral and SAS scores. (**d**) Correlation between ReHo value of left lingual and SDS scores. (**e**) Correlation between ReHo value of left postcentral and SDS scores. (**f**) Correlation between fALFF value of left occipital SDS scores. (**g**) Correlation between fALFF value of left postcentral and SDS scores.

and depressive symptoms in NT1 patients. The mean RSL was also negatively correlated with the SDS. These results suggest that poor sleep quality may lead to abnormal emotional states. Sleep, particularly rapid eye movement (REM), is important for maintaining mental health. REM sleep is associated with emotional regulation, including maintaining emotional balance, reactivity, and consolidation and emotional information.[26,27] Disruption of sleep architecture, particularly abnormalities in REM sleep, is considered a key factor in mood disorders.[28,29] For example, abnormal REM sleep patterns and short REM sleep latency are potential indicators of the risk of developing depression.[30] In addition, nighttime sleep interruption and sleep instability in NT1 patients are the main characteristics of their insomnia and are also one of the key factors leading to emotional disorders.[28,31] However, emotions can have a reciprocal influence on sleep. For example, individuals with depression often have reduced REM sleep latency and increased REM sleep density, indicating a dysfunction in emotional processing.[32] Anxiety disorders are linked to increased awakening during NREM sleep, leading to fragmented sleep and impaired emotional regulation.[33]

Functional Brain Activity Changes in NT1 Evaluated Using 7T Rs-MRI

MRI has been widely used to examine functional and structural brain networks in healthy subjects and in patients with specific brain diseases. Compared with 3T-MRI, 7T-MRI has higher spatial resolution, signal-to-noise ratio, and gray/white matter contrast, thus providing richer information for evaluating brain networks.[34,35] Considering these advantages, we employed 7T-MRI to examine functional brain activity changes in NT1. The rs-fMRI results revealed abnormal ReHo and fALFF activities in NT1 patients in 15 brain regions, including the insula, calcarine, lingual gyrus, and postcentral

regions, and many of these brain regions have been reported in previous studies.[36–38] These results suggest a wide alteration in the brain networks of patients with NT1. In alignment with our findings, previous studies have revealed abnormalities in the functional connectivity of executive and salience networks in adult narcolepsy patients.[38,39] This study identified the left thalamus, putamen, anterior cingulate gyrus, bilateral precentral gyrus, and bilateral frontal gyrus, which are the components of the thalamo-striatal-frontal circuit. Previous studies have documented dysfunction within the thalamo-striatal-frontal circuit in NT1 patients,[16,18] which aligns with the findings of this study. The present study also found elevated neural activity in the brain regions primarily engaged in processing visual information, including the calcarine, left lingual, left occipital inferior, and superior temporal gyri. These findings expand on previous reports showing activation of the visual cortex in narcolepsy.[17,37,40] Interestingly, the present study found increased functional activity in the volume of the paracentral lobule, in contrast to the previously reported decreased volume of this region.[41] Our study introduces a novel finding of compensatory increases in brain function in this region, suggesting a potential adaptive response in NT1 patients.

The functional brain activity alterations were significantly correlated with the sleep parameters in NT1 patients, including TST, sleep efficiency, and NSS-EDS. EDS is the main clinical symptom of NT1 and sleepiness alone is an independent factor affecting functional brain activity.[1,2] In the present study, the NSS-EDS showed a weak but significant negative correlation with increased activity in only one of the 15 abnormal brain regions in NT1, the ReHo value of right cerebellum. These results suggest that the sleepiness alone may not fully account for the observed abnormalities in NT1 in the present study. Moreover, neuroimaging results revealed distinct brain functional and structural changes between NT1 and neurological diseases characterized by EDS but without hypocretin/orexin deficiency, the idiopathic hypersomnia, for example. Idiopathic hypersomnia patients exhibit posterior default mode network alterations and precuneus gray matter expansion,[42] which were not observed in the present study. These differences indicate that the present study observed functional brain alterations are more likely driven by hypocretin/orexin deficiency rather than generalized sleepiness. Nevertheless, residual confounding from unmeasured EDS-related factors (eg, circadian disruption) may still contribute to the present findings.

As for the potential influences of medication, the majority of patients were newly diagnosed and medication-naïve. Only 3 patients had a history of long-term medication use, 3 months for pitolisant, 6 months for modafinil, and 24 months for methylphenidate, respectively. The relatively small percentage of patients (3/20) with previous medication treatment suggests potential minimal pharmacological confounding. Moreover, prior studies revealed different functional brain activities changes for stimulant drugs induced when compared with that in the present study. Modafinil enhances functional connectivity in healthy individuals (eg, putamen-inferior frontal gyrus coupling) and induces long-term cingulo-frontal network plasticity.[43,44] Methylphenidate shows no significant impact on resting-state brain activity.[45] No evidence exists to date linking modafinil or pitolisant to ReHo/fALFF abnormalities similar to those observed in NT1. Thus, the core ReHo/fALFF alterations in our NT1 cohort are more likely to reflect chronic neural remodeling driven by hypocretin/orexin deficiency. Future studies are needed to strengthen present findings in large cohort with medication-naïve patients.

The Relationship Between Brain Functional Impairment and Anxiety and Depressive Symptoms in NT1

In the present study, we found that anxiety in NT1 patients was associated with increased brain function in the insular and the left postcentral region. The insula is a complex brain region involved in the orchestration of interoception, emotion and affective processing.[46] For emotion processing, the most well-established role of the insula is mediating anxiety. Patients with anxiety disorder exhibited increased insula activity, leading to heightened fear responses and anticipatory.[47] Abnormal activities of insula have also been observed in NT1 patients.[17] Particularly, increased BOLD signals was found in the anterior insula region during emotion-induced cataplexy.[48] The increased insula activity in NT1 patients in the present study was consistent with these findings. Moreover, we observed a positive correlation between increased insula ReHo and fALFF activities and SAS, suggesting increase insula activities are associated with anxiety in NT1. These findings not only further support the important role of insula in anxiety but also revealed a potential implication of the

insula in emotional disorder in NT1. The activation of the insula could be associated with the autonomic and physical changes occurring during cataplexy, or with the visceral responses related to the pleasurable rewarding experience.

The postcentral gyrus is the center for somatosensory processing from various parts of the body. The somatosensory cortex has also been demonstrated to be involved in different stages of emotional processing.[49] Notably, patient with anxiety or depression showed structural and functional changes in the somatosensory cortex.[50,51] Consistent with these observations, we found that the increased activities of postcentral gyrus, where somatosensory cortex locates, are positively correlated with both SAS and SDS in NT1. In NT1 patients, the postcentral gyrus exhibits increased activation in response to neutral-rated movies, suggesting its potential involvement in the altered emotional processing observed in NT1.[52] In addition, hypermetabolism was found in postcentral gyrus during cataplectic attacks.[40] Combined with these findings, our results highlight a possible role of postcentral gyrus dysfunction in emotional disorders in NT1.

In NT1 patients, depression is associated with increased brain function in the left lingual gyrus, left postcentral region, and left inferior occipital gyrus (IOG). The lingual gyrus is a part of the visual cortex and is closely related to the processing of visual information, emotional regulation, and memory functions.[53] Recent studies have found that structural and functional abnormalities of the lingual gyrus may be associated with depression.[54,55] Structural MRI results revealed reduced gray matter volume in the lingual gyrus in patients with depression by analyzing gray matter volume and cortical thickness in different brain areas.[54] In addition, fMRI results showed abnormal activity of the lingual gyrus during emotional processing tasks in patients with depression.[56,57] For the left IOG, studies have identified a significant link between the left IOG and depression. In patients with bipolar depression, the clustering coefficient in the left IOG was notably reduced compared with that in healthy controls.[57] Furthermore, studies have shown that in patients with first-episode depression, there is a significant increase in dynamic functional connectivity between the left IOG and left hypothalamus, which is negatively correlated with clinical symptom severity.[57] Consistent with prior evidence, our findings indicate that functional alterations in the left IOG are associated with depressive symptomatology, with observed abnormalities potentially correlating with disruptions in emotional and cognitive processing.

Limitations

This study has several limitations that warrant further investigation. First, the cohort in the present study comprised 20 NT1 patients and 20 healthy controls, which limits statistical power to detect subtle behavioral associations. Larger cohorts are needed to confirm the generalizability of our findings in the future. Second, the enrolled NT1 patients exhibited heterogeneity in disease duration. In addition, although only 3 patients have previous medication history and a standardized 2-week washout protocol was implemented, long-term structural or neurochemical modifications induced by prior pharmacotherapy likely persist, potentially biasing resting-state activity patterns. Third, the present study was cross-sectional designed and was absent of longitudinal data. This limitation precluded causal inferences regarding whether functional alterations predispose to neuropsychiatric symptoms or emerge as downstream consequences of chronic NT1. Fourth, NT1 patients in the present study were diagnosed based on the clinical symptoms according to the ICSD-3. Hypocretin-1 or human leukocyte antigen (HLA) allele (eg, HLA-DQB1*0602) was not detected. Studies addressing the correlation between fMRI abnormalities and hypocretin-1 or HLA-DQB1*0602 will provide further insights into the pathogenesis of NT1. Finally, the present study focused on regional fMRI metrics (ReHo/fALFF) but did not investigate structural connectivity or network-level interactions, which may jointly contribute to emotional dysregulation.

Conclusions

Based on the findings of this study, we conclude that the high prevalence of anxiety and depressive symptoms in NT1 patients is associated with sleep structure disruption and functional activity impairment in the brain. The analysis of functional brain activity alteration in NT1 patients can provide new perspectives and methods for assessing the risk of emotional disorders. Future research should further explore the neural mechanisms of emotional disorders in patients with NT1, and using multidisciplinary strategies to treat NT1 comorbid with emotional disturbances.[58]

Data Sharing Statement

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

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The Zung Self-Rating Depression Scale (SDS), Zung Self-Rating Anxiety Scale (SAS), Insomnia Severity Index (ISI), and Narcolepsy Severity Scale (NSS) used in this study have obtained permission for use from the respective copyright holders.

Author Contributions

Yang Chen (Co-First Author)—Conceptualization, Methodology, Writing - Original Draft, Data Analysis, Funding Acquisition.

Jingyi Ye (Co-First Author)—Investigation, Data Collection, Data Analysis, Writing - Original Draft, Funding Acquisition.

Jiafei Chen—Data Curation, Formal Analysis, Validation, Writing - Original Draft.

Zhiming Zhen—Visualization, Data Analysis, Writing - Review & Editing.

Chenglin Tang—Resources, Technical Support, Validation, Writing - Original Draft.

Shuancheng Ren—Visualization, Data Analysis, Writing - Review & Editing, Funding Acquisition.

Qi Han (Co-Corresponding Author)—Supervision, Analysis and Interpretation, Writing - Review & Editing.

Dong Gao (Co-Corresponding Author)—Conceptualization, Supervision, Writing - Review & Editing.

All authors drafted, substantially revised, or critically reviewed the article, and agreed on the final version of the manuscript. Furthermore, all authors have agreed on the journal to which the manuscript will be submitted and take responsibility for all aspects of the work. They ensure any questions related to the accuracy or integrity of the work are appropriately addressed.

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Disclosure

The authors declare no competing interests in this work.

References

1. Scammell TE. Narcolepsy. *New Engl J Med*. 2015;373(27):2654–2662. doi:10.1056/NEJMra1500587
2. Kornum BR, Knudsen S, Ollila HM, et al. Narcolepsy. *Nat Rev Dis Primers*. 2017;3(1):16100. doi:10.1038/nrdp.2016.100
3. Bassetti CLA, Adamantidis A, Burdakov D, et al. Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nat Rev Neurol*. 2019;15(9):519–539. doi:10.1038/s41582-019-0226-9
4. Sum-Ping O, Mignot E. What is narcolepsy? *JAMA*. 2023;329(20):1802. doi:10.1001/jama.2023.5149
5. Mahoney CE, Cogswell A, Koralnik IJ, Scammell TE. The neurobiological basis of narcolepsy. *Nat Rev Neurosci*. 2019;20(2):83–93. doi:10.1038/s41583-018-0097-x
6. Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*. 2000;27(3):469–474. doi:10.1016/s0896-6273(00)00058-1
7. Tabuchi S, Tsunematsu T, Black SW, et al. Conditional ablation of orexin/hypocretin neurons: a new mouse model for the study of narcolepsy and orexin system function. *J Neurosci*. 2014;34(19):6495–6509. doi:10.1523/jneurosci.0073-14.2014
8. Ruoff CM, Reaven NL, Funk SE, et al. High rates of psychiatric comorbidity in narcolepsy: findings from the burden of narcolepsy disease (BOND) study of 9312 patients in the United States. *J Clini Psych*. 2017;78(2):171–176. doi:10.4088/JCP.15m10262
9. Abenza-Abildua MJ, Suárez-Gisbert E, Lores-Gutiérrez V, et al. Anxiety and depression in patients with narcolepsy. *J Sleep Res*. 2023;32(4):e13812. doi:10.1111/jsr.13812
10. Fortuyn HA, Lappenschaar MA, Furer JW, et al. Anxiety and mood disorders in narcolepsy: a case-control study. *General Hospital Psychiatry*. 2010;32(1):49–56. doi:10.1016/j.genhosppsych.2009.08.007

11. Yu J, Zhang Y, Cai L, et al. The changed nocturnal sleep structure and higher anxiety, depression, and fatigue in patients with narcolepsy type 1. *Nat Sci Sleep*. 2024;16:725–735. doi:10.2147/nss.S452665
12. Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. *J Sleep Res*. 2001;10(1):75–81. doi:10.1046/j.1365-2869.2001.00234.x
13. Lee MJ, Lee SY, Yuan SS, et al. Comorbidity of narcolepsy and depressive disorders: a nationwide population-based study in Taiwan. *Sleep Med*. 2017;39:95–100. doi:10.1016/j.sleep.2017.07.022
14. Biscarini F, Bassi C, Menchetti M, et al. Co-occurrence of anxiety and depressive symptoms, suicidal thoughts, and hopelessness in patients with narcolepsy type 1. *Sleep Med*. 2024;124:141–145. doi:10.1016/j.sleep.2024.09.023
15. Iglesias JE, Billot B, Balbastre Y, et al. SynthSR: a public AI tool to turn heterogeneous clinical brain scans into high-resolution T1-weighted images for 3D morphometry. *Sci Adv*. 2023;9(5):eadd3607. doi:10.1126/sciadv.add3607
16. Cavaliere C, Longarzo M, Fogel S, Engström M, Soddu A. Neuroimaging of narcolepsy and primary hypersomnias. *Neuroscientist*. 2020;26(4):310–327. doi:10.1177/1073858420905829
17. Xu L, Xue R, Ai Z, et al. Resting-state functional magnetic resonance imaging as an indicator of neuropsychological changes in type 1 narcolepsy. *Acad Radiol*. 2024;31(1):69–81. doi:10.1016/j.acra.2023.08.026
18. Wada M, Mimura M, Noda Y, et al. Neuroimaging correlates of narcolepsy with cataplexy: a systematic review. *Neurosci Res*. 2019;142:16–29. doi:10.1016/j.neures.2018.03.005
19. Dauvilliers Y, Barateau L, Lopez R, et al. Narcolepsy severity scale: a reliable tool assessing symptom severity and consequences. *Sleep*. 2020;43(6). doi:10.1093/sleep/zsaa009
20. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601–608. doi:10.1093/sleep/34.5.601
21. Zung WW. A rating instrument for anxiety disorders. *Psychosomatics*. 1971;12(6):371–379. doi:10.1016/s0033-3182(71)71479-0
22. Zung WW. A SELF-RATING DEPRESSION SCALE. *Arch Gen Psychiatry*. 1965;12(1):63–70. doi:10.1001/archpsyc.1965.01720310065008
23. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. *Neuroimage*. 2004;22(1):394–400. doi:10.1016/j.neuroimage.2003.12.030
24. Zou QH, Zhu CZ, Yang Y, et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neuroscience Methods*. 2008;172(1):137–141. doi:10.1016/j.jneumeth.2008.04.012
25. Huang B, Qian Z, Wang Z, et al. Fluctuation of primary motor cortex excitability during cataplexy in narcolepsy. *Ann Clin Transl Neurol*. 2019;6(2):210–221. doi:10.1002/acn3.670
26. Vandekerckhove M, Cluydts R. The emotional brain and sleep: an intimate relationship. *Sleep Med Rev*. 2010;14(4):219–226. doi:10.1016/j.smrv.2010.01.002
27. Baran B, Pace-Schott EF, Ericson C, Spencer RM. Processing of emotional reactivity and emotional memory over sleep. *J Neurosci*. 2012;32(3):1035–1042. doi:10.1523/jneurosci.2532-11.2012
28. Maski K, Mignot E, Plazzi G, Dauvilliers Y. Disrupted nighttime sleep and sleep instability in narcolepsy. *J Clin Sleep Med*. 2022;18(1):289–304. doi:10.5664/jcsm.9638
29. Brink-Kjaer A, Christensen JAE, Cesari M, Mignot E, Sorensen HBD, Jennum P. Cortical arousal frequency is increased in narcolepsy type 1. *Sleep*. 2021;44(5). doi:10.1093/sleep/zsaa255
30. Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. REM sleep dysregulation in depression: state of the art. *Sleep Med Rev*. 2013;17(5):377–390. doi:10.1016/j.smrv.2012.11.001
31. Goldstein AN, Walker MP. The role of sleep in emotional brain function. *Ann Rev Clin Psychol*. 2014;10(1):679–708. doi:10.1146/annurev-clinpsy-032813-153716
32. Riemann D, Krone LB, Wulff K, Nissen C. Sleep, insomnia, and depression. *Neuropsychopharmacology*. 2020;45(1):74–89. doi:10.1038/s41386-019-0411-y
33. Schantz BL, Toner ER, Brown ML, et al. Examining the relationship between emotion regulation, sleep quality, and anxiety disorder diagnosis. *J Mood Anxiety Disord*. 2024;8:100072. doi:10.1016/j.xjmad.2024.100072
34. Obusez EC, Lowe M, Oh SH, et al. 7T MR of intracranial pathology: preliminary observations and comparisons to 3T and 1.5T. *Neuroimage*. 2018;168:459–476. doi:10.1016/j.neuroimage.2016.11.030
35. Trattnig S, Springer E, Bogner W, et al. Key clinical benefits of neuroimaging at 7T. *Neuroimage*. 2018;168:477–489. doi:10.1016/j.neuroimage.2016.11.031
36. Joo EY, Tae WS, Kim ST, Hong SB. Gray matter concentration abnormality in brains of narcolepsy patients. *Korean J Radiol*. 2009;10(6):552–558. doi:10.3348/kjr.2009.10.6.552
37. Huang YS, Liu FY, Lin CY, Hsiao IT, Guilleminault C. Brain imaging and cognition in young narcoleptic patients. *Sleep Med*. 2016;24:137–144. doi:10.1016/j.sleep.2015.11.023
38. Fulong X, Spruyt K, Chao L, Dianjiang Z, Jun Z, Fang H. Resting-state brain network topological properties and the correlation with neuropsychological assessment in adolescent narcolepsy. *Sleep*. 2020;43(8). doi:10.1093/sleep/zsaa018
39. Xiao F, Lu C, Zhao D, et al. Independent component analysis and graph theoretical analysis in patients with narcolepsy. *Neurosci Bull*. 2019;35(4):743–755. doi:10.1007/s12264-018-0307-6
40. Dauvilliers Y, Comte F, Bayard S, Carlander B, Zanca M, Touchon J. A brain PET study in patients with narcolepsy-cataplexy. *J Neurol Neurosurg*. 2010;81(3):344–348. doi:10.1136/jnnp.2009.175786
41. Schaer M, Poryazova R, Schwartz S, Bassetti CL, Baumann CR. Cortical morphometry in narcolepsy with cataplexy. *J Sleep Res*. 2012;21(5):487–494. doi:10.1111/j.1365-2869.2012.01000.x
42. Pomares FB, Boucetta S, Lachapelle F, et al. Beyond sleepy: structural and functional changes of the default-mode network in idiopathic hypersomnia. *Sleep*. 2019;42(11). doi:10.1093/sleep/zsz156
43. Ellis CM, Monk C, Simmons A, et al. Functional magnetic resonance imaging neuroactivation studies in normal subjects and subjects with the narcoleptic syndrome. Actions of modafinil. *J Sleep Res*. 1999;8(2):85–93. doi:10.1046/j.1365-2869.1999.00142.x
44. Olazadeh K, Borumandnia N, Khadembashi N, Alavi Majd H. Effect of Modafinil on functional connectivity in healthy young people using resting-state fMRI data. *American J Neurodegenerative Dis*. 2022;11(1):1–9.

45. Zhu Y, Gao B, Hua J, et al. Effects of methylphenidate on resting-state brain activity in normal adults: an fMRI study. *Neurosci Bull*. 2013;29(1):16–27. doi:10.1007/s12264-013-1306-2
46. Zhang R, Deng H, Xiao X. The insular cortex: an interface between sensation, emotion and cognition. *Neurosci Bull*. 2024;40(11):1763–1773. doi:10.1007/s12264-024-01211-4
47. Pang J, Tang X, Li H, et al. Altered interoceptive processing in generalized anxiety disorder-A heartbeat-evoked potential research. *Front Psychiatry*. 2019;10:616. doi:10.3389/fpsyt.2019.00616
48. Meletti S, Vaudano AE, Pizza F, et al. The brain correlates of laugh and cataplexy in childhood narcolepsy. *J Neurosci*. 2015;35(33):11583–11594. doi:10.1523/jneurosci.0840-15.2015
49. Kropf E, Syan SK, Minuzzi L, Frey BN. From anatomy to function: the role of the somatosensory cortex in emotional regulation. *Rev Bras Psiquiatr*. 2019;41(3):261–269. doi:10.1590/1516-4446-2018-0183
50. Cui H, Zhang J, Liu Y, et al. Differential alterations of resting-state functional connectivity in generalized anxiety disorder and panic disorder. *Hum Brain Mapp*. 2016;37(4):1459–1473. doi:10.1002/hbm.23113
51. Schmaal L, Hibar DP, Sämann PG, et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA major depressive disorder working group. *Mol Psychiatry*. 2017;22(6):900–909. doi:10.1038/mp.2016.60
52. Juvodden HT, Alnæs D, Lund MJ, et al. Hypocretin-deficient narcolepsy patients have abnormal brain activation during humor processing. *Sleep*. 2019;42(7). doi:10.1093/sleep/zsz082
53. Palejwala AH, Dadario NB, Young IM, et al. Anatomy and white matter connections of the lingual gyrus and cuneus. *World Neurosurg*. 2021;151:e426–e437. doi:10.1016/j.wneu.2021.04.050
54. Couvy-Duchesne B, Strike LT, de Zubicaray GI, et al. Lingual gyrus surface area is associated with anxiety-depression severity in young adults: a genetic clustering approach. *eNeuro*. 2018;5(1):ENEURO.0153–17.2017. doi:10.1523/eneuro.0153-17.2017
55. Jung J, Kang J, Won E, et al. Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in major depressive disorder: a voxel-based morphometry study. *J Affect Disord*. 2014;169:179–187. doi:10.1016/j.jad.2014.08.018
56. Li X, Wang J. Abnormal neural activities in adults and youths with major depressive disorder during emotional processing: a meta-analysis. *Brain Imaging Behav*. 2021;15(2):1134–1154. doi:10.1007/s11682-020-00299-2
57. Yang J, Tao H, Sun F, et al. The anatomical networks based on probabilistic structurally connectivity in bipolar disorder across mania, depression, and euthymic states. *J Affect Disord*. 2023;329:42–49. doi:10.1016/j.jad.2023.02.109
58. Varallo G, Franceschini C, Rapelli G, et al. Navigating narcolepsy: exploring coping strategies and their association with quality of life in patients with narcolepsy type 1. *Sci Rep*. 2024;14(1):11837. doi:10.1038/s41598-024-62698-5