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ORIGINAL RESEARCH

Acupoint Sensitivity in Patients with Primary Insomnia and Its Correlation with Polysomnography and Heart Rate Variability: A Cross-Sectional Study

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Background: Primary insomnia (PI) is the most common clinical sleep disorder that can be effectively treated with acupuncture. However, the selection of optimal acupoints remain contentious.

Objective: To investigate the pain sensitization phenomenon of specific acupoints commonly used in treating PI, we evaluated the threshold and sensitization rate of acupoint sensitization and their correlations with sleep questionnaire scores, polysomnography (PSG) and heart rate variability (HRV) to identify the optimal sensitized points.

Methods: This study recruited 73 PI patients and 73 age- and sex-matched healthy controls in the outpatient acupuncture clinic of the Third Affiliated Hospital of Zhejiang University of Traditional Chinese Medicine from January 31, 2024 to March 31, 2025. Pressure pain thresholds (PPT) were tested at 10 specific points commonly used in PI. The primary outcome measure was calculated as the acupoint hyperalgesia rate using the receiver operating characteristic (ROC) curve. Secondary outcome measures included PSG and HRV indices of some subjects.

Results: Compared with the control group, PI patients showed significantly lower PPTs at specific acupoints such as RN14 and BL15, along with increased pain sensitivity rates. The pain sensitization rate in the T5-T8 nerve segments of PI patients was markedly elevated. Additionally, the degree of acupoint pain sensitization was negatively correlated with age and positively correlated with disease duration. Higher PSQI scores were associated with a greater likelihood of pain sensitization at EX-HN3, EX-HN0, and HT7. The probability of GV20 pain sensitization increased with higher SDS scores but decreased with increased high-frequency components in HRV.

Conclusion: Pain sensitization was observed at specific points commonly used in PI patients. BL15 and RN14 may be the best acupoints for clinical diagnosis and treatment. Furthermore, acupoint pain sensitization was correlated with age, high-frequency, disease duration, PSQI, and SDS. Acupoint pain sensitization can be used as a screening and assessment index for acupuncture treatment in insomnia patients, providing an objective basis for individualized treatment.

Keywords: primary insomnia, acupoint sensitization, polysomnography, heart rate variability, case-control study

Introduction

Insomnia, the most prevalent sleep disorder globally, affects approximately 50% of the adult population, with its incidence rising annually.[1,2] Primary insomnia (PI), characterized by sleep disturbances and impaired daytime functioning in the absence of secondary factors (such as other sleep disorders, psychiatric conditions, or physical illnesses), is a distinct clinical entity. Persistent sleep deprivation associated with PI significantly impairs mental health and cardiovascular function.[3,4] Chronic insomnia affects approximately 10% of adults globally, costs more than $100 billion in healthcare annually, and is associated with a 2–3 times higher risk of depression and cardiovascular disease.[5,6] Current pharmacological treatments are limited by the risks of dependency and adverse effects,[7] highlighting the need for safer alternatives. Acupuncture has shown promise in improving both subjective sleep quality and objective polysomnographic

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(PSG) parameters, such as sleep efficiency and modulation of N3/REM sleep.[8,9] However, the therapeutic efficacy of acupuncture is critically dependent on accurate acupoint selection.

The emerging acupoint sensitization theory provides a physiological basis for dynamic point localization. When functional impairment occurs within the body, specific acupoints transition from a relatively "quiet" state to a relatively "active" state (ie, sensitization).[10] Among these, allodynia constitutes the core manifestation of acupoint sensitization, being associated with the activation of peripheral nerve fibers such as C-fibers and Aδ-fibers—the nociceptive receptors.[11,12] The neurogenic inflammation theory posits that during the body's inflammatory response, mast cells release inflammatory mediators[13] (such as histamine [HA], substance P [SP], serotonin [5-HT], prostaglandins [PG], bradykinin [BK], and nerve growth factor [NGF]), thereby forming an "inflammatory pool" for these peripheral receptors. This induces abnormal responses in the sensory receptive fields at acupoint locations. Furthermore, neurons within the thalamic-mesencephalic grey matter and cerebral cortex also participate in the central mechanisms of pain sensitization.[14] International studies[15] have also demonstrated the association between insomnia and abnormal pain modulation, ie, insomnia leads to elevated sympathetic tone, which triggers central sensitization through activation of spinal dorsal horn neurons, which in turn lowers the pain threshold at acupoints.

Pathological conditions are known to reduce the pressure-pain threshold (PPT) at disease-relevant acupoints, meaning even minimal stimulation can evoke marked tenderness.[10] Crucially, the magnitude of PPT reduction correlates with nociceptive sensitization intensity and disease severity, making it a potential biomarker for PI.[16,17] Stimulating "sensitized points" (ie, acupoints in an active state) has been shown to significantly enhance treatment efficacy.[18,19] Consequently, investigating the pattern of acupoint sensitization in PI patients is essential for identifying optimal therapeutic targets and maximizing acupuncture efficacy. However, evidence regarding the spatial distribution, critical thresholds, and sleep physiology-related correlations of acupoint sensitization in PI patients remains inconsistent.

To address these gaps, this study aims to conduct an observational case-control study to map PPT changes and the distribution of pain-sensitizing acupoints in PI patients. Additionally, the study will establish a quantitative cut-off for acupoint sensitization, determine the sensitization rate at specific loci. To objectively bridge traditional diagnostic theories with measurable physiological markers, PSG and heart rate variability (HRV) testing were introduced to investigate the relationship between acupoint sensitivity rates and these physiological indicators.

Methods and Analysis

Study Design

This single-center, age- and sex-matched, cross-sectional study was conducted at the Department of Acupuncture, the Third Affiliated Hospital of Zhejiang Chinese Medical University (ZCMU). The flow chart of the study design is displayed in Figure 1 and Supplementary Table 1.

Participants

Between 31 January 2024 and 31 March 2025, 73 PI patients and 73 healthy controls were randomly recruited from the outpatient clinic and underwent an observational trial. Screening was conducted before the initiation of any treatment.

According to the description in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)[20] established by the American Psychological Association (APA), the diagnostic criteria for PI patients in this study are as follows: (1) self-reported dissatisfaction with sleep quantity or quality, as evidenced by one or more of the following: prolonged sleep-onset latency, frequent or prolonged nocturnal awakenings, or early-morning awakenings with an inability to resume sleep; (2) clinically significant distress or impairment in social, occupational, educational, or other important domains of functioning; (3) sleep difficulties occurring on at least three nights per week and persisting for at least one month; and (4) insomnia not attributable to the physiological effects of a substance or another medical or mental disorder.

The inclusion and exclusion criteria for PI patients and healthy control groups are shown in Table 1.

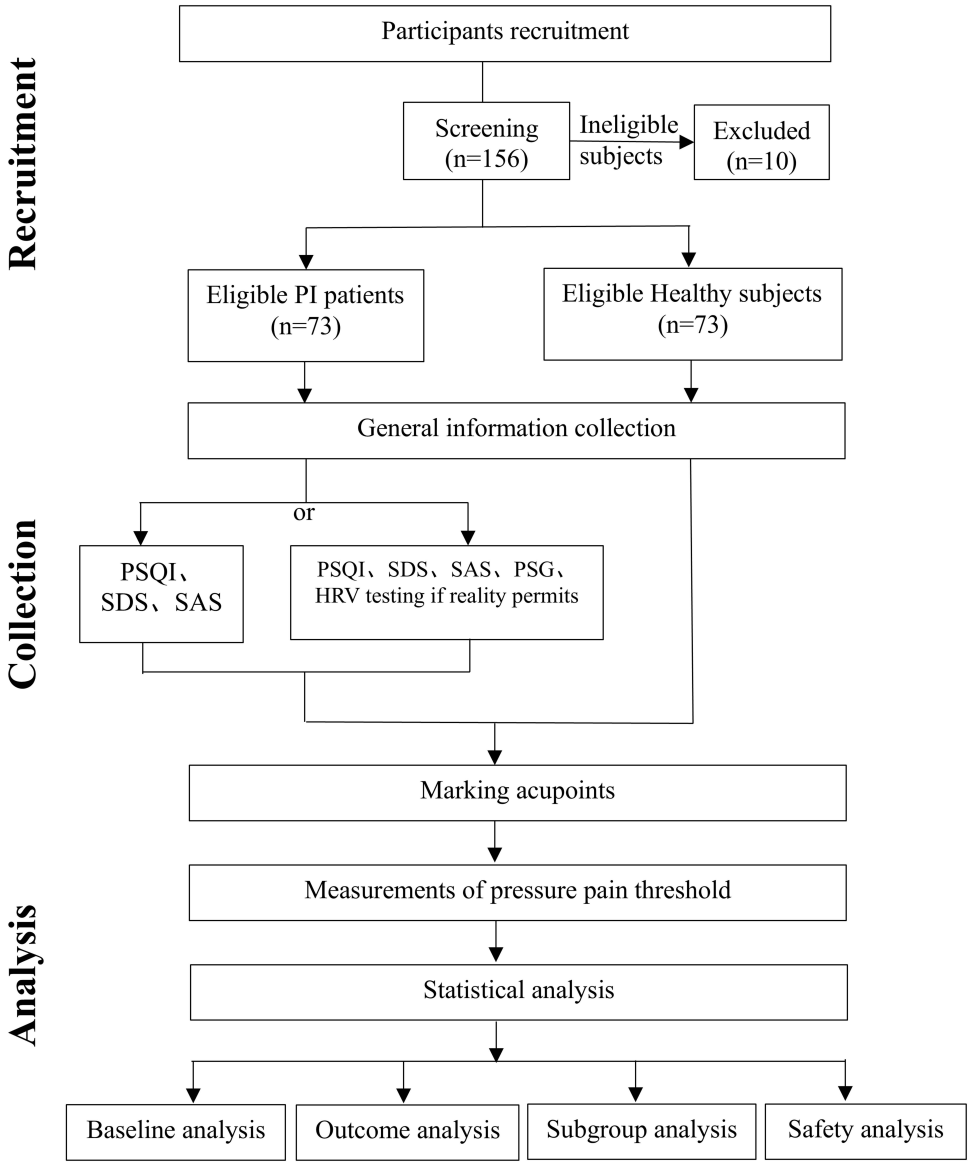

Figure 1 Flowchart of the study design.
Abbreviations: PI, Primary insomnia; PSQI, Pittsburgh Sleep Quality Index; SDS, Self-Rating Depression Scale; SAS, Self-Rating Anxiety Scale; PSG, Polysomnography; HRV, Heart rate variability.

Proceeding

All participants completed several questionnaires after signing informed consent forms, including demographic data (age, gender, educational attainment, etc).

PI patients were screened for eligibility based on established inclusion and exclusion criteria. Anxiety and depression severity were quantified using the SAS and the SDS. Sleep quality was assessed using the PSQI, where total scores range from 0 to 21, with higher scores indicating poorer sleep quality (11–15: average; 16–21: poor). Subsequent PSG and HRV assessments were performed based on individual clinical indications.

According to systematic reviews[21,22] and expert consensus on PI treatment, ten commonly used acupoints in clinical practice were selected for this study (Supplementary Table 2). To assess pain sensitivity at the acupoints, the following ten points were marked on both sides of the participants' bodies: *Baihui* (GV20), *Yintang* (EX-HN3), *Taiyang* (EX-HN5), *Anmian* (EX-HN0), *Fengchi* (GB20), *Shenmen* (HT7), *Neiguan* (PC6), *Sanyinjiao* (SP6), *Juque* (RN14), and *Xinshu* (BL15). These acupoints were circled using a marker pen (Supplementary Figure 1).

Table 1 The Inclusion and Exclusion Criteria for PI Group and Control Group

PI Group	
Inclusion criteria	(1) meeting the diagnostic criteria for sleep disorders;
	(2) aged 18–80 years, without gender restrictions;
	(3) no communication or cognitive impairments;
	(4) no use of or discontinuation of antianxiety or other psychiatric medications within the past month;
	(5) no major physical illnesses;
	(6) willingness to participate in the study, complete all questionnaire assessments, and, if feasible, undergo polysomnography and heart rate variability testing;
	(7) signing an informed consent form before the study begins.
Exclusion criteria	(1) failure to meet inclusion criteria;
	(2) individuals with severe mental disorders or a history of severe head trauma with significant impaired consciousness;
	(3) individuals with severe liver or kidney dysfunction or a tendency to bleed;
	(4) individuals who abuse alcohol (≥100 mL of spirits per day), smoke heavily (≥15 cigarettes per day), use illicit drugs, or take psychotropic medications;
	(5) individuals with other sleep disorders (sleep apnoea hypopnoea syndrome, rapid eye movement sleep behavior disorder);
	(6) pregnant or breastfeeding women;
	(7) individuals with other serious, poorly controlled illnesses;
	(8) individuals with skin damage at the acupoint site;
	(9) individuals who refuse to sign the informed consent form.
Control Group	
Inclusion criteria	(1) Aged 18–80 years, without gender restrictions;
	(2) no history of the following symptoms: difficulty falling asleep, light sleep, frequent awakenings, vivid dreams, early awakening, difficulty returning to sleep after awakening, daytime fatigue or sleepiness;
	(3) no regular use of sleep aids, anti-anxiety medications, or other psychotropic medications;
	(4) participants demonstrate good compliance, voluntarily participate, and sign an informed consent form.
Exclusion criteria	(1) failure to meet the inclusion criteria;
	(2) history of excessive alcohol consumption;
	(3) diagnosis of a serious illness within the past year, mental illness, or allergic constitution;
	(4) pregnant or lactating women;
	(5) refusal to sign the informed consent form;
	(6) skin damage at the acupoint site;
	(7) individuals meeting any of the above criteria.

Abbreviation: PI, Primary insomnia.

Measurement of PPTs

The PPT is a semi-objective method commonly used in clinical practice to quantify local pain sensitivity, which was quantified using an FDIX force gauge (Force One FDIX, Wagner Instruments, USA) equipped with an 8-mm rubber head (Supplementary Figure 2). Pressure was applied perpendicularly to the acupoints at a rate of 100 gf/s until participants

reported the onset of pain. To eliminate visual bias, participants were blindfolded during testing. Two measurements were recorded for each acupoint with a 2-minute interval, and the mean was calculated. If the difference between measurements exceeded 500 gf, a third measurement was performed, and the average of the two closest values was used. All assessors were standardized in training and blinded to participant groups and acupoint characteristics.

Measurement of PSG and HRV

Prior to acupoint pressure pain testing, eligible patients underwent overnight PSG using the Philips Alice 6 system at the Sleep Disorders Centre (Third Affiliated Hospital of ZCMU). Patients adhered to their habitual sleep–wake schedules. Sleep parameters were analyzed via Sleepware G3 software. Additionally, HRV data were acquired using Seer12 Holter monitors and processed with GE MARS software. Both sleep parameters and HRV indices were evaluated for correlations with acupoint sensitization (Supplementary Figure 3 and Supplementary Table 3).

Outcome Measurements

Primary Outcome

Definition of Acupoint Sensitization: PPT values were pooled to establish a diagnostic threshold using Receiver Operating Characteristic (ROC) curve analysis. The optimal cutoff was defined as the value maximizing the Youden index (sensitivity + specificity - 1). Acupoints were dichotomized as "sensitized" or "non-sensitized" based on this threshold. Two metrics were derived: (1) Acupoint sensitization rate (proportion of sensitized participants for a specific acupoint); and (2) Individual sensitization rate (proportion of sensitized acupoints for a specific participant).

Secondary Outcome

(1) PSG: Including sleep latency (s), sleep efficiency (%), arousal after sleep onset (times), percentage of slow-wave sleep (N3 stage) (%), and percentage of rapid eye movement (REM) stage (%).

(2) HRV: HRV frequency domain analysis encompasses four key components. HRV frequency domain analysis included Very Low Frequency (VLF, 0.0033–0.04 Hz) for sympathetic activity, Low Frequency (LF, 0.04–0.15 Hz) for mixed sympathetic-parasympathetic modulation, High Frequency (HF, 0.15–0.4 Hz) for parasympathetic tone (unit is ms^2), and the LF/HF ratio for sympathovagal balance. The correlations between these indices and acupoint sensitization were also examined. The correlation between these indices and acupoint sensitization was also analyzed.

Sample Size Calculation

This study employed a matched case-control design, with the case group consisting of patients with primary insomnia and the control group comprising healthy subjects. The primary exposure factor under investigation was the rate of acupoint sensitization. In the matched design, the age difference between participants in the case group and their matched controls was restricted to within ±3 years, with a matching ratio of 1:1. According to a previous study[23] and the results of the pre-test, the acupoint sensitization rate in patients ranged from 20% to 70%; thus, a 50% rate was assumed for calculating the minimum required sample size. The sensitization rate in healthy participants was set at 20%, and the odds ratio (OR) for the occurrence of acupoint sensitization in patients with primary insomnia was expected to be 4. The correlation between the cases and the first matched control was assumed to be Phi=0.2, with α=0.05 and β=0.01, and the control-to-case ratio was 1:1. Sample sizes for both the case and control groups were calculated using PASS 2021 software, yielding N1=N2=66. Accounting for a 10% nonresponse rate, the final sample size was adjusted to 146 participants (N1=N2=73).

Data Analysis

Data management and statistical analysis were conducted using EpiData 3.1 for data validation and error checking, and SPSS 25.0 (SPSS Inc., Chicago, Illinois, USA) software. This study adopted a retention strategy for missing data without imputation. Continuous variables (such as age, height, weight) were expressed as mean ± standard deviation (Mean ± SD), while categorical variables (such as gender, occupation, education level) were presented as frequency (percentage) [n (%)]. Intraclass correlation coefficients (ICC) were employed to analyze the consistency between two measurements

of the PPT. An ICC ≥ 0.75 indicates good agreement, 0.4 ≤ ICC < 0.75 denotes moderate agreement, and an ICC < 0.4 signifies poor agreement. The normality of data was comprehensively assessed using Shapiro–Wilk test, histograms, and Q-Q plots. Comparisons of PPT between groups were performed using parametric tests (independent samples *t*-test) or non-parametric tests (Wilcoxon rank-sum test) based on data distribution characteristics. ROC curves were plotted to determine the optimal PPT cutoff value for distinguishing between sensitized and non-sensitized states. Differences in acupoint sensitization rates between groups were compared using chi-square test (χ^2) or Fisher's exact probability method. For regression and correlation analysis, verify assumptions such as linearity, independence, and multicollinearity. Correlation analysis between influencing factors and PPT values was conducted using Pearson correlation analysis or Spearman rank correlation analysis depending on the type of data distribution. Logistic regression models were used to estimate unadjusted odds ratios (OR) and their 95% confidence intervals (95% CI) for factors associated with acupoint sensitization, where OR > 1 indicated a risk factor and OR < 1 indicated a protective factor. Covariates (such as age, gender) selected based on clinical expertise and univariate analysis results (P < 0.05) were included in stepwise logistic regression models to calculate adjusted odds ratios (Adjusted OR) and their 95% CI, quantifying the independent association strength between each factor and acupoint sensitization. To verify the robustness of the results, reliability assessment was performed through sensitivity analysis (eg, using alternative variable coding methods, delete incomplete data in pairs). Since implementation of PSG and HRV monitoring is influenced by a number of factors, it is predicted that the reduced sample sizes of the PSG and HRV subgroups will result in a possible lack of statistical validity in correlation analyses of the PSG/HRV parameters, and therefore, they are used only as exploratory analyses. All tests were two-sided, with a significance level α set at 0.05, and P < 0.05 considered statistically significant.

Results

Recruitment and Baseline Analysis

Pairwise deletion was used to deal with missing data, and the final sample size included in the analysis was 146 cases. A total of 73 patients with PI (27 males and 46 females) with a mean age of 47.63±13.88 years were included in this study. All patients with PI were categorized by the type of insomnia, which was difficulty falling asleep (31, 42.5%), difficulty maintaining sleep (8, 11.0%), early awakening (15, 20.5%), and mixed (19, 26.0%). The healthy control group consisted of 25 male and 48 female subjects with a mean age of 47.34 ± 15.25 years. PSQI, SAS, SDA, duration of illness, type of insomnia, and frequency of episodes were related to the disease state and, therefore, mentioned only in the case group (Table 2). And the intragroup correlation coefficient (ICC) ICC 0.786–0.884, P < 0.05, indicating good agreement between the two PPT tests.

Primary Outcome

Comparison of Acupoint PPT and Pain Sensitization Rate

All continuous variables conformed to normal distribution (Shapiro–Wilk test, p>0.05), comparisons between groups were made using independent samples t-tests, and variance chi-squared tests showed chi-squaredness (Levene test, p>0.05). Compared with the control group, the PPT was lower at all specific points in the case group (P<0.05). After plotting the ROC curves of pressure pain measurements at all tested acupoints in PI patients and healthy people, the cut-off values that could distinguish between PI patients and healthy people with relatively best sensitivity and specificity were selected, and the results showed that the area under the curve of most acupoints (8) was greater than 0.7, and Youden's index was greater than 0.3 for most of the acupoints (9); among them, Juquei (RN14), Xinshu (BL15), Anmian (EX-HN0), Fengchi (GB20), Baihui (GV20), and Sanyinjiao (SP6). The truncation value defined the effect relatively well (Table 3).

Calculating and comparing the acupoint sensitization rates of all acupoints in PI patients and healthy individuals, it was found that there was a significant difference between the acupoint sensitization rates of acupoints in PI patients and healthy individuals, and the acupoint sensitization rates of patients' acupoints were significantly higher than those of healthy individuals (P<0.05), and the specific differences were in the acupoints of Juquei (RN14), Xinshu (BL15), Fengchi (GB20), Anmian (EX-HN0), Sanyinjiao (SP6), Baihui (GV20) and Neiguan (PC6), with a difference of greater than 40% (Tables 4, 5 and Figure 2).

Table 2 Characteristics of the PI Group and Control Group

Characteristics	PI Group (n=73)	Control Group (n=73)	χ2/t	*P*
Sex, n (%)			0.119	0.730
Male	27(37.0%)	25(34.2%)		
Female	46(63.0%)	48(65.8%)		
Age (years)	47.63±13.88	47.34±15.25	0.014	0.905
Level of education			0.214	0.644
Below the graduate level	61(83.6%)	63(86.3%)		
Graduate degree or above	12(16.4%)	10(13.7%)		
BMI	22.42±2.28	23.32±3.04	4.139	0.044*
PSQI	16.00(13.00, 19.00)	–		
SAS	46.42±8.50	–		
SDS	43.00(36.00, 50.50)	–		
PI duration				
3-6 months	11(15.1%)	–		
6-12 months	9(12.3%)	–		
12-36 months	27(37.0%)	–		
>36 months	26(35.6%)	–		
Types of insomnia				
Difficulty falling asleep	31(42.5%)	–		
Difficulty staying asleep	8(11.0%)	–		
Early riser	15(20.5%)	–		
Hybrid type[a]	19(26.0%)	–		
Frequency of occurrence				
3 times a week	15(20.5%)	–		
4-5 times a week	24(32.9%)	–		
>5 times a week	34(46.6%)	–		

Notes: *Indicates *P*<0.05, the difference is statistically significant; [a] indicates two or more types of insomnia.
Abbreviations: PI, Primary insomnia; BMI, Body Mass Index; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

Table 3 ROC Curves Showing the Diagnostic Performance of PPT Values Distinguishing PI from Controls

	Area Under the Curve (AUC)	*p* value	Cutoff Value	Sensitivity	1-Specificity	Youden Index
GV20	0.828	<0.001	1270.000	0.863	0.342	0.521
EX-HN3	0.702	<0.001	1197.500	0.849	0.521	0.328
EX-HN5	0.679	<0.001	1223.750	0.808	0.493	0.315
EX-HN0	0.848	<0.001	1395.000	0.808	0.260	0.548
GB20	0.838	<0.001	1637.500	0.740	0.164	0.576
HT7	0.682	<0.001	1485.000	0.562	0.301	0.261
PC6	0.789	<0.001	1422.500	0.822	0.411	0.411
SP6	0.821	<0.001	1608.750	0.685	0.164	0.521
RN14	0.888	<0.001	2072.500	0.808	0.164	0.644
BL15	0.942	<0.001	1640.000	0.877	0.082	0.795

Abbreviations: ROC, Receiver Operating Characteristic; PPT, Pressure Pain Threshold; PI, Primary insomnia.

Comparison of Individual Sensitization Rates at Acupoints

There was a significant difference in the rate of individual pain sensitization at acupoints in patients with PI compared with healthy individuals, and the rate of individual pain sensitization at acupoints in patients with PI was higher than that of healthy individuals, with a statistically significant difference (P<0.05) (Table 6 and Figure 3).

Table 4 Acupoint PPT for PI and the Control Group (Mean±SD, Gf)

	PI Group	Control Group	t	Cohen's d	*p* value
GV20	1204.45±272.82	1602.60±336.88	7.847	1.299	<0.001*
EX-HN3	1251.16±350.09	1496.71±310.36	4.484	0.742	<0.001*
EX-HN5	1253.19±303.53	1451.85±280.14	4.109	0.680	<0.001*
EX-HN0	1283.63±231.66	1783.84±465.52	8.219	1.360	<0.001*
GB20	1383.87±254.63	1897.19±501.63	7.796	1.290	<0.001*
HT7	1372.84±240.16	1640.41±411.54	4.798	0.794	<0.001*
PC6	1376.82±264.57	1747.12±377.03	6.869	1.137	<0.001*
SP6	1394.93±225.18	1980.68±658.89	7.188	1.190	<0.001*
RN14	1813.25±324.86	2614.18±737.25	8.494	1.406	<0.001*
BL15	1340.27±276.17	1961.37±340.46	12.105	2.00	<0.001*

Notes: * indicates P<0.05; the difference is statistically significant.
Abbreviations: PPT, Pressure Pain Threshold; PI, Primary insomnia.

Table 5 Acupoint Sensitization Rate for PI and the Control Group (n(%))

	PI Group	Control Group	x2	*p* value
GV20	47(64.4%)	10(13.7%)	39.400	<0.001*
EX-HN3	35(47.9%)	11(15.1%)	18.282	<0.001*
EX-HN5	37(50.7%)	14(19.2%)	15.941	<0.001*
EX-HN0	54(74.0%)	14(19.2%)	44.042	<0.001*
GB20	61(83.6%)	19(26.0%)	48.777	<0.001*
HT7	51(69.9%)	32(43.8%)	10.080	<0.001*
PC6	43(58.9%)	13(17.8%)	26.071	<0.001*
SP6	61(83.6%)	23(31.5%)	40.481	<0.001*
RN14	61(83.6%)	14(19.2%)	60.566	<0.001*
BL15	67(91.8%)	9(12.3%)	92.320	<0.001*

Note: *Indicates *P*<0.05; the difference is statistically significant.
Abbreviation: PI, Primary insomnia.

Comparison of PPT and Acupoint Sensitization Rates at Various Nerve Segment Acupoints

Each clinically used specific point was divided into five nerve segments according to the difference of the nerve segment in which it was located, including segments V1-V3 of the trigeminal nerve (*Baihui* (GV20), *Yintang* (EX-HN3), and *Taiyang* (EX-HN5)), segments C2-C3 (*Anmian* (EX-HN0) and *Fengchi* (GB20)), segments C6-T1 (*Neiguan* (PC6) and *Shenmen* (HT7)), segments T5-T8 (*Xinshu* (BL15) and *Juque* (RN14)), and segments L3-S3 (*Sanyinjiao* (SP6)). Comparisons revealed that the PPT of acupoints of PI patients was significantly lower than that of healthy subjects in each ganglion (P<0.05).

After their sub-segmental acupoint PPT was plotted on the ROC curve, the results showed that the five ganglionic acupoints were better defined, and the pain sensitization rate of each ganglionic acupoint was further calculated. Comparison revealed that the pain sensitization rate of acupoints of patients with PI was significantly higher than that of healthy people in all segments (P<0.05), with a greater difference (58%) in the T5-T8 ganglia (Tables 7, 8 and 9) (Figure 4).

Secondary Outcomes

Insomnia Type, Duration, and Frequency of Episodes and Acupoint Sensitization

The PPT and acupoint sensitization rates of acupoints in patients with PI did not differ significantly by insomnia type and were not statistically different (P>0.05) (Supplementary Tables 4 and 5). Pressure-pain measurements at the *Yintang* (EX-HN3), *Taiyang* (EX-HN5), *Fengchi* (GB20), *Neiguan* (PC6), and *Sanyinjiao* (SP6) points in patients with PI differed significantly (P<0.05) under different disease duration stratification; and the difference of pain sensitization rate of the

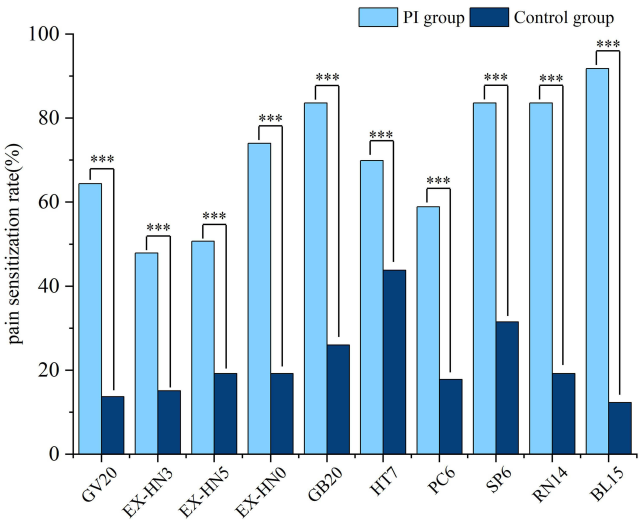

Figure 2 Acupoints pain sensitization rate for participants.
Notes: ***Indicates *P*<0.001, the difference is statistically significant.

Shenmen (HT7) acupoints in patients with PI under different disease duration stratification was significantly (P<0.05) (Supplementary Tables 6 and 7). The PPT at the *Xinshu* (BL15) acupoint in PI patients was lower at 3 insomnia episodes/week than at 4–5 insomnia episodes/week and at more than 5 insomnia episodes/week (P<0.05). There was no significant difference in the pain sensitization rate of all the acupoints of the PI patients in terms of the frequency of insomnia episodes (P>0.05) (Supplementary Tables 8 and 9).

PSG Parameters and Acupoint Sensitization

Sleep Continuity and Acupoint Sensitization

In this study, PSG parameters were collected from 25 patients with PI. The PPT and sleep continuity parameters (including sleep latency, sleep efficiency, and time of awakening after sleep onset) of all the specific points of these 25 patients with PI were correlated and analyzed. Multiple linear regression analysis was conducted, and the scatter plot results revealed no linear relationship or overall monotonicity, with normality tests indicating that the data did not follow a normal distribution. Consequently, Spearman correlation analysis was employed to examine the relationships between each acupoint and sleep latency, sleep efficiency, and time awake after sleep onset. The results showed a significant correlation between the PPT of Yingtang (EX-HN3) and sleep latency in patients with primary insomnia ($r = -0.468$, $P = 0.021$) (Supplementary Table 10). No significant correlations were found between acupoint sensitization and sleep continuity parameters ($P > 0.05$) (Supplementary Table 11).

Sleep Depth and Acupoint Sensitization

PPT and sensitization rates at individual acupoints in 25 patients with PI were examined for associations with sleep-depth parameters-specifically, stage N3 duration and N3 percentage. Multiple linear regression was applied to analyze the data; however, the scatter plot results revealed no linear relationship. As the N3 duration and N3 percentage increased, the acupoint

Table 6 Individual Acupoint Sensitization Rate

Group	Individual Acupoint Pain Sensitivity Rate (n(%))		χ^2	*p* value
	≤50%	>50%		
PI group	20(27.4%)	53(72.6%)	65.906	<0.001*
Control group	68(93.2%)	5(6.8%)		

Note: *Indicates *P*<0.05; the difference is statistically significant.
Abbreviation: PI, Primary insomnia.

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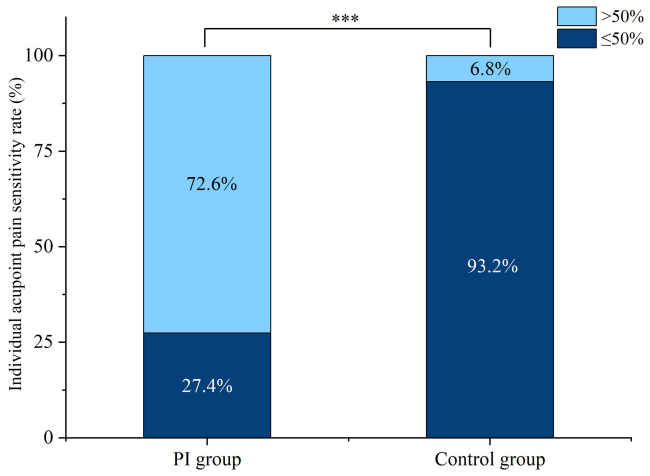

Figure 3 Individual acupoint sensitization rate.
Notes: ***Indicates *P*<0.001, the difference is statistically significant.

PPT also showed a general increase corresponding to each sleep depth parameter, suggesting a monotonic relationship. Given the lack of normality in the data, Spearman correlation analysis was employed to examine the associations between each acupoint and both N3 duration and N3 percentage. The results showed that a significant correlation was found between the PPT of *Baihui* (GV20) acupoint and N3 percentage in PI patients (r = 0.448, P = 0.047) (Supplementary Table 12). No significant correlation was found between acupoint sensitization and sleep depth parameters (P > 0.05) (Supplementary Table 13).

REM Phase and Acupoint Sensitization

The PPT and pain sensitization rate of all acupoints in these 25 PI patients were correlated with the REM phase parameters (including REM latency and REM occupancy) individually. Multiple linear regression was performed to analyze the data, and the scatter plot results revealed no linear relationship. As REM latency and REM occupancy increased, the PPT at each

Table 7 ROC Curves Showing the Diagnostic Performance of PPT Values of Different Neural Segments Between PI and the Control Group

Nerve Segment	Area Under the Curve (AUC)	*p* value	Cutoff Value	Sensitivity	1-Specificity	Youden Index
V1-V3	0.740	<0.001	1223.750	0.845	0.466	0.380
C2-C3	0.831	<0.001	1473.750	0.782	0.260	0.522
C6-T1	0.735	<0.001	1547.500	0.562	0.226	0.336
T5-T8	0.859	<0.001	1757.500	0.890	0.308	0.582
L3-S3	0.821	<0.001	1608.750	0.685	0.164	0.521

Abbreviations: ROC, Receiver Operating Characteristic; PPT, Pressure Pain Threshold; PI, Primary insomnia.

Table 8 Comparison of PPT at Acupoints in Different Nerve Segments Between PI and the Control Group (Mean±SD, Gf)

Nerve Segment	PI Group	Control Group	t	Cohen's d	*P*
V1-V3	1236.27±309.84	1515.80±314.84	9.375	0.895	<0.001*
C2-C3	1333.75±247.73	1838.20±484.73	11.205	1.311	<0.001*
C6-T1	1374.83±251.80	1693.77±396.93	8.198	0.960	<0.001*
T5-T8	1576.76±382.87	2287.77±659.34	11.268	1.319	<0.001*
L3-S3	1394.93±225.18	1980.68±658.89	7.188	1.190	<0.001*

Note: *Indicates *P*<0.05; the difference is statistically significant.
Abbreviations: PPT, Pressure Pain Threshold; PI, Primary insomnia.

Table 9 Comparison of Acupoint Sensitization Rate in Different Nerve Segments Between PI and the Control Group (n(%))

Nerve Segment	PI Group	Control Group	x^2	*p* value
V1-V3	117(53.4%)	34(15.5%)	70.121	<0.001*
C2-C3	108(74.0%)	32(21.8%)	80.006	<0.001*
C6-T1	113(77.4%)	64(43.8%)	34.443	<0.001*
T5-T8	101(69.2%)	16(11.0%)	103.038	<0.001*
L3-S3	61(83.6%)	23(31.5%)	40.481	<0.001*

Note: *Indicates *P*<0.05; the difference is statistically significant.
Abbreviation: PI, Primary insomnia.

acupoint decreased in a roughly monotonic manner. Given that the normality test indicated non-normal distribution, Spearman correlation analysis was employed to assess the relationship between each acupoint and REM latency as well as REM occupancy. The results showed that no statistically significant correlation was found between PPT and REM parameters for all acupoints in patients with primary insomnia (Supplementary Table 14). Additionally, no significant correlation was found between acupoint sensitization and REM period parameters (P > 0.05) (Supplementary Table 15).

HRV and Acupoint Sensitization

In this study, HRV data were obtained from same 25 patients diagnosed with PI. Specific parameters included VLF, LF, and HF, with the LF/HF ratio used to reflect the autonomic balance between the sympathetic and parasympathetic nervous systems. Multiple linear regression was used for the analysis, and the scatter plot results revealed no linear relationship between the data. As VLF, LF, HF, and LF/HF increased, the PPT at each acupoint decreased in response to each HRV parameter, showing an overall monotonic relationship. Since the normality test indicated a non-normal distribution, Spearman correlation analysis was employed to assess the relationship between each acupoint and the VLF, LF, HF, and LF/HF ratio. The results showed a significant correlation between PPT and LF/HF at the *Baihui* (GV20) acupoint (r = −0.476, P = 0.016), as well as a significant correlation between PPT and LF at the *Sanyinjiao* (SP6) acupoint (r = −0.397, P = 0.049) in patients with PI (Supplementary Table 16).

The VLF abnormality significantly affected the likelihood of sensitization at the Baihui (GV20) acupoint (OR = 1.972, 95% CI 0.945–1.000, P = 0.049), and the HF abnormality also significantly influenced the likelihood of sensitization at the Baihui (GV20) acupoint (OR = 1.722, 95% CI 0.523–0.998, P = 0.048) (Table 10 and Table 11).

Analysis of Factors Affecting Acupoint Sensitivity Rates

Age, gender, BMI, PSQI, SAS, and SDS were incorporated into the logistic regression model. In addition, Supplementary Table 7 performed one-way ANOVA on the disease duration of PI patients, and the results showed a significant difference in the pain sensitization rate at the *Shenmen* (HT7) acupoint (P < 0.05) across different disease durations, necessitating their inclusion in the logistic regression analysis based on disease duration. Table 10 performed a one-way logistic regression analysis on the frequency domain parameters of HRV in PI patients, and the results indicated a significant correlation between the sensitization rate at the *Baihui* (GV20) acupoint and VLF and HF (P < 0.05), warranting their inclusion in the logistic regression analysis for VLF and HF. Insomnia type, duration of insomnia, frequency of episodes, and PSG parameters were not significantly associated with the sensitization rate of acupoint pain after one-way ANOVA (P > 0.05) and were therefore excluded from the logistic regression analysis.

Multifactorial logistic regression analysis revealed that older age was associated with a lower likelihood of pain sensitization at the Yintang (EX-HN3), Taiyang (EX-HN5), Anmian (EX-HN0), and Shenmen (HT7) acupoints. Higher PSQI scores were associated with an increased likelihood of pain sensitization at the Yintang (EX-HN3), Anmian (EX-HN0), and Shenmen (HT7) acupoints. Higher SDS scores were correlated with an increased likelihood of pain sensitization at the Baihui (GV20) and Sanyinjiao (SP6) acupoints. Higher HF values were associated with a reduced likelihood of pain sensitization at the Baihui (GV20) acupoint. The duration of the disease was an influential factor in the occurrence of pain sensitization at the Shenmen (HT7), with longer disease duration increasing the likelihood of pain sensitization at this acupoint. Gender, BMI, and SAS were not found to be significant factors for pain sensitization at acupoints in patients with PI (Table 12).

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Table 10 VLF, LF, HF: Single-Factor Logistic Regression of Acupoint Sensitivity and HRV Parameters (ms^2)

	VLF (0.000–0.040Hz)						LF (0.040–0.150Hz)						HF (0.150–0.400Hz)					
	B	**SE**	**Wald**	***P***	***OR***	**95% CI (Lower Bound-Upper Bound)**	**B**	**SE**	**Wald**	***P***	***OR***	**95% CI (Lower Bound-Upper Bound)**	**B**	**SE**	**Wald**	***P***	***OR***	**95% CI (Lower Bound-Upper Bound)**
GV20	−0.029	0.015	3.865	0.049*	1.972	(0.945−1.000)	0.225	0.115	3.851	0.050	1.253	(1.000−1.569)	−0.325	0.165	3.894	0.048*	1.722	(0.523−0.998)
EX-HN3	0.028	0.030	0.869	0.351	1.028	(0.970−1.029)	0.059	0.058	1.054	0.305	1.061	(0.947−1.189)	−0.118	0.102	1.339	0.247	0.889	(0.727−1.085)
EX-HN5	0.065	0.045	2.125	0.145	1.068	(0.978−1.166)	−0.004	0.054	0.005	0.943	0.996	(0.895−1.108)	−0.055	0.100	0.301	0.583	0.947	(0.779−1.151)
EX-HN0	−0.045	0.046	0.994	0.319	0.956	(0.874−1.045)	0.392	0.320	1.498	0.221	1.480	(0.790−2.771)	−0.099	0.340	0.085	0.770	0.905	(0.465−1.764)
GB20	0.000	0.017	0.000	0.999	1.000	(0.968−1.033)	0.033	0.081	0.167	0.683	1.034	(0.882−1.212)	−0.077	0.137	0.312	0.576	0.926	(0.707−1.212)
HT7	1.106	1.491	0.551	0.458	3.023	(0.163−5.614)	1.529	2.175	0.494	0.482	4.612	(0.065−3.273)	−1.896	2.717	0.487	0.485	1.150	(0.001−3.085)
PC6	0.021	0.034	0.396	0.529	1.021	(0.956−1.091)	−0.053	0.097	0.296	0.587	0.948	(0.784−1.148)	0.136	0.198	0.475	0.490	1.146	(0.778−1.689)
SP6	0.070	0.076	0.842	0.359	1.072	(0.924−1.244)	−0.085	0.093	0.843	0.358	0.918	(0.766−1.101)	0.093	0.180	0.268	0.605	1.098	(0.771−1.562)
RN14	0.029	0.052	0.316	0.574	1.030	(0.930−1.140)	0.167	0.111	2.272	0.132	1.182	(0.951−1.468)	0.323	0.189	2.922	0.087	1.382	(0.954−2.001)
BL15	0.078	0.066	1.363	0.243	1.081	(0.949−1.231)	0.052	0.144	0.131	0.718	1.053	(0.795−1.396)	0.111	0.249	0.200	0.654	1.118	(0.687−1.819)

Note: *Indicates $P<0.05$; the difference is statistically significant. B indicates regression coefficient, SE indicates standard error, Wald indicates statistical value.
Abbreviations: HRV, Heart rate variability; VLF, Very Low Frequency; LF, Low Frequency; HF, High Frequency; *OR*, odds ratios; 95% CI, 95% confidence intervals.

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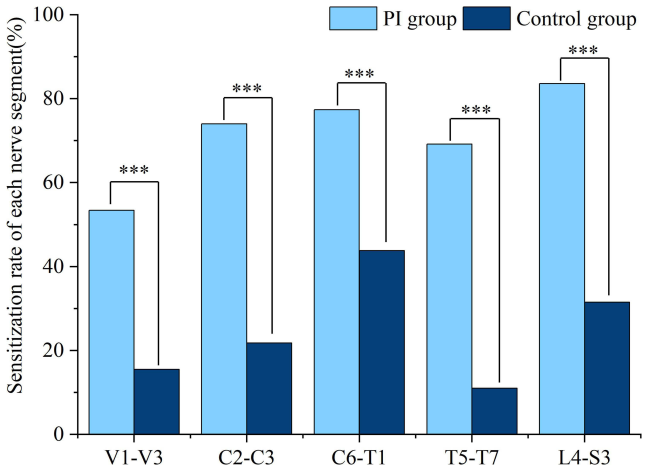

Figure 4 Sensitization rate of each nerve segment.
Notes: ***Indicates *P*<0.001, the difference is statistically significant.

Discussion

Our study demonstrated that the PPTs of all specific acupoints in PI patients were significantly lower than those of healthy subjects, while the acupoint sensitization rates were notably higher, with significant variations observed among individual acupoints. This finding provides robust evidence for the widespread and significant acupoint sensitization in patients with PI. Further analysis revealed that acupoint sensitization was not randomly distributed, demonstrating specific patterns. The sensitization rates of *Juque* (RN14, 91.8%), *Xinshu* (BL15, 83.6%), *Sanyinjiao* (SP6, 83.6%), and *Fengchi* (GB20, 83.6%) were particularly prominent, with these highly sensitized acupoints primarily localized to the T5-T8 ganglion.

Blunt pressure stimulation-induced pain is mediated by C fibers,[24] and a lower PPT value indicates a reduced pain perception threshold. The mean pain sensitization rate increased by 49.06% in the patient group, suggesting that PPT may serve as an objective measure for assessing insomnia. Low-frequency episodes of insomnia represent the transition from acute to chronic insomnia. It has been suggested[25] that acute sympathetic over-activation sensitizes spinal dorsal-horn neurons, amplifies nociceptive signaling, and induces acupoint hyperalgesia; conversely, chronic insomnia, whether frequent or protracted, drives sustained hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, depletes endogenous analgesics (eg, endorphins), and elicits compensatory down-regulation of nociceptive control, manifesting as elevated pain thresholds. This was consistent with the finding that the PPT at the *Xinshu* (BL15) acupoints of PI patients with 3 insomnia episodes/week was lower than that in patient with 4–5 episodes/week and more than 5 episodes/week (P<0.05). Emerging evidence indicates that

Table 11 LF/HF: Single-Factor Logistic Regression of Acupoint Sensitivity and HRV Parameters (ms^2)

	LF/HF					
	B	**SE**	**Wald**	***P***	***OR***	**95% CI (Lower Bound-Upper Bound)**
GV20	−0.042	0.113	0.137	0.711	0.959	(0.769−1.197)
EX-HN3	−0.019	0.106	0.034	0.855	0.981	(0.796−1.208)
EX-HN5	0.009	0.115	0.007	0.935	1.009	(0.805−1.266)
EX-HN0	0.455	0.427	1.140	0.286	1.577	(0.683−3.638)
GB20	0.078	0.268	0.084	0.772	1.081	(0.639−1.829)
HT7	2.648	3.176	0.695	0.404	1.413	(0.028−1.138)
PC6	0.980	1.410	0.483	0.487	2.665	(0.168−4.223)
SP6	0.583	1.228	0.225	0.635	1.791	(0.161−1.988)
RN14	−0.235	0.599	0.155	0.694	0.790	(0.244−2.555)

Notes: B indicates regression coefficient, SE indicates standard error, Wald indicates statistical value.
Abbreviations: HRV, Heart rate variability; *OR*, odds ratios; 95% CI, 95% confidence intervals.

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Table 12 Multifactorial Logistic Analysis of Acupoint Sensitization

Influences	GV20			EX-HN3			EX-HN5			EX-HN0			GB20		
	P	*OR*	95% CI (Lower Bound-Upper Bound)	*P*	*OR*	95% CI (Lower Bound-Upper Bound)	*P*	*OR*	95% CI (Lower Bound-Upper Bound)	*P*	*OR*	95% CI (Lower Bound-Upper Bound)	*P*	*OR*	95% CI (Lower Bound-Upper Bound)
Age	0.362	0.961	(0.883–1.047)	0.028*	0.954	(0.915–0.995)	0.002*	0.934	(0.893–0.976)	0.012*	0.936	(0.889–0.986)	0.117	0.957	(0.905–1.011)
Sex	0.131	0.185	(0.021–1.653)	0.346	0.574	(0.181–1.824)	0.247	0.508	(0.161–1.599)	0.520	0.663	(0.189–2.320)	0.577	0.674	(0.169–2.692)
BMI	0.786	1.073	(0.647–1.780)	0.105	1.236	(0.956–1.598)	0.215	1.176	(0.910–1.520)	0.512	1.105	(0.820–1.488)	0.744	0.948	(0.689–1.305)
PSQI	0.079	5.065	(0.829–3.092)	0.016*	1.220	(0.064–0.751)	0.425	0.616	(0.188–2.023)	0.031*	1.916	(0.516–0.711)	0.168	0.295	(0.052–1.674)
SAS	0.386	5.680	(0.112–2.890)	0.872	0.908	(0.281–2.936)	0.446	0.634	(0.196–2.049)	0.219	0.437	(0.116–1.638)	0.523	0.604	(0.129–2.839)
SDS	0.038*	1.053	(0.890–0.988)	0.393	0.561	(0.149–2.109)	0.731	0.790	(0.207–3.019)	0.198	2.567	(0.610–1.083)	0.447	0.842	(0.145–4.868)
VLF	0.097	0.981	(0.959–1.003)												
HF	0.049*	0.916	(1.056–1.227)												
Influences	**HT7**			**PC6**			**SP6**			**RN14**			**BL15**		
	P	*OR*	95% CI (Lower Bound-Upper Bound)	*P*	*OR*	95% CI (Lower Bound-upper Bound)	*P*	*OR*	95% CI (Lower Bound-Upper Bound)	*P*	*OR*	95% CI (Lower Bound-Upper Bound)	*P*	*OR*	95% CI (Lower Bound-Upper Bound)
Age	0.003*	0.905	(0.847–0.967)	0.092	0.966	(0.929–1.006)	0.741	0.991	(0.940–1.045)	0.231	0.969	(0.919–1.021)	0.471	1.025	(0.959–1.095)
Sex	0.212	2.561	(0.586–1.120)	0.524	1.432	(0.475–4.319)	0.949	1.050	(0.235–4.698)	0.894	1.098	(0.277–4.356)	0.522	1.863	(0.277–1.251)
BMI	0.075	1.385	(0.968–1.981)	0.948	1.008	(0.791–1.284)	0.116	0.758	(0.537–1.071)	0.483	0.893	(0.651–1.225)	0.219	0.773	(0.513–1.166)
Duration															
3-6 months		Ref													
6-12 months	0.044*	1.012	(1.116–1.513)												
12-36 months	0.591	1.781	(0.217–1.463)												
>36 months	0.719	0.780	(0.201–3.022)												
PSQI	0.031*	1.169	(0.033–0.854)	0.201	0.464	(0.143–1.506)	0.562	1.576	(0.339–7.319)	0.540	1.570	(0.371–1.640)	0.449	0.398	(0.037–4.317)
SAS	0.294	2.132	(0.519–8.761)	0.746	1.204	(0.392–3.694)	0.115	0.237	(0.040–1.418)	0.268	0.406	(0.082–2.001)	0.801	0.727	(0.061–1.672)
SDS	0.870	1.138	(0.241–5.365)	0.182	2.390	(0.664–8.601)	0.046*	1.441	(0.787–0.905)	0.408	0.393	(0.043–3.600)	0.063	1.341	(0.905–1.787)

Notes: *Indicates *P*<0.05, the difference is statistically significant.
Abbreviations: *OR*, odds ratios; 95% CI, 95% confidence intervals.

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insomnia engages vasoactive-intestinal-polypeptide-expressing interneurons within the primary somatosensory cortex (S1) during NREM stage via the parabrachial- anterior nucleus of the basal forebrain-S1 (PB-aNB-S1) pathway, which induces de-suppression of pyramidal neurons and anomalous pain, leading to a reduction in central analgesia.[26] In the present study, the PPT at *Yingtang* (EX-HN3) acupoint in the patients with PI was correlated with the sleep latency ($r = -0.468$, $P = 0.021$), with pain sensitivity increasing with prolonged sleep latency, supporting this hypothesis.

Irwin et al found that differential loss of sleep and subsequent increase in cellular inflammation during the N3 phase are important drivers of pain sensitivity.[27] However, this finding is contradicted by the fact that, in the present study, the PPT at *Baihui* (GV20) acupoints in patients with PI shows a correlation with the N3 occupancy ratio ($r = 0.448$, $P = 0.047$). The degree of pain sensitization at these acupoints decreases as the N3 phase increases, providing contradictory evidence to the aforementioned findings. Abnormalities in VLF and HF were correlated with the odds of sensitization of *Baihui* (GV20) points (OR = 1.972, 95% CI 0.945–1.000, $P = 0.049$) and (OR = 1.722, 95% CI 0.523–0.998, $P = 0.048$). These abnormalities may be related to the lowering of pain thresholds and the amplification of injurious signals through the activation of α2-adrenergic receptors on sensory neurons.[28] Furthermore, the rate of pain sensitization at the *Shenmen* (HT7) point in the control group was as high as 43.8%, which could be attributed to its heightened sensitivity to stimulation due to the dense ulnar lateral nerve endings at the wrist.

The hypersensitivity of T5-T8 ganglionic segments observed in the present study aligns with the pattern of somatic pain sensitization in previous visceral diseases (eg, coronary artery disease, gastric ulcer). In coronary artery disease, pain sensitization is concentrated in the C8-T5 dermatomes,[29] while in gastric ulcer, pain sensitization areas correspond to the T5-T10 ganglia,[30] and lung disease affects the C5-T7 dermatomes.[31] This suggests that the "visceral-somatic reflex" may represent a generalized pathophysiological process. Autonomic dysfunction, characterized by sympathetic excitation and parasympathetic inhibition, in patients with PI leads to pain sensitization at acupuncture points in areas innervated by the corresponding ganglion, via the "sympathetic-sensory coupling" mechanism.[28] The lowering of the nociceptive threshold of acupuncture points in the region of PI leads to pain sensitization. Specifically for the hypersensitive points, the hypersensitive state of *Juque* (RN14) point may be related to its potential role in regulating vascular endothelial function, which may indirectly affect sleep regulation by improving myocardial contraction.[32] The hypersensitivity of *Xinshu* (BL15), a dorsal point of the heart, is closely associated with abnormal cardiac function and central neurotransmitter imbalances.[33] Similarly, *Sanyinjiao* (SP6), as a meeting point of the liver, spleen, and kidney meridians, may reflect the complexity of PI, which involves dysfunction of multiple organs. It is related to the plastic regulation of the PKA/CREB and BDNF/TrkB signaling pathways in the hippocampus and may contribute to the repair of cognitive impairment associated with primary insomnia.[34] Additionally, the high sensitization of *Fengchi* (GB20), located near the medulla oblongata and innervated by the vagus nerve, is likely linked to the dysregulation of autonomic control in PI. Stimulation of *Fengchi* (GB20) can alleviate cerebral vascular spasms, improve local microcirculation, and inhibit abnormal brain discharges, promoting a true relaxation state in the body.[35]

Our further analyses identified factors such as age, disease duration, insomnia severity (PSQI score), depression level (SDS score), and autonomic function (Heart Rate Variability HF index), each of which plays a role in the modulation of acupoint sensitization in patients with PI to varying degrees.

Age

Longitudinal comparisons showed a negative correlation between age and the pain sensitization rate of acupoints such as *Yintang* (EX-HN3), *Taiyang* (EX-HN5), *Anmian* (EX-HN0), and *Shenmen* (HT7), which may be related to the decrease in responsiveness of acupoints caused by "gradual weakening of the qi and blood, and degenerative changes of the nerves" in elderly patients. Modern medical research suggests that degenerative changes in the nervous system and fluctuations in estrogen levels in women may serve as potential mechanisms.[36]

Disease Duration

Multifactorial logistic regression analysis revealed that disease duration was an independent risk factor for the occurrence of pain sensitization at *Shenmen* (HT7) acupoints. Specifically, a longer disease duration was associated with a greater susceptibility to pain sensitization at these acupoints. This is consistent with findings that the mechanical pain threshold

of acupoints in patients with chronic pelvic inflammatory disease decreases with disease duration, and the rate of pain sensitization gradually increases.[37] The mechanism may involve a decrease in N-arachidonyl dopamine (NADA) levels in the thalamic reticular nucleus (TRN).[38] The continuous input of pain factors or pathological stimuli may lead to the sensitization of sensory neurons.

Insomnia and Depression Level

PSQI scores were correlated with pain sensitization at the *Yintang* (EX-HN3), *Anmian* (EX-HN0), and *Shenmen* (HT7) points, while SDS scores were correlated with pain sensitization at the *Baihui* (GV20) and *Sanyinjiao* (SP6) points. This suggested that the more severe the symptoms of insomnia and depression, the more prone individuals are to pain sensitization at the corresponding acupoints. These findings align with previous research indicating that PPTs at dorsal acupoints were reduced in patients with PI.[33] The insula of the brain is consistently associated with insomnia and symptoms of depression and anxiety, as reported in an fMRI study,[39] emphasizing the common neural correlation between depression, anxiety, and insomnia. Specifically, the sensitized state of the *Baihui* (GV20) point may reflect emotional abnormalities and alterations in central neurotransmitter metabolism or receptor function due to dysfunction of the internal organs.[40] In contrast, the sensitization of the *Sanyinjiao* (SP6) point may be related to the disruption of the neuro-endocrine-immune network in the depressed state. Electroacupuncture of *Sanyinjiao* (SP6) can regulate depression by lowering the serum NE level and downregulating the excitability of the sympathetic-adrenomedullary system,[41] providing evidence of the close connection between this acupoint and the depressive state. Psychophysiological interaction modulation is of general relevance in chronic pain sensitization. Recent studies in fibromyalgia (FM) patients have shown that the high co-morbidity (53.3%) of post-traumatic stress disorder (PTSD) may exacerbate the process of central sensitization through the dual mediation of anxiety and reduced pain acceptance, as evidenced by a significant positive correlation between anxiety scores and central sensitization indices (CSIs), and a reduced level of pain acceptance, which then amplifies nociceptive perceptual signals.[42] It is suggested that similar psycho-neurological pathways may be involved in the cave pain sensitization process in patients with primary insomnia: chronic sleep deprivation may induce overactivation of central pain processing networks (eg, anterior cingulate cortex, insula) through activation of the hypothalamo-pituitary-adrenal axis and the sympathetic nervous system, whereas negative emotions, such as anxiety, may act as a catalyst to reduce pain by decreasing the pain perception signals.[43,44] Negative emotions such as anxiety may act as a "catalyst" by lowering the pain threshold, weakening endogenous analgesic mechanisms, and ultimately leading to abnormally elevated nociceptive sensitivity at acupoints.

Autonomic Function

The HF index in heart rate variability (which reflects parasympathetic excitability) is negatively correlated with pain sensitization at the *Baihui* (GV20) acupoints. The higher the HF value (indicating higher parasympathetic excitability), the less likely the *Baihui* (GV20) acupoints are to undergo pain sensitization. This is consistent with the modern medical understanding of the pathophysiological mechanism of PI, wherein patients generally exhibit autonomic imbalance, characterized by sympathetic excitability and parasympathetic insufficiency, leading to symptoms such as difficulty falling asleep and poor sleep quality.[45] In normal sleep architecture, an increase in REM-phase HF contributes to sleep stage transitions,[46] whereas a decrease in NREM-phase HF is associated with reduced total sleep time and increased insomnia severity.[47] In juvenile fibromyalgia (JFM), a typical central sensitization-related disorder, reduced HRV has been shown to significantly correlate with the degree of central sensitization. Notably, up to 73.3% of JFM patients with insomnia showed a significant negative correlation between reduced HRV and anxiety scores ($r=-0.56$, $p<0.01$),[48] suggesting that autonomic dysfunction (sympathetic overactivation and parasympathetic inhibition) may amplify the effects of central sensitization through the cascade effect of "anxiety-central sensitization-sleep disorders". The results of this study suggest that the pain sensitization characteristics of acupoints are closely linked to the state of autonomic function, further supporting the theory that acupoints serve as a window into the functional state of internal organs.

This study was designed as a case-control study, enrolling healthy subjects matched for age and gender with the PI patients to minimize baseline bias, which facilitated the exploration of relevant acupoint sensitization cut-off values. At the same time, the findings have potential clinical and public health implications, such as: a. Acupuncture point

sensitivity assessment may become a complementary tool to existing diagnostic screening tools for insomnia, or an objective indicator of the efficacy of acupuncture treatments. b. These findings suggest new therapeutic targets or biomarkers for personalized acupuncture treatment.

However, this study has several limitations. First, the subjects were restricted to patients with primary insomnia, and secondary insomnia (eg, sleep apnea syndrome, restless leg syndrome, cancer-related insomnia, etc.) was not included in the comparative analysis, limiting the ability to determine whether pain sensitization is a PI-specific manifestation. Second, this study only examined deep (fascial/muscular) PPT of the acupoints and lacked data on superficial mechanical pain sensitization. In addition, the small PSG/HRV subsample size (n=25) may affect statistical efficacy and results should be interpreted with caution; the cross-sectional design was unable to derive causality, only correlation; and the PPT test may be subject to measurement bias; Although matching by age and sex was performed, other potential confounders such as chronic pain conditions were not captured and taken into account. Future research should address four key objectives: (1) delineate differences in pain sensitization between primary and secondary insomnia to establish pathological specificity; (2) develop a comprehensive model that integrates deep-tissue and superficial mechanical pain thresholds; (3) implement multi-center, large-scale investigations; (4) A longitudinal study was conducted to assess changes in acupoint sensitivity after the intervention. (5) Whether a return to normalization of the PPT correlates with improved sleep quality. (6) Investigate neuroimaging or biochemical correlates of acupoint sensitization. In conclusion, these correlational analyses are exploratory and should be interpreted with caution.

Conclusion

Patients with PI exhibited significant acupoint sensitization at commonly used clinical points, characterized by a decrease in PPT and an increase in pain sensitization rate. This phenomenon was more pronounced at specific points (eg, *Juque* (RN14) and *Xinshu* (BL15)), which may be the best acupoints for clinical diagnosis and treatment, and segmental nerves (T5-T8). This phenomenon of pain sensitization was negatively correlated with the patient's age and high-frequency power in HRV, and positively correlated with disease duration, PSQI, and SDS. However, the usefulness of these findings for clinical decision-making is still in the exploratory stage.

Abbreviations

PI, Primary Insomnia; PPT, Pressure Pain Threshold; ROC, Receiver Operating Characteristic; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; PSG, Polysomnography; HRV, Heart Rate Variability; VLF, Very Low Frequency; LF, Low Frequency; HF, High Frequency; SWS, Slow-Wave Sleep; NREM, Non-Rapid Eye Movement; REM, Rapid Eye Movement; BMI, Body Mass Index; CRFs, Case Report Forms.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. And the raw data supporting the findings of this study are available upon request from the corresponding author.

Ethics Declarations

The study was conducted in accordance with the Helsinki Declaration and approved by the Research Ethics Committee of the Third Affiliated Hospital of Zhejiang Chinese Medical University (ID: ZSLL-ZN-2024-017-01), which has been registered in the main registration center of the WHO Global Registry Network (China Clinical Trial Registry: ChiCTR2400082288).

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Author Contributions

X.-Y. (Xiao-Shuai Yu): Conceptualization, Methodology, Software, Validation, Investigation, Formal Analysis, Data Curation, Writing - Original Draft, Writing – review and editing, Visualization. Y.-L. (Yi-Ming Liu) & W.P. (Wei Pan) & X.W. (Xiao-Ying Wang) & L.L. (Li-Nan Lin): Conceptualization, Project administration, Writing – review and editing. Q.S. (Qiong-Ying Shen) & H.Z. (Han Zhang) & S.Z. (Si-Yi Zheng) & N.N. (Na Nie) & B.J. (Bo Jin): Investigation, Data curation, Validation, Project administration, Supervision Writing – review and editing. Y.L. (Yi Liang) & Y.L. (Ying-Jun Liu) & J.F. (Jian-Qiao Fang): Methodology, Funding acquisition, Resources, Writing – review and editing. All authors approved the final version of the paper, agreed to submit it to this journal, and agree take responsibility for all aspects of the work.

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