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ORIGINAL RESEARCH

Impaired Vigilance in Patients with Narcolepsy Type 1: A Psychomotor Vigilance Task Study

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Purpose: The psychomotor vigilance task (PVT) is one of the main methods to measure sustained vigilance/attention in sleep research. Vigilance is the main factor affecting daytime function in patients with narcolepsy type 1 (NT1). We aimed to quantify the negative effects of sleep–wake disorders on vigilance and investigate potential neural mechanisms.

Patients and Methods: We compared data from 42 patients and 31 healthy controls, including sociodemographics, nighttime sleep quality (Pittsburgh Sleep Quality Index, PSQI), sleepiness (Epworth Sleepiness Scale, ESS), cognitive abilities (Montreal Cognitive Assessment, MoCA), emotional control (Barratt Impulsiveness Scale-11, BIS-11), depressive symptoms (Patient Health Questionnaire-9, PHQ-9), and PVT performance. PVT outcomes analyzed included number of lapses, reaction time (RT), variability in RT, and the slowest and fastest 10% of RTs. All patients were diagnosed with NT1 based on The International Classification of Sleep Disorders-Third Edition.

Results: Patients with NT1 had a significantly higher body mass index and longer duration of education than healthy controls. The patients also had a greater tendency for daytime sleepiness and poorer nighttime sleep quality, higher depression and impulsiveness scores, and more severe cognitive dysfunction. PVT performance was better in the healthy controls than in patients with NT1. We also noticed that emotional changes and the proportion of rapid eye movement sleep at night are related to PVT performance.

Conclusion: More severe sleepiness and an increased emotional burden could underlie the arousal and vigilance deficits seen in patients with NT1. We speculate that impaired vigilance in patients with NT1 is associated with abnormal brain function caused by a resource allocation imbalance related to hypothalamic orexin neuron damage, sleep inertia may also have a slight impact on this. Future studies should delve into this topic more deeply.

Keywords: narcolepsy, psychomotor vigilance task, vigilance, sleepiness, reaction time

Introduction

Narcolepsy type 1 (NT1), which was first reported by Gelineau in the late 19th century, is a sleep disorder characterized by excessive daytime sleepiness (EDS), cataplexy, hallucinations, and sleep paralysis. The irreversible damage to orexin (hypocretin) neurons in the lateral hypothalamus (LH) caused by the T-lymphocyte-mediated immune response is widely believed to underlie the pathogenesis of NT1. Although orexin neurons only occupy a small portion of the LH, the neural projections are distributed throughout the brain to regulate the sleep–wake cycle, attention, memory, and appetite.[1–5] Thus, patients with NT1 not only complain of sleep problems but also have difficulties with concentration and memory loss. In cognitive and attention-related studies, patients with NT1 usually perform worse on lengthy and monotonous tasks, suggesting that their vigilance is severely impaired.[6,7] Vigilance is the part of the attention system involved in sustained attention and tonic alertness. The alerting network is regulated by the ascending reticular activating system and the right hemisphere of the brain (associated with vigilance) and is the basis for our response to external stimuli.[8,9]

The psychomotor vigilance task (PVT) is one of the most reliable paradigms for assessing vigilance in sleep research due to its high sensitivity, simplicity, and low threshold (low educational requirements) for testing. Moreover, in existing studies on central disorders of hypersomnolence like narcolepsy, it is considered a reliable and objective measurement

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method.[10,11] By analyzing the reaction time (RT) of visual stimuli that occurs at random intervals during the task, the degree of vigilance loss of subjects is evaluated through error rate, and the information processing speed of participants is represented. PVT could collect a large amount of data from a single subject through the characters for short durations and multiple trials. This feature enhances its sensitivity, allowing us to detect small changes in the subject's response during analysis. This cognitive test is highly sensitive to acute total sleep deprivation and chronic sleep restriction.[12–14] Except in the field of sleep disorders and various other contexts, such as hepatic encephalopathy and alcoholism, the PVT is simpler and more effective than other measures such as Antisaccade, Stroop, and N-back paradigms.[15] Furthermore, there is no evidence to suggest that participants can adapt to the frequent false-negative results occurring after multiple tests. In addition to the 10-min standard laboratory version used in this study, the 5-min, 3-min, and handheld versions have improved operability greatly and have been well applied.[16]

Here, we used the PVT to assess the degree of vigilance loss and the reaction speed of the subjects to investigate the issue of impaired vigilance in patients with NT1, including its possible causes. We also evaluated whether the PVT could serve as a clinical auxiliary diagnostic tool for the sleep center.

Methods

Subjects

We reviewed data from patients in the Department of Neurology of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, China, from October 2021 to October 2023. We recruited 42 patients who were diagnosed with NT1 according to the International Classification of Sleep Disorders-3.[17] All recordings were completed during the diagnostic tests, so none of the patients took medication that affected their sleepiness. The 31 healthy controls were matched for age and gender and were recruited from schools or the community. All subjects were 15–45 years old, right-handed, had normal or corrected-to-normal vision, and were from the East China region. This research was approved by the Clinical Research Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University and was carried out following the principles of the Declaration of Helsinki. All subjects or their legal representatives gave written informed consent to participate in this study.

Among them, 22 individuals (52.38%) underwent measurement of orexin concentration in cerebrospinal fluid (CSF). The control group confirmed their health through self-reported questionnaires and pretest interviews. Individuals with mental disorders, other sleep disorders such as obstructive sleep apnea (OSA), abnormal circadian rhythms, sleep deprivation, or any history of alcohol or drug abuse are not included.

NT1 was diagnosed at a professional sleep center based on the clinical presentation, Multiple Sleep Latency Test (MSLT), polysomnography (PSG). Among them, 22 individuals (52.38%) underwent measurement of orexin concentration in cerebrospinal fluid (CSF). The control group was confirmed to be healthy through self-reported questionnaires and an interview conducted before the test.

Questionnaires

Participants were required to complete a set of questionnaires before the PVT. The Montreal Cognitive Assessment (MoCA) was used to assess cognitive function. The degree of EDS was measured using the Epworth Sleepiness Scale (ESS). The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality over the past month. The Barratt Impulsiveness Scale-11 (BIS-11) and the Patient Health Questionnaire-9 (PHQ-9) were used to examine emotional fluctuations in the participants.

Psychomotor Vigilance Task

The participants were asked to press a button as soon as a red timer (stimulus) appeared on the screen. After pressing the button, the screen displayed an RT of 1 s, providing immediate feedback on performance. The stimulus appeared randomly at intervals of 2–10 s. The experiment lasted for 10 min and consisted of approximately 75 stimuli. To ensure that all subjects remained awake during the test, they were instructed to take a 15-minute nap in a dark room before the test (Figure 1). All participants underwent a habituation test before the main test. We assessed the following outcome

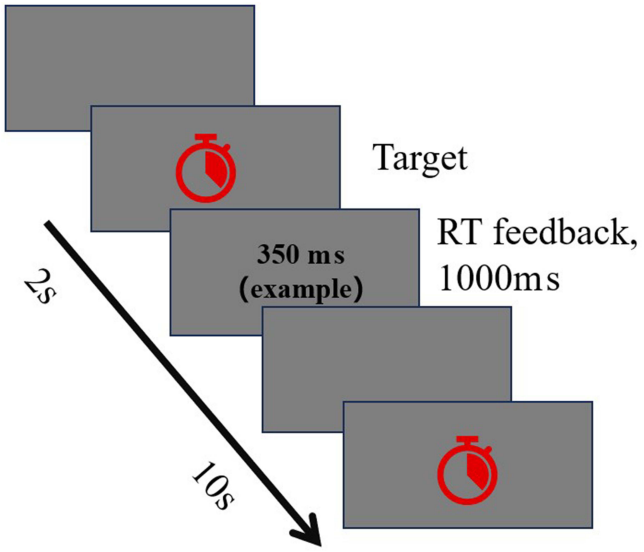

Figure 1 Psychomotor vigilance task paradigm. The 10 min PVT consists of presenting the target (a red timer) 75 times on a black computer screen. The interval between targets is 2–10 seconds. The subjects respond to the appearance of each target by pressing the spacebar. After pressing the button, the screen displayed an RT of 1 s, providing immediate feedback on performance.

measures: the number of lapses (RT > 500ms) divided by the number of stimuli (reported as a percentage); reaction speed [RT (lapses included), RT500 (lapses excluded), RT-1s (>1000ms excluded) and RT-L30 (the last 30 out of 75 stimuli)]; the fastest and slowest 10% of RTs (F-RT1s and S-RT1s); and the variability in RT-1s (90th percentile RT-1s - 10th percentile RT-1s).[10,14]

We conducted the correlation analysis between scale scores and PVT outcomes. In the NT1 group, we also analyzed the clinical manifestations including PSG, MSLT and orexin concentration in the CSF with PVT results.

Statistical Analysis

All analyses were performed with IBM SPSS Statistics 22 software (IBM Corp., Armonk, NY, USA). The *t*-test, Mann–Whitney *U*-test, chi-square test and correlation analysis were used to analyze the demographic, questionnaire, and behavioral data. A p-value < 0.05 was considered significant.

Results

Participant Characteristics

Table 1 shows the participants' demographic, psychometric, and clinical data. Gender ($p = 0.624$), age ($p = 0.435$), and disease duration were comparable between the two groups. The NT1 group had a significantly higher body mass index ($p < 0.001$), greater subjective sleepiness (ESS score, $p < 0.001$), heavier "sleep drunkenness like" experience in daytime (SIQ sum score, $p < 0.001$), and poorer sleep quality (PSQI score, $p = 0.002$), which are typical narcolepsy-related clinical features. The NT1 group had higher scores for depression (PHQ-9 score, $p < 0.001$) and impulsiveness (BIS-11 score, $p < 0.001$). Moreover, the patients had fewer years of education ($p < 0.001$) and lower MoCA scores than the controls ($p = 0.001$).

Behavioral Measures

The accuracy and RT measures are summarized in Table 2. The NT1 group had a higher error rate than the control group ($p < 0.001$). The RT of the patients was significantly slower than that of the healthy controls, regardless of whether the lapses were excluded or included (both $p < 0.001$). We conducted a preliminary analysis of the RT of the entire NT1 group and found that patients experienced brief concentration after one omission, and as the task progressed, the frequency of omissions increased, and the RT increased. If we only used 500ms as a screening error frequency, it may cause result bias. Based on the

Table 1 Demographic and Clinical Features

	NT1(n=42)	Control(n=31)	P value
Male, n (%) [c]	25(59.50)	21(67.70)	0.624
Age, y [IQR] [a]	23.00[19.00, 34.25]	23.00[22.00, 24.00]	0.435
Disease duration, y [IQR] [a]	7.00[4.00, 12.25]	–	–
BMI, kg/m^2, [IQR] [a]	25.59[22.50, 31.23]	21.07[19.72, 24.73]	<0.001
Educational year, y, [IQR] [a]	12.00[9.00, 15.00]	15.00[14.00, 16.00]	<0.001
MoCA score, [IQR] [a]	26.00[25.00, 28.50]	29.00[28.00, 29.00]	0.001
ESS score, M(SD)[b]	16.50±4.07	9.00±3.37	<0.001
PSQI score, [IQR] [a]	6.00[5.00, 10.00]	4.00[3.00, 5.00]	<0.001
PHQ-9 score, M(SD)[b]	7.14±4.12	3.52±2.46	<0.001
BIS-11 score, M(SD)[b]	81.71±16.26	66.13±11.28	<0.001
SIQ sum score, M(SD) [b]	59.30±15.10	25.60±9.86	<0.001

Notes: Data are presented as n (%), mean ± standard deviation or Interquartile Range; [a]Mann–Whitney *U*-test; [b]*t* test; [c]chi-square proportion test. P-values < 0.05 are shown in bold.
Abbreviations: NT1, narcolepsy type 1; BMI, body mass index; MoCA, Montreal Cognitive Assessment; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; PHQ-9, Patient Health Questionnaire-9; BIS-11, Barratt Impulsiveness Scale Version 11; SIQ, the Sleep Inertia Questionnaire.

Table 2 Differences in PVT Performance Between NT1 Patients and Healthy Controls

	NT1(n=42)	Control(n=31)	P value
False RT, %, [IQR] [a]	24.67[14.34, 45.67]	4.00[1.33, 9.33]	<0.001
RT, ms, [IQR] [a]	484.80[409.39, 849.39]	338.72[308.70, 374.94]	<0.001
RT500, ms, M(SD)[b]	371.37±44.06	318.72±35.58	<0.001
RT-1s, ms, [IQR] [a]	428.67[387.19, 492.57]	329.02[299.68, 369.76]	<0.001
RT-L30, ms, [IQR] [a]	508.49[422.95, 1140.71]	339.47[298.49, 387.43]	<0.001
F-RT1s, ms, [IQR] [a]	287.51[259.28, 328.44]	248.03[230.65, 273.57]	<0.001
S-RT1s, ms, [IQR] [a]	730.40[629.31, 831.64]	498.59[401.72, 631.90]	<0.001
RTV-1s, [IQR] [a]	441.17[343.60, 518.11]	115.04[233.11, 373.66]	<0.001

Notes: Data are presented as mean ± standard deviation or Interquartile Range; [a]Mann–Whitney *U*-test; [b]*t* test. P-values < 0.05 are shown in bold.
Abbreviations: NT1, narcolepsy type 1; RT: lapses (RT > 500ms) included; RT500: lapses excluded; RT-1s: reaction times >1000ms excluded; RT-L30: the last 30 out of 75 stimuli; F-RT1s and S-RT1s: the fastest and slowest 10% of RTs; RTV-1s: the variability in RT-1s (90th percentile RT-1s - 10th percentile RT-1s).

experimental results, we compared the results with RT of less than 1s (RT-1s), as well as compare the last 30 results (RT-L30) , the comparison of the above two items indicates that the NT1 group needs more time to complete the trial (both $p < 0.001$). And according to the fastest 10% ($p < 0.001$) and slowest 10% ($p < 0.001$) RT-1s data, the overall reaction speed of the NT1 group was slower. The NT1 group also showed greater variability in RT-1s ($p < 0.001$).

Meanwhile, we performed correlation analysis between RTs and accuracy for each group to determine whether there were differences in strategies for balancing speed and accuracy between groups (S-Table 1). The Spearman rank-order correlation analysis indicated that the PHQ-9 score was weak positively correlated with RT in the group NT1 ($r = 0.320$, $P < 0.05$). In the analysis of clinical examination results and PVT manifestations in the NT group, we found that the proportion of REM Sleep at night is weak positively correlated with reaction time (RT500, $r = 0.360$, $P < 0.05$; RT-1s, $r = 0.420$, $P < 0.05$) (Figure 2 and S-Table 2).

Discussion

Our NT1 group had a higher obesity rate and fewer years of education than the controls. The patients also had poorer self-rated sleep quality and emotions. A significant difference in performance on the PVT was detected between the two groups.

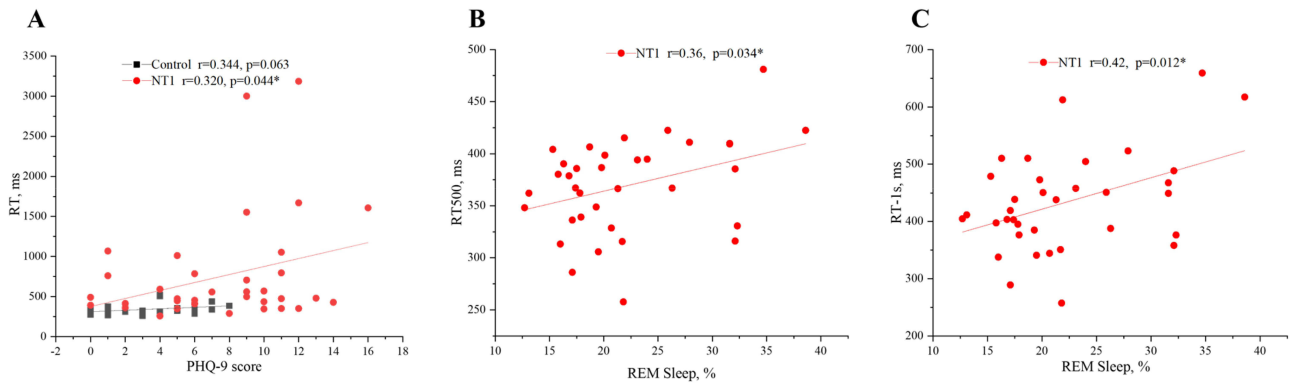

Figure 2 Partial correlation analysis between clinical manifestations and PVT results. *: refers to the result with P<0.05. (**A**), the PHQ-9 score was positively correlated with RT in the group NT1. (**B**) and (**C**), the proportion of REM Sleep at night is correlated with RT500 and RT-1s.

Sleep deprivation can affect the regulation of appetite and lead to an imbalance significantly increasing the risk of obesity.[18] A prospective study suggested that children who have poorer nighttime sleep also have a higher risk of obesity.[19] Our analysis indicated that the obesity rate of the NT1 group was much higher than that of the controls, as stated above, which may be due to the loss of orexin neurons in the LH. The root cause of this is not only the compensatory increase in sugar and calorie intake caused by sleep–wake rhythm disorders but also disruption of the orexin system, which directly affects food intake and metabolism.[20] A recent study revealed the presence of specific types of eating disorders, such as night eating syndrome (NES), in patients with narcolepsy type 1.[21] The loss of orexin neurons in the LH is a typical pathological change in NT1 whereby the secretion of orexin decreases and eventually stops completely. The hypothalamus is a secondary center located beneath the cerebral cortex that regulates various physiological functions, including circadian rhythms and endocrine activities. It integrates appetite-regulating (hunger/satiety) signals to maintain normal weight.[22] Orexin participates in eating, energy expenditure, and circadian rhythms.

As with appetite, sleep and emotions also affect each other.[23] Our NT1 group had higher scores on the PHQ-9 and BIS-11, which aligns with previous research: individuals with sleep disorders report more symptoms of depression and anxiety, and more anger and negative behaviors. The notion that sleep disorders are associated with psychological and interpersonal problems is recognized by the public. The PVT requires continuous attention and a rapid response from participants. As expected, the longer RTs and higher error rate of our NT1 patients compared with controls were consistent with previous studies, reflecting the associations of sleep restrictions and deficiency with impaired vigilance and sustained attention. We analyzed the number of errors, psychomotor speed (slowest and fastest 10% of RT-1s), variability in RT-1s and average/median RT, as these metrics are more sensitive to sleep deprivation and vigilance. Our findings are consistent with previous studies using different tests (sustained attention to response task, SART), showing that the vigilance of patients with NT1 is impaired. The findings suggest that the PVT may aid the diagnosis of sleep disorders. Previous PVT studies have also indicated that the PVT can distinguish specific sleep–wake disturbances.[10] However this study did not include other sleep-deprived populations. In addition to analyzing the results of the PVT in isolation, we explored whether performance on the PVT was related to clinical indicators.

However, no correlations were detected between the PVT score and disease duration, sleep latency from the NT1 group. Although the low level of orexin in the CSF are a characteristic pathological change of NT1, we have not found any evidence to suggest a correlation with behavior (RT-1s, $r = 0.024$, $P = 0.912$) or error rate ($r = 0.004$, $p = 0.984$), which may have been due to our small sample size; orexin was measured in only 22 patients (52.38%). Additional research with larger samples is needed to further evaluate this correlation.

We speculate that the vigilance in the NT1 group was impaired because of EDS, abnormal brain function, and resource allocation imbalance associated with damage to hypothalamic orexin neurons sleep inertia (SI). The attention system consists of alerting, orienting, and executive control networks.[24] Functional magnetic resonance imaging has confirmed that these three major networks correspond to regions in the brain. The regions associated with the orienting network include the upper part of the parietal lobe, the temporoparietal joint area, and the superior thalamus. The

executive control network is distributed in areas such as the anterior cingulate cortex and the lateral frontal lobe. The alerting network is composed of the locus coeruleus, the thalamus, the parietal lobe, and the frontal cortex (noradrenergic pathway), and mainly relies on the right hemisphere.[11,25] Here, we focused on the alerting network, which is responsible for maintaining a clear and alert state, thus allowing individuals to react at any time.

Research on event-related potentials (ERPs) has shown that decreases in N200 and P300, which are related to alertness in those with sleepiness, mainly occur in the right frontal cortex, which coincides with the alerting network.[26–28] When receiving information suddenly, NT1 patients may experience the above-mentioned electrophysiological changes, which affect the strength of activation signals received by encephalic regions and the level of resources.

The most prominent pathological change in patients with NT1 is damage to orexin neurons.[2] The extensive projections of orexin neurons in the brain allow orexin to regulate various physiological processes. Previous studies have shown that orexin plays a positive role in the normal functioning of neural networks related to learning and memory. Orexin allows for long-term synaptic plasticity (presumably related to learning) by coordinating cholinergic, glutamatergic, GABAergic, and noradrenergic signaling in the hippocampus.[29,30] The pyramidal neurons in the PFC are postsynaptically activated by orexin, indicating that orexin neurons participate in advanced cognitive behaviors.[31,32] In an animal experiment, Lambe et al demonstrated that orexin affects the attention span and decision-making processes.[33] This was consistent with our finding that the NT1 group had lower MoCA scores and shorter education duration than controls. In addition, orexin neurons projecting to the basal forebrain increase the release of acetylcholine and strengthen the activity of cortical neurons, helping to awaken and activate memory-processing nuclei.[34,35] The ventral tegmental area (VTA) is related to reward/punishment and addictive activities, and the dopaminergic neurons inside the VTA can be directly excited by orexin neurons. The orexin–VTA pathway activates basic antagonistic processes upon exposure to addictive substances, playing an important role in the transition to and maintenance of an alert state.[36,37] The lack of orexin in patients with NT1 leads to changes in the electrical signals connecting encephalic regions and impairs the functions mentioned above. This may explain why patients with NT1 have more difficulties with work, learning, and concentration than the general population. SI refers to difficulty in waking up after sleep, as well as slow responses and impaired vigilance that lasts for several minutes to hours after waking and is often seen in individuals with EDS.[38] There is no standardized process for evaluating SI, and its duration and frequency are often assessed using self-report measures. The optimal measurement tool for sleep inertia in central disorders of hypersomnolence has not yet been determined. The Sleep Inertia Questionnaire (SIQ) proposed in previous studies has been preliminarily validated.[39] In our study, we found that the NT1 group had higher SIQ scores and reported more symptoms of daytime brain fog (lack of concentration, blank mind). Behavior and attention during the transition between sleep and complete wakefulness are unstable, which is reflected in PVT performance.[40] Our study first required all participants to take a 15-minute nap, with the PVT then being performed within 5–10 min after waking. This nap was originally intended to minimize the occurrence of drowsiness during the experiment; due to the short transition period, some patients could not switch to a "normal task state". The fastest and slowest 10% of RT-1s showed that the NT1 group had greater variability in RT than the controls, indicating poorer sustained attention in the former group. In other words, the RTV-1s demonstrated that maintaining attention was more difficult for the NT1 group. The sleep stage one is in before awakening is a key factor affecting the occurrence of SI. People who are awakened during slow wave sleep (particularly stage 3 (N3), characterized by non-rapid eye movement) are more likely to experience SI.[38] Previous studies have shown that the general population finds it difficult to enter N3 during a 15-minute nap, thereby reducing the "interference" caused by being awakened.[39,41] However, patients with NT1 can enter rapid eye movement sleep (REM Sleep) in an extremely short time, and the cerebral blood flow velocity is difficult to match between sleep and the time shortly after awakening.[42] It takes time for the prefrontal cortex (PFC) to recover to baseline after waking. The pyramidal neurons in the PFC are difficult to activate due to the absence of orexin in patients with NT1.[32] Therefore, SI could contribute to the decline in vigilance in NT1 patients seen during the day.

However, this study only included patients with NT1 and central sleepiness disorders and lacked data on patients diagnosed with idiopathic hypersomnia. It is unclear whether the decrease in vigilance seen in patients with NTI is due to the loss of orexin neurons, insufficient sleep, or both. Therefore, in subsequent studies, we will include patients with other hypersomnia diagnoses, identify possible causes, and analyze the feasibility of the PVT as a clinical tool to assist in

diagnosing central sleepiness disorders. The PVT is considered a promising method for assessing the severity of drug-induced damage, but further research is needed on patients who are taking antidepressants or other sleep-enhancing drugs.

Conclusion

In this study, we speculate that impaired vigilance in patients with NT1 is associated with abnormal brain function caused by a resource allocation imbalance related to hypothalamic orexin neuron damage, sleep inertia may also have a slight impact on this. The PVT is widely used in sleep research and may have a place in clinical evaluations of patients with NT1, as it exhibits impaired vigilance. Further research is needed on the mechanism of impaired vigilance in patients with NT1.

Abbreviations

NT1, Narcolepsy type 1; EDS, excessive daytime sleepiness; LH, lateral hypothalamus; PVT, psychomotor vigilance task; RT, reaction time; MSLT, multiple sleep latency test; PSG, polysomnography; CSF, cerebrospinal fluid; MoCA, Montreal Cognitive Assessment; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; BIS-11, Barratt Impulsiveness Scale-11; PHQ-9, the Patient Health Questionnaire-9; SART, sustained attention to response task; SI, sleep inertia; REM Sleep, rapid eye movement sleep; PFC, the prefrontal cortex; ERPs, event-related potentials; VTA, ventral tegmental area.

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Disclosure

The authors report no conflicts of interest in this work.

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