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LETTER TO THE EDITOR Open Access

Maladaptive reorganization of mediodorsal thalamus as a central mechanism in neuropathic pain-related sleep disorders

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Dear Editor,

Chronic neuropathic pain and sleep disturbances exhibit high comorbidity, with bidirectional interactions forming a self-perpetuating "pain-sleep disturbance" vicious cycle that exacerbates clinical outcomes [1,2]. Although evidence and mechanisms have been established linking poor sleep to the development of neuropathic pain [3,4], the precise impact of neuropathic pain on sleep neurophysiology in clinical settings remains to be fully elucidated.

Zoster-associated neuralgia (ZAN), resulting from herpes zoster infection, represents a particularly severe clinical phenotype of neuropathic pain [5,6]. Nevertheless, scant research has comprehensively examined the detailed characteristics of ZAN-associated sleep disturbances. Standardized questionnaires confirmed elevated pain severity [Neuropathic Pain ID Pain Scale (ID Pain), Visual Analogue Scale (VAS), Present Pain Intensity (PPI), and Numerical Rating Scale (NRS)] in 37 ZAN patients without pre-existing chronic insomnia, with subsequent sleep evaluations revealing a positive correlation between pain severity and Insomnia Severity Index (ISI) (Additional file 1: Materials and Methods; Table S1; Figs. S1, S2).

Polysomnography (PSG) analysis revealed that ZAN patients manifested by an 51.30% increase in the number of awakenings (P=0.009), exhibited increased wake time after sleep onset (WASO) (P=0.004), when compared to healthy controls (HC). The duration (P=0.003) and percentage (P=0.006) of rapid eye movement (REM) sleep and sleep efficiency (P=0.018) declined significantly, while the percentage (P=0.006) of non-rapid eye movement (NREM) sleep increased significantly. The total sleep time, sleep onset latency, duration of NREM sleep, and duration and percentage of each NREM sleep stage remained comparable to HC (Fig. 1a; Additional file 1: Table S2). Transitional sleep patterns showed distinct instability, particularly in NREM stages: non-rapid eye movement sleep stage 2 (N2)-wakefulness (W)-non-rapid eye movement sleep stage 1 (N1) (P=0.025), N2-W-N2 (P=0.017), and non-rapid eye movement sleep stage 3 (N3)-N2-W (P=0.009) transitions occurred more frequently, while the number of other transition patterns did not change (Additional file 1: Table S3). The pain severity was positively correlated with these significant transition patterns (Additional file 1: Fig. S3). These results indicate that the sleep instability caused by ZAN primarily manifests as increased transitions from NREM sleep to wakefulness.

Next, the oscillatory network mechanisms underlying this sleep instability were explored. Despite the electroencephalogram spectral power didn't show any significant difference across different brain lobes in distinct sleep stages when compared with HC (Additional file 1: Fig. S4), phase synchrony between the temporal and parietal lobes showed a significant reduction predominantly observed during N2 and N3 stages of NREM sleep as well as during REM sleep stage (Additional file 1: Table S4, Fig. S5a), and manifested across slow, delta, theta, alpha, beta, and gamma oscillation (Fig. 1b). Functionally, the synchronous activity between the

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temporal lobe and parietal lobe was significantly negatively correlated with the transition patterns: N2-W-N1, N2-W-N2, and N3-N2-W. And decreased synchronicity during NREM sleep was positively correlated with the duration of REM sleep (Additional file 1: Fig. S5b-d), indicating that temporoparietal desynchronization may lead to the neuropathic pain-associated sleep instability.

Lastly, the structural and functional brain changes underlying temporoparietal desynchronization were investigated. Neuroimaging analysis revealed that ZAN patients exhibited a significant volume reduction in the mediodorsal thalamus (P<0.001; Fig. 1c) after family-wise error correction when compared to HC. The mediodorsal thalamic atrophy was significantly correlated with the phase-locking value (PLV) between the temporal lobe and parietal lobe across various oscillations during N2, N3, and REM sleep stages, except for the gamma oscillation during N3 sleep, and the slow and delta oscillations during REM sleep (Additional file 1: Table S5). The atrophy of brain regions is always accompanied by changes in functional activity. Indeed, a significant increase in amplitude of low-frequency fluctuations was detected in ZAN patients (P=0.046; Fig. 1d). This result is consistent with previous reports showing that the dorsomedial thalamus plays a crucial role in both nociceptive signaling and sleep-wake dynamics [7] and its overactivation contributes to neuropathic pain development [8], suggesting that alterations in its functional activity and connectivity may contribute to pain-associated sleep disturbances. Additionally, the mediodorsal

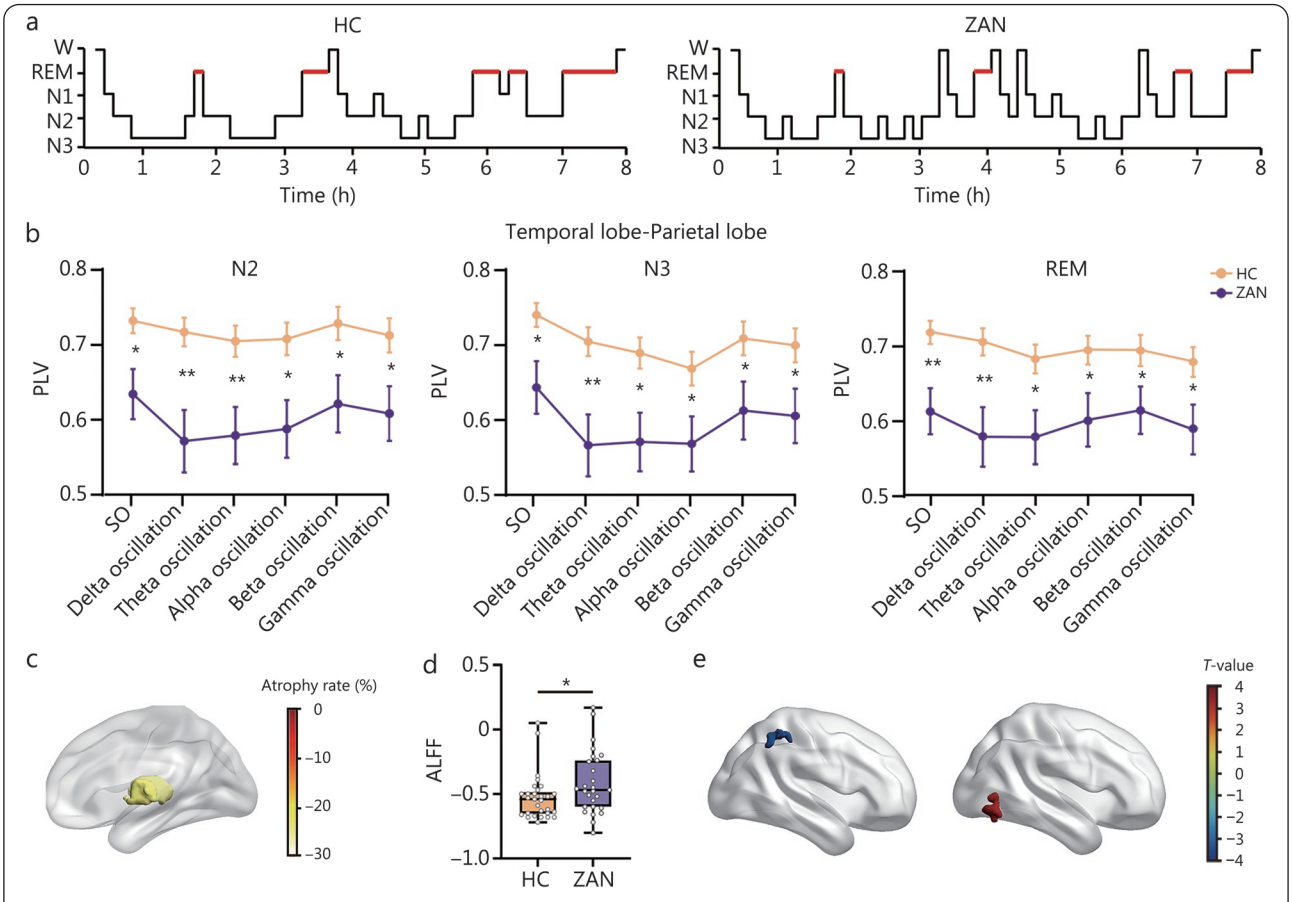

Fig. 1 Maladaptive reorganization of mediodorsal thalamus may lead to temporal-parietal desynchronization and ZAN-associated sleep disturbance.

a The representative hypnograms for HC and ZAN patients. **b** PLV for different oscillations during N2, N3, and REM sleep. **c** The atrophy rate of the mediodorsal thalamus in ZAN patients. **d** The ALFF of mediodorsal thalamus differences in HC and ZAN patients. **e** The alterations in the functional connections between mediodorsal thalamus and right inferior parietal lobe (left), right inferior temporal gyrus (right). Red regions represent significantly higher functional connections in ZAN patients, while blue indicates significantly lower. Group differences were analyzed using a two-sample *t*-test with age and sex as covariates, and a linear mixed model with subjects treated as a random effect and age and sex included as covariates. W. Wakefulness; N1. Non-rapid eye movement sleep stage 1; N2. Non-rapid eye movement sleep stage 2; N3. Non-rapid eye movement sleep stage 3; REM. Rapid eye movement; HC. Healthy controls; ZAN. Zoster-associated neuralgia; SO. Slow oscillation; PLV. Phase-locking value; ALFF. Amplitude of low-frequency fluctuations

thalamus in ZAN patients exhibited significantly diminished functional connectivity with the right inferior parietal lobe (T=–3.686, P<0.001; Fig. 1e), while showing notably enhanced connectivity with the right inferior temporal gyrus (T=3.431, P<0.001; Fig. 1e). Of note, functional connectivity between mediodorsal thalamus and three other prefrontal regions including the right superior gyrus, right middle gyrus and right inferior gyrus was also decreased in ZAN patients (Additional file 1: Fig. S6).

Consistent with our human findings, rodent models of neuropathic pain demonstrate sleep fragmentation [9]. However, these rats exhibit selective NREM reduction without REM alterations, contrasting with the human ZAN phenotypes. This rodent-specific pathology associates with reticular thalamic nucleus hyperexcitability [9]. The differential sleep manifestations likely reflect distinct neuropathic pain etiologies (e.g., acute vs. chronic) and species-specific neural adaptations.

Targeted thalamic modulation represents a promising therapeutic strategy for pain-related sleep disorders. While a recent pilot study confirmed the safety of anterior cingulate cortex stimulation alone or combined with sensory thalamic stimulation, it demonstrated that isolated sensory thalamic stimulation failed to alleviate neuropathic pain [10]. Our findings revealed the possible mechanisms whereby neuropathic pain exacerbates sleep disturbances. The patients with ZAN experience a reduction of synchronization between the temporal and parietal lobes due to mediodorsal thalamus atrophy, and decreased functional connectivity between the mediodorsal thalamus and the prefrontal cortex. These complementary structural and functional thalamic alterations constitute a central pathophysiological axis underlying neuropathic pain-related sleep pathology. Thus, preventing dorsomedial thalamic degeneration or correcting its specific network dysregulation may constitute effective interventions for comorbid neuropathic pain and sleep disturbances.

Abbreviations

HC: Healthy controls
ID Pain: Neuropathic Pain ID Pain Scale
ISI: Insomnia severity index
NRS: Numerical Rating Scale
N1: Non-rapid eye movement sleep stage 1
N2: Non-rapid eye movement sleep stage 2
N3: Non-rapid eye movement sleep stage 3
NREM: Non-rapid eye movement
PLV: Phase-locking value
PPI: Present Pain Intensity
PSG: Polysomnography
REM: Rapid eye movement
VAS: Visual Analogue Scale
W: Wakefulness
WASO: Wake time after sleep onset
ZAN: Zoster-associated neuralgia

Supplementary information

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Additional file 1. Materials and Methods. Fig. S1 Participant recruitment flowchart. **Fig. S2** Correlation between pain severity (ID Pain, VAS, PPI, and NRS) and ISI. **Fig. S3** Correlation between transition patterns and pain severity (ID Pain, VAS, PPI, and NRS). **Fig. S4** Spectral power for different brain lobes in distinct sleep stages. **Fig. S5** The impaired temporoparietal synchronization was associated with both NREM sleep instability and REM sleep suppression. **Fig. S6** Altered functional connections between the mediodorsal thalamus and the cortical regions. **Table S1** Demographics and clinical characteristics of participants. **Table S2** The differences in sleep structures between healthy controls and ZAN patients (mean±SD). **Table S3** The 25 most probable two-step transitions in HC and ZAN patients (mean±SD). **Table S4** Phase-locking value (PLV) among different brain lobes for different stages (mean±SD). **Table S5** Correlation between atrophy rate of mediodorsal thalamus and PLV.

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Authors' contributions

CH, YL, and XLZ were responsible for the study concept and the design of the study. LL, QH, and QX performed the measurements and collected the data. HLB analyzed the data and created the tables and figures. LL, QH, and HLB wrote the paper. XH, JFC, ZMZ, XQL, YJZ, MML, XW, SYL, JXX, YW, and ZAH participated in discussions of the results and the paper. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information file. The raw structural MRI, functional MRI, and PSG data are publicly available on Open Neuro (https://openneuro.org/datasets/ds007181). All other data are available from the corresponding author upon reasonable request. Custom-made codes for two-sample *t*-test analysis, partial correlation analysis, linear mixed effect model analysis, spindles detection, PLV, and spectral power analyses are available on GitHub (https://github.com/ellebai/Publication-pain-and-sleep.git).

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Xinqiao Hospital of the Third Military Medical University of China (2021-Research No. 045-01). Written informed consent was obtained from all the participants. The diagnosis of ZAN was based on S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia (2019 edition).

Consent for publication

Not applicable.

Competing interests

The authors declared that they have no competing interests.

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