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CLINICAL TRIAL REPORT

Acupuncture with the Sancai Acupoint Matching Method for Primary Insomnia: A Randomized Controlled Trial

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Study Objectives: Primary insomnia (PI) remains a widespread public health concern. This study aims to evaluate the efficacy and safety of the novel Sancai acupoint matching method for PI, and to explore its potential peripheral biochemical mechanisms.

Methods and Design: 76 PI patients were randomly assigned to either the real-acupuncture (RA) group or the sham-acupuncture (SA) group, with 38 cases in each group. The RA group received verum acupuncture based on the stated principle over an 8-week treatment period (20 sessions), while the SA group received sham acupuncture. Assessments were conducted at baseline, immediately post-treatment, and at 1, 4- and 12-week follow-ups using the Insomnia Severity Index (ISI) as the primary outcome measure, along with the Pittsburgh Sleep Quality Index (PSQI), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS). Objective sleep parameters were monitored via polysomnography (PSG), and serum levels of 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF) were measured before and after treatment.

Results: Improvements in ISI, PSQI, SAS and SDS scores were superior in the RA group compared to the SA group ($P < 0.05$). The objective sleep parameters in the RA group were significantly improved, and the levels of serum 5-HT and BDNF were significantly increased ($P < 0.05$).

Conclusion: The Sancai acupoint matching method is a safe and effective treatment for primary insomnia, significantly improving patients' subjective sleep quality, emotional symptoms, and objective sleep parameters, and upregulating peripheral blood levels of 5-HT and BDNF. These findings support the clinical application of this acupuncture protocol and provide a foundation for subsequent mechanistic studies.

Clinical Trial Registration: The study was registered at the Chinese Clinical Trial.
Registry, registration ID: ChiCTR2300072229, China.

Keywords: acupuncture, Sancai acupoint matching method, primary insomnia, randomized controlled trial, 5-HT, BDNF

Introduction

Primary insomnia (PI) is a common sleep disorder characterized by difficulties in falling asleep, maintaining sleep, and experiencing fatigue upon waking. Globally, approximately 30%-35% of adults suffer from transient insomnia symptoms, while the prevalence of chronic insomnia is around 10%.[1] Epidemiological surveys in China indicate that the overall incidence of insomnia among adults is 37.7%, with a significantly higher rate among women (41.5%) compared to men (32.3%).[2] The rising prevalence of PI is largely attributable to increasing societal, familial, and individual pressures.[3] Growing evidence suggests a strong association between PI and various physical and mental disorders,[4] significantly impacting psychological well-being, quality of life, and work efficiency. Modern medicine suggests PI pathogenesis is closely related to a hyperarousal state, involving neurotransmitter imbalances, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and abnormal activity in brain networks processing cognition and emotion.[5] In Traditional Chinese Medicine (TCM), the pathogenesis of insomnia

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is often closely related to the functional dysregulation of the Heart, Liver, and Spleen. The Heart governs mental activity, the Liver regulates emotions, and the Spleen is responsible for producing Qi and blood. Emotional stress can disrupt the Liver's function, which in turn weakens the Spleen's ability to produce vital energy and blood. When the Spleen is deficient, it fails to nourish the Heart, leaving the mind unsettled and leading to difficulty sleeping.[6]

The first-line clinical treatment for insomnia primarily relies on benzodiazepine sedative-hypnotic drugs. Although these medications are effective in the short term, long-term use carries multiple risks, including drug dependence, drug tolerance, daytime residual sedation, and rebound insomnia after discontinuation—consequences that can ultimately become more challenging to manage than the severity of the primary condition.[7–9] Although cognitive behavioral therapy for insomnia (CBT-I) is recommended as a first-line treatment, its accessibility is limited by high therapist requirements, time intensity, and limited availability.[10] Acupuncture, as a distinctive and advantageous therapy in China for preventing and treating insomnia, has been proven to effectively improve patients' sleep architecture, enhance sleep quality, alleviate anxiety and depression, and regulate immune function in individuals with insomnia.[11–13] Based on the theoretical framework of Traditional Chinese Medicine, which posits that the pathogenesis of insomnia is related to the heart, liver, and spleen, this study detailed an acupuncture treatment regimen rooted in the Sancai principle. The "Sancai Method" proposed in the classic acupuncture text "Compendium of Acupuncture and Moxibustion" indicates that heaven, human, and earth correspond to the upper, middle, and lower regions of the human body. This approach targets three specific domains: the head (Heaven Domain) for regulating mental activity, the abdomen (Human Domain) for harmonizing the Heart and Middle Jiao, and the lower limbs (Earth Domain) for soothing the Liver and fortifying the Spleen. Unlike conventional acupuncture protocols that often focus on single or localized points, the Sancai method employs a holistic, multi-target strategy to restore mental balance and regulate visceral function. Emerging evidence suggests that such acupoint compatibility yields superior efficacy compared to single-point acupuncture for primary insomnia.[14] This method, through multidisciplinary collaborative integration, aims to restore mental balance and regulate visceral function, thereby improving sleep. Therefore, we conducted this randomized controlled trial to evaluate its efficacy in patients with PI.

Insomnia commonly co-occurs with symptoms of anxiety and depression. The shared biological basis may involve dysregulation of key molecules such as 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF). 5-HT is a key neurotransmitter promoting sleep initiation and maintenance, its elevation helps reduce hyperarousal.[15] BDNF, a factor essential for neuroplasticity and emotional regulation,[16] may be implicated in the therapeutic benefit of acupuncture against comorbid anxiety and depression. Therefore, investigating the effects of acupuncture on these two biomarkers is crucial for elucidating the underlying mechanisms of its therapeutic effects on insomnia.

This study employed a multi-dimensional evaluation system, integrating subjective scales, objective polysomnography, and serum biomarkers. It aims not only to reaffirm the efficacy of the Sancai protocol for PI but also to explore its association with peripheral biochemical changes, providing a more comprehensive scientific basis for its clinical application.

Methods

Study Design

This randomized controlled trial was conducted between June 2023 and June 2024 at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine in Shanghai, affiliated with Shanghai University of Traditional Chinese Medicine, China (ChiCTR2300072229). Patient recruitment began one week after clinical trial registration. No protocol changes occurred during the study period; the trial was conducted strictly in accordance with the registered protocol. The study protocol was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, affiliated with Shanghai University of Traditional Chinese Medicine (Approval No. 2022–113). All patients signed informed consent before participation. This study followed the Consolidated Standards of Reporting Trials (CONSORT)[17] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).[18]

Participants

Patients included in this study were recruited from the Acupuncture Department and the Insomnia Specialty Clinic of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, affiliated with Shanghai University of

Traditional Chinese Medicine, between June 2023 and June 2024. Eligible participants were men or women aged 18 to 65 years; met the ICSD-3 diagnostic criteria[19] for PI; stable use of sedative sleep aids for at least 3 months, or no medication use prior to study enrollment; had not participated in any other clinical trials within the previous 3 months; and were willing to participate and provided signed informed consent. Key exclusion criteria included severe impairment of heart, liver, or kidney function; hematological, respiratory, or severe psychiatric disorders; infectious diseases such as hepatitis or HIV/AIDS, or unhealed severe trauma; severe digestive system diseases or severe malnutrition; pregnancy or lactation; and any other conditions deemed inappropriate for acupuncture treatment.

Randomization and Blinding

The random allocation sequence of 76 participants was generated by an independent statistician using SPSS 26.0 software with a permuted block design (block size of 4) to ensure the balance of group allocation. A research assistant who was not involved in participant recruitment, treatment, or outcome assessment prepared sequentially numbered envelopes, each containing the group assignment. These envelopes were opaque and sealed, and were stored in a locked filing cabinet accessible only to this assistant to prevent tampering. After a participant provided informed consent and met all eligibility criteria, a study coordinator (who was not involved in recruitment or outcome assessment) checked the sealing integrity of the next consecutive numbered envelope in front of the subject, and it was opened before the first treatment session. The subjects were randomly assigned to the RA or the SA, thereby confirming irreversible group assignment.

Importantly, all personnel involved in recruitment, enrollment, baseline assessment, PSG scorers as well as all the participants were blinded to the allocation sequence, and outcome assessors and data analysts remained blinded throughout the trial. Laboratory personnel conducting the enzyme-linked immunosorbent assay (ELISA) for serum 5-HT and BDNF were also blinded to group allocation. The data analyst who performed the statistical analyses was blinded to group assignment until the analysis was completed. While the acupuncturists could not be blinded due to the nature of the intervention.

Upon completion of treatment, participants were asked to indicate whether they believed they had received RA, SA, or were uncertain of their assignment. The success of blinding was quantitatively evaluated using Bang's Blinding Index (BBI), with values between −0.2 and 0.2 indicating adequate blinding. To maintain blinding throughout the study, we implemented several measures: (1) participants in the sham acupuncture group received non-penetrating sham needling using validated placebo needles with foam pads, producing a similar pricking sensation without skin penetration; (2) treatment providers did not communicate group allocation or treatment expectations to participants; (3) all outcome assessments were conducted by blinded assessors who were not involved in treatment delivery; and (4) participants were treated in separate rooms to prevent communication between groups.

Interventions

RA Group

This study employed the Sancai acupoint matching method to treat patients with PI. The acupoint prescription was as follows, Heaven domain: Baihui (GV20), Shenting (GV24). Human domain: Xinshu (BL15) and Danzhong (CV17). Earth domain: Taibai (SP3), Taichong (LR3)[20] (Figure 1). The subjects were positioned in a lateral position for needle insertion. During the lateral position, a soft pillow was placed under the ankle joint of the lower limb to fully expose the SP3. After routine disinfection, a sterilized 3mm inner diameter foam insulating pad was placed on each acupoint. Using 0.25×40 mm disposable sterile acupuncture needle (produced by China Suzhou Medical Equipment Factory Co., Ltd.) inserted through the insulation pad for acupuncture. The points were needled conventionally. Special attention should be paid to the direction, angle, and depth of needle insertion (Table 1). Needles were manipulated until "DeQi" sensation (a composite of soreness, numbness, distention, or heaviness perceived by the patient) was achieved. If there was no obvious discomfort during the retention period, the needle was not moved again. The needle was removed after 30 minutes, and the needle hole was pressed to prevent bleeding or subcutaneous hematoma.

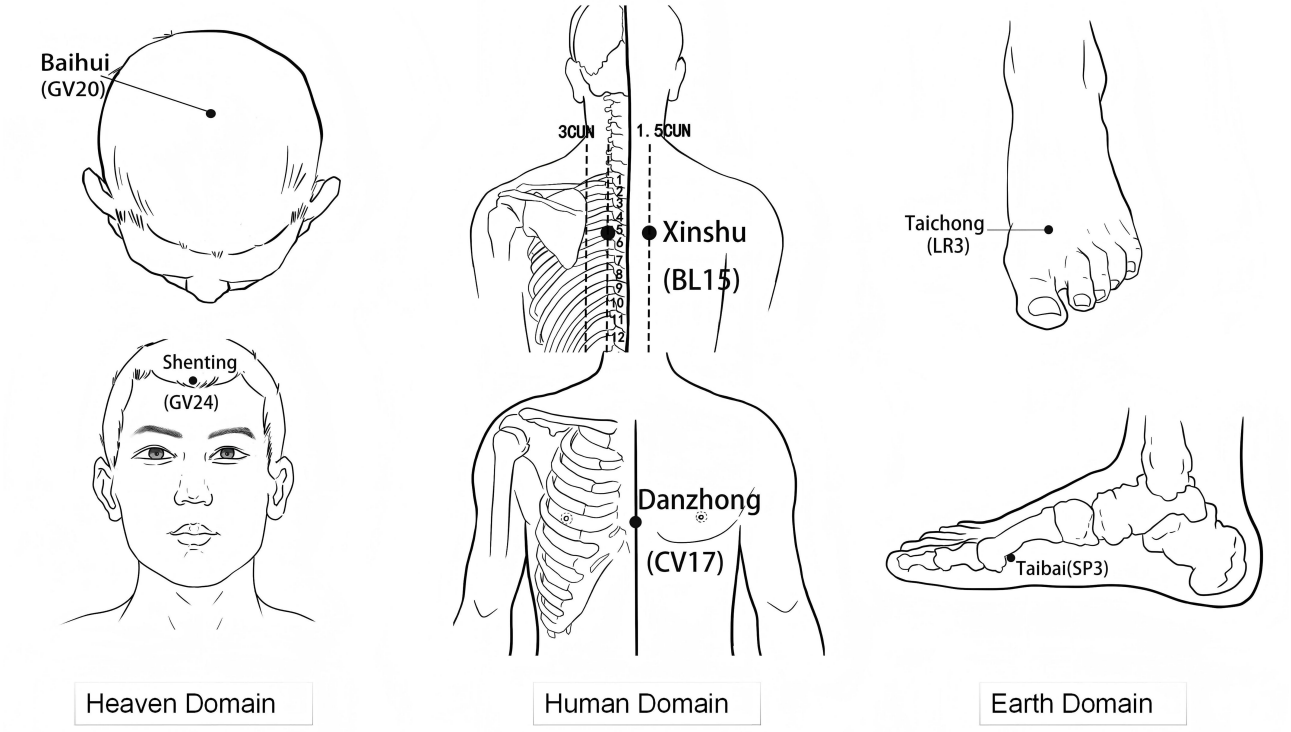

Figure 1 Locations of the Acupoints.

SA Group

Received sham acupuncture using sham-needles (Suzhou Medical Appliance Factory Co., Ltd., China). Select the same acupoints (including the back-shu point BL15) and body position as the RA group. After routine disinfection, a sterilized 3mm inner diameter foam insulating pad was placed on each acupoint. A customized 0.25×40 mm Huatuo brand placebo blunt needle[21] was pressed against the skin through the foam pad until it reached the adhesive layer, producing a mild sensation of pain without skin penetration. No needle manipulation was performed. The duration of the needle retention was the same as that in the RA group.

Table 1 Acupuncture Point Specifications

Acupoint	Localization	Depth and Angle of Insertion
Baihui (GV20)	On the head, 5cun directly above the anterior hairline, at the midpoint connecting both ears.	0.5cun. Subcutaneous, posteriorly or anteriorly.
Shenting (GV24)	On the head, 0.5cun superior to the anterior hairline.	0.5cun. Subcutaneous, posteriorly or horizontally.
Xinshu (BL15)	In the spinal region, at T5 level, 1.5cun lateral to the posterior midline.	0.3cun. Oblique towards the spine.
Danzhong (CV17)	On the anterior median line of the chest, at the level of the fourth intercostal space, midway between the two nipples.	0.3cun. Subcutaneous, horizontally directed superiorly or inferiorly.
Taibai (SP3)	Dorsum of foot, depression proximal to 1st metatarsophalangeal joint, at the dorso-ventral skin boundary.	0.5cun. Perpendicular
Taichong (LR3)	Dorsum of foot, depression distal to the junction of the 1st - 2nd metatarsal bones.	0.5cun. Perpendicular

Treatment was administered by two licensed TCM practitioners, both of whom held the title of Attending Physician, a Master's degree, and had a minimum of five years of clinical experience. All therapists and research assistants underwent a three-day training session prior to the commencement of the study. Each treatment session involved needle retention for 30 minutes. Treatments were administered 3 times per week during weeks 1 to 4, and twice per week during weeks 5 to 8, resulting in a total of 20 treatment sessions.

Outcomes Measurements

Primary Outcome Measure

The Insomnia Severity Index (ISI)[22] was used to evaluate the nature and severity of insomnia and its impact on patients' daytime functioning. It served for initial screening of insomnia and for assessing therapeutic efficacy in clinical research. A total score of 8–14 indicates subthreshold clinically significant insomnia, while a score >14 indicates clinically significant insomnia.

Secondary Outcome Measures

1) The Pittsburgh Sleep Quality Index (PSQI)[23] was used to assess sleep quality in both groups. A higher score indicates poorer sleep quality and more pronounced sleep disturbances. 2) The Self-Rating Anxiety Scale (SAS)[24] was employed to quantify the severity of subjective anxiety experienced during the test or over the past week. A higher score indicates more significant anxiety. 3) The Self-Rating Depression Scale (SDS)[25] was used to directly reflect the subjects' subjective depressive feelings and their changes during treatment. 4) Polysomnography (PSG) is internationally recognized as the gold standard for diagnosing sleep disorders.[26] The JE-922A PSG monitoring system (Nihon Kohden, Japan) was used to monitor all-night sleep before and after treatment. All PSG recordings were scored according to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events,[27] which remains a widely accepted and validated standard for sleep stage classification. This standard was chosen to ensure consistency with previous insomnia trials and to allow comparability with historical data. Prior to the study, all PSG scorers underwent comprehensive standardized training and certification in sleep stage classification. Throughout the study period, regular consensus meetings were held among scorers to ensure consistent application of scoring rules and to resolve any ambiguous epochs. All scoring was performed by trained sleep technologists who were blinded to group assignment. The indicators analyzed by PSG include: a. Total Sleep Time (TST): the total minutes of sleep from sleep onset to final awakening. b. Sleep Efficiency (SE): (Total Sleep Time / Total Time in Bed) × 100%. c. Sleep Latency (SL): the time from lights out to the first epoch of any sleep stage. d. Wake After Sleep Onset (WASO): the minutes of wakefulness from sleep onset to final awakening. e. Arousal Index: the number of arousals per hour of sleep. f. Sleep Stage Proportions (N1%, N2%, N3%, REM%): the percentage of each stage relative to total sleep time. 5) Serum levels of 5-HT and brain-derived neurotrophic factor (BDNF) were measured using enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer instructions. Fasting serum samples collected at baseline and within 48 hours post-treatment were stored at −80°C until analysis. The specific kits used were: Human 5-HT ELISA Kit (Catalog No. E-EL-0033, Elabscience, Wuhan, China) and Human BDNF ELISA Kit (Catalog No. E-EL- H0011c, Elabscience, Wuhan, China). The intra- and inter-assay coefficients of variation were <10% and <15% for 5-HT, and <10% and <15% for BDNF, with detection ranges of 50–800 ng/mL and 1.562–50 ng/mL, respectively. All samples were assayed in duplicate, and the average value was used for analysis. Samples with duplicate CVs exceeding 15% were reanalyzed. Laboratory personnel were blinded to group allocation and time-point.

Timing of Outcome Assessments

Outcome assessment timing: All questionnaire-based assessments (ISI, PSQI, SAS, SDS) were conducted at baseline, immediately post-treatment, and at follow-up weeks1, 4 and 12 post-treatment. PSG and blood sample collection were performed at baseline and within 3 days after the final treatment session. ISI was preset as the primary outcome with immediate post-treatment assessment designated as the primary time point.

Safety Assessments

Throughout the study, we systematically monitored and recorded all potential adverse events related to acupuncture at each treatment visit through direct observation and participant interview. Monitored events included: fainting during treatment (vasovagal reaction), needle site pain, bleeding, subcutaneous hematoma or bruising, infection, broken needles, needling site discomfort, and any unexpected serious adverse events. All observed or reported adverse events were documented in the adverse event form, regardless of severity or perceived relationship to treatment. Researchers assessed and analyzed all adverse reactions during the study period and conducted safety evaluations according to CONSORT harms reporting guidelines. The safety assessment was graded using a standardized scale (level 1: safe, no clinically significant adverse reactions; level 2: relatively safe, mild adverse reactions requiring no intervention; level 3: safety concerns, moderate adverse reactions requiring intervention; level 4: unsafe, severe adverse reactions leading to study discontinuation).

Sample Size

The sample size calculation was based on the ISI[28] as the primary outcome measure. In previous studies, a minimum clinically important difference (MCID) of more than 4 points on the ISI scale was considered a significant clinical treatment effect.[29] Our pilot trial results indicated that the estimated standard deviation of the ISI score after acupuncture treatment was 5.7. Assuming a two-sided significance level (α) of 0.05, a power (1-β) of 80%, and an equal allocation ratio between groups, a minimum of 32 participants per group was required. Accounting for a potential dropout rate of 15%, 38 participants were allocated to each group, resulting in a total sample size of 76. The following formula was used:

$$n_1 = n_2 = 2\left[\frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)}{\delta/\sigma}\right]^2$$

Statistical Analysis

All data were independently double-entered by two researchers to ensure accuracy. Baseline characteristics were analyzed following the intention-to-treat principle with missing data handled using the last observation carried forward (LOCF) method. Statistical analyses were performed using SPSS 26.0. Normally distributed continuous variables were presented as mean ± standard deviation (SD) and analyzed using independent for two-group comparisons. Paired samples were analyzed using the paired *t*-test. For repeated-measures analysis of variance (ANOVA) to assess the effects of group, time, and their interaction. When the overall F-test was significant, we applied Fisher's Least Significant Difference (LSD) method for post-hoc pairwise comparisons at different time points. All tests were two-sided with statistical significance set at $P < 0.05$.

The comparison of ISI scores between groups at week 8 is the only confirmatory test; its P-value is interpreted as definitive evidence of efficacy. All other analyses, including (i) secondary outcomes (PSQI, SAS, SDS) at all time points; (ii) polysomnography parameters; and (iii) serum biomarkers (5-HT, BDNF), are explicitly labeled as exploratory in the manuscript. To assess the robustness of our findings to missing data, we conducted a sensitivity analysis comparing the primary intention-to-treat analysis (using LOCF) with results obtained before imputation. The consistency of effect estimates, confidence intervals, and statistical significance between these two approaches was evaluated to determine the potential impact of missing data on the study conclusions. No interim analyses or stopping guidelines were pre-specified for this trial. The study was conducted as planned without early termination, and individual participant withdrawals did not affect the overall trial process.

Results

Baseline Demographic and Clinical Characteristics

Figure 2 shows 102 subjects were initially screened. Among them, 26 patients were excluded due to failure to meet the inclusion criteria. Ultimately, 76 eligible patients were enrolled and randomly assigned to two groups (38 in the RA

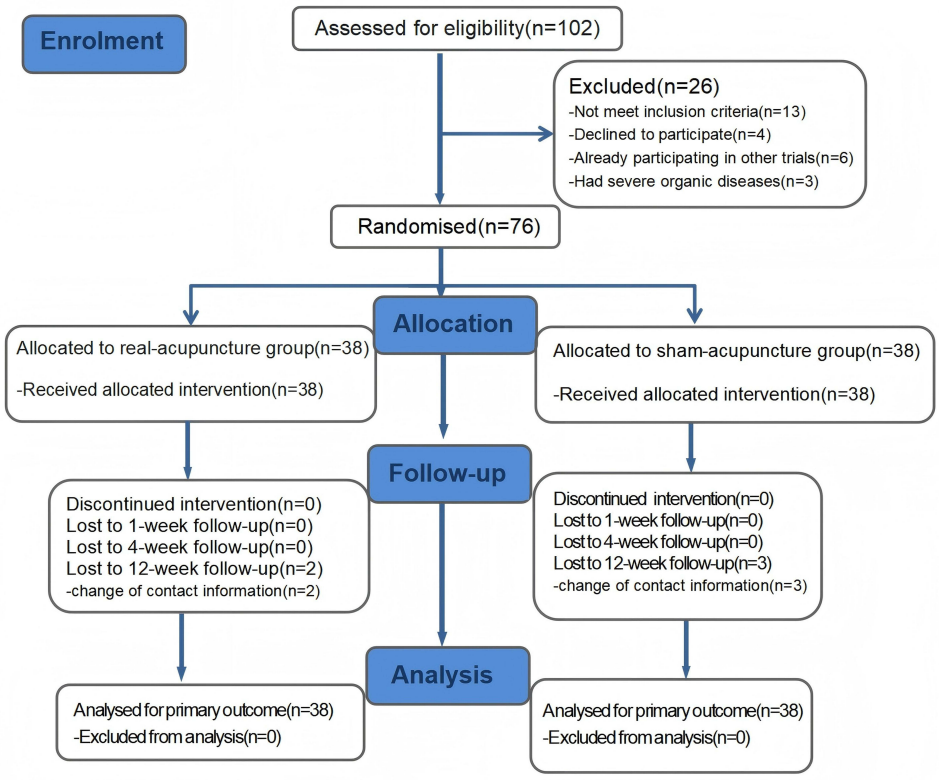

Figure 2 CONSORT Flow Diagram of Participant Progress Through the Study flowchart.

group and 38 in the SA group). During the treatment period, 2 patients in the RA group and 3 in the SA group dropout from the study.

Baseline characteristics were comparable between groups (Table 2). The overall sample consisted of 28 males (36.8%) and 48 females (63.2%), with a mean age of 44.54 ± 8.62 years and mean disease duration of 1.55 ± 0.73 years. No significant differences were observed in gender distribution (P=0.634), age (P=0.087), or disease duration (P=0.789), confirming successful randomization and group matching at baseline.

Subjective Outcome Assessments

All primary analyses were conducted based on the intention-to-treat population, which included all 76 randomized participants. At the 12-week follow-up, subjective scale data (ISI, PSQI, SAS, SDS) were missing for 2 patients in the RA group and 3 patients in the SA group due to loss of contact to follow-up, and we used the last observation carried forward (LOCF) method to impute missing values. The results showed that baseline scores for ISI, PSQI, SAS and SDS did not differ significantly between groups. Repeated measures ANOVA of ISI, PSQI, SAS, and SDS scores between the

Table 2 Comparison of Baseline Characteristics

Group	N	Gender		Age (Years)	Disease Duration (Years)
		Male	Female		
SA	38	13	25	45.42±7.76	1.42±0.71
RA	38	15	23	43.66±9.48	1.68±0.74
Statistical value	——	0.226		3.014	0.072
P	——	0.634		0.087	0.789

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two groups at various time points revealed significant main effects of time (F=62.693, 34.798, 13.269, 7.809, respectively, all $P<0.001$) and group (F=185.247, 78.926, 11.502, 7.640, respectively, all $P<0.05$) on all outcome measures, indicating that scores changed significantly over time and that the two treatments had differential effects. Additionally, significant group-by-time interaction effects were observed for ISI and PSQI (F=13.445, 30.727, respectively, $P<0.001$), suggesting that the patterns of change over time differed between the two groups. No significant group-by-time interaction effects were observed for SAS and SDS (F=1.048, 1.276, respectively, $P=0.383$, 0.282), indicating that the patterns of change over time did not differ between the two groups.

Following the treatment, the RA group showed significant within-group improvements ($P < 0.05$) in all outcome measures at the post-treatment and week 1 follow-up. Improvements in ISI and SAS remained significant at week 12. The SA group showed short-term improvements in ISI, SAS at post-treatment ($P < 0.05$), but these were not sustained at later follow-ups, and no significant changes were observed in PSQI or SDS scores at any time point. Between-group comparisons revealed that the RA group achieved superior outcomes versus SA, with significantly greater reductions in: ISI scores at all assessment time points; PSQI scores at post-treatment and weeks 1, 4; SAS scores at weeks 8 and 12; and SDS score at week 8 ($P< 0.05$) (Figure 3 and Table 3). No other inter-group differences reached statistical significance ($P> 0.05$).

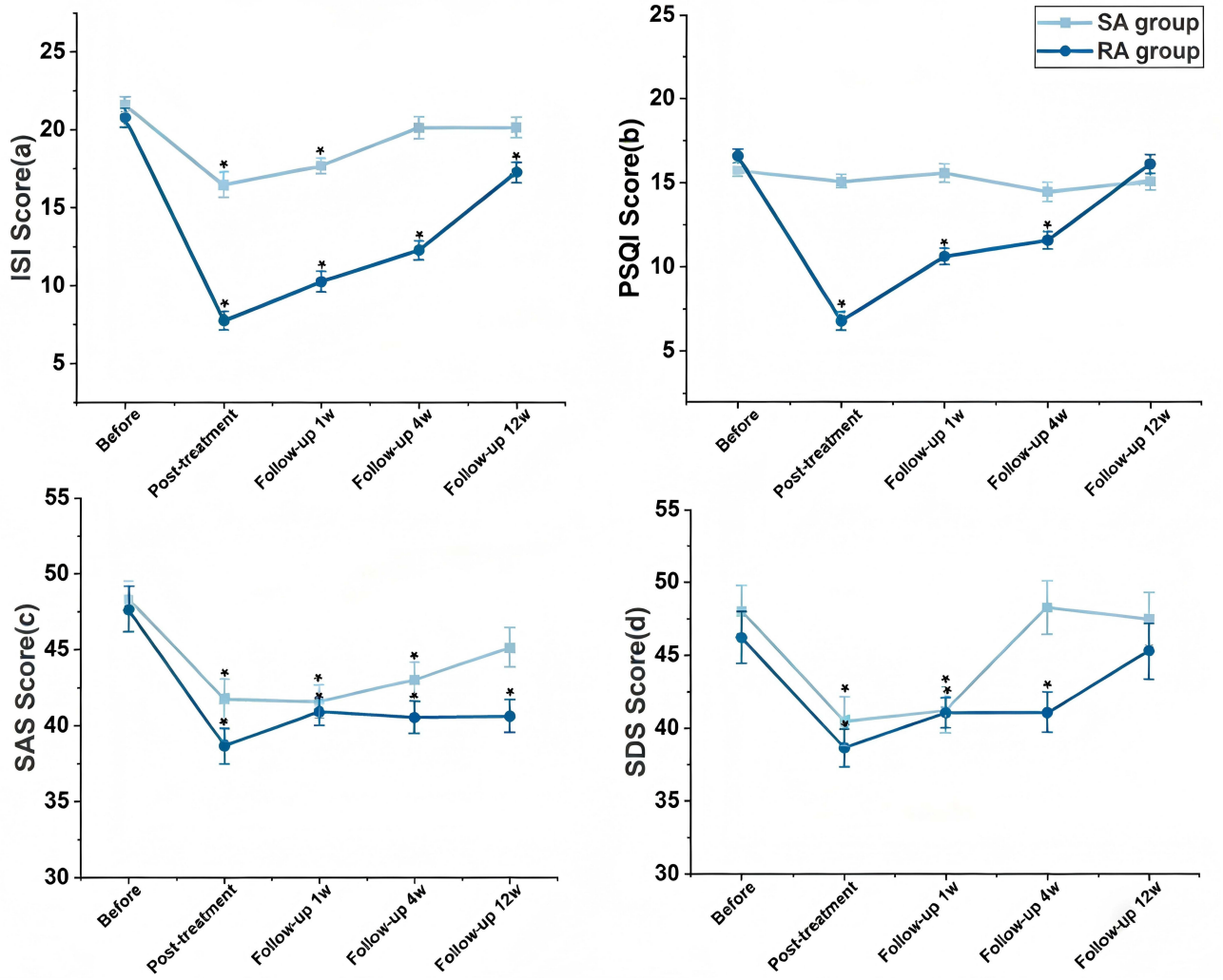

Figure 3 Longitudinal changes in clinical scale scores. Comparisons with baseline within the same group: *$P < 0.05$.

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Table 3 Comparison of the Outcome Scores in the SA Group and RA Group

Outcomes	SA (n=38)	RA (n=38)	F	*P*	SMD (95% CI)
ISI Score					
Baseline	21.58±2.98[a]	20.84±3.30[a]	3.324	0.073	0.443 (−0.038, 0.925)
Post-treatment	16.45±4.53[b]	7.80±3.54[b]	7.619	<0.001	2.130 (1.535, 2.725)
Follow-Up 1w	17.70±2.80[b]	10.29±3.90[bc]	80.163	<0.001	2.183 (1.582, 2.784)
Follow-Up 4w	20.12±4.20[ab]	12.29±3.68[cd]	67.169	<0.001	1.985 (1.404, 2.565)
Follow-Up 12w	20.15±3.71[a]	17.26±3.77[d]	10.176	0.002	0.774 (0.281, 1.267)
PSQI Total Score					
Baseline	15.70±2.38[a]	16.60±2.37[a]	2.462	0.121	0.381 (−0.099, 0.861)
Post-treatment	15.09±2.23[a]	6.80±3.29[b]	146.408	<0.001	2.952 (2.265, 3.640)
Follow-Up 1w	15.58±3.31[a]	10.66±2.80[c]	44.031	<0.001	1.606 (1.059, 2.153)
Follow-Up 4w	14.48±3.46[a]	11.60±3.16[c]	12.910	0.001	0.871 (0.373, 1.368)
Follow-Up 12w	15.06±2.81[a]	16.11±3.37[a]	1.953	0.167	0.340 (−0.139, 0.819)
SAS Score					
Baseline	48.39±6.82[a]	47.66±8.65[a]	0.151	0.699	0.095 (−0.381, 0.570)
Post-treatment	41.73±7.72[b]	38.71±6.67[b]	2.074	0.089	0.418 (−0.063, 0.898)
Follow-Up 1w	41.61±6.24[b]	40.94±4.98[b]	0.236	0.629	0.117 (−0.359, 0.593)
Follow-Up 4w	43.00±6.70[ab]	40.57±6.34[b]	4.559	0.036	0.518 (0.034, 1.001)
Follow-Up 12w	45.18±7.33[ab]	40.66±6.12[b]	7.669	0.007	0.670 (0.181, 1.159)
SDS Score					
Baseline	48.03±10.96[a]	46.20±10.17[a]	0.510	0.478	0.173 (−0.303, 0.649)
Post-treatment	40.48±9.56[ab]	38.69±7.56[a]	0.745	0.391	0.209 (−0.268, 0.686)
Follow-Up 1w	41.27±8.96[ab]	41.09±5.99[a]	0.010	0.919	0.025 (−0.451, 0.500)
Follow-Up 4w	48.30±10.51[b]	41.11±8.12[a]	9.957	0.002	0.763 (0.270, 1.255)
Follow-Up 12w	47.52±10.42[ab]	45.29±11.67[a]	0.687	0.410	0.201 (−0.275, 0.678)

Notes: Data was presented as Mean±SD. Repeated-measures analysis of variance (ANOVA) was used, followed by Fisher's LSD post hoc test for pairwise comparisons. Superscript letters (a, b, c, d) indicate significant differences among different time points within the same group. Letters are assigned in descending order of the mean values for each time point. The time point with the highest mean is assigned the letter "a", the second highest is assigned "b", and so forth. Values sharing the same letter indicate no significant difference ($P>0.05$), whereas different letters indicate a significant difference ($P<0.05$). A combination of letters (eg, "ab") indicates no significant difference from groups labeled with either "a" or "b".

Abbreviations: ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

Objective Outcome Assessments

PSG

Groups exhibited comparable sleep progression and architecture at baseline.

Post-intervention, the RA group demonstrated significant improvements in total sleep time (TST) and sleep efficiency (SE), along with reduced sleep latency (SL), wake after sleep onset (WASO), and micro-arousal index (all $P < 0.05$). In contrast, wake bouts (W Bouts) and Rapid Eye Movement sleep latency (REM SL) remained unchanged. The SA group

showed a reduction only in micro-arousal index ($P < 0.05$). Between-group analyses confirmed the superiority of RA over SA across all aforementioned parameters except REM SL ($P < 0.05$). Regarding sleep staging, the RA group displayed a significant decrease in N1% and increase in N3% ($P < 0.05$), whereas N2% and REM% were unaltered. No significant changes occurred in the SA group. Inter-group comparisons revealed significantly lower N1% and higher N3% in the RA group ($P < 0.05$), with no differences in N2% or REM% (Table 4). The PSG data is complete with no missing values, directly supporting the reliability of the observation effect.

5-HT, BDNF

Serum 5-HT and BDNF levels were comparable between groups at baseline. Post-treatment, serum levels of 5-HT and BDNF increased significantly in the RA group relative to baseline ($P < 0.05$). The SA group showed a significant increase only in 5-HT ($P < 0.05$), with BDNF remaining unchanged. Inter-group comparisons confirmed significantly

Table 4 Comparison of PSG Parameters in the SA Group and RA Group

Outcomes	SA (n=38)	RA (n=38)	*t*	*P*	SMD (95% CI)
PSG Sleep Process					
Total Sleep Time, min					
Baseline	285.48±79.28	315.14±58.20	−1.766	0.082	0.426 (−0.054, 0.907)
Post-treatment	287.97±49.45	366.83±59.96*	−5.897	<0.001	1.435 (0.902, 1.968)
Sleep Efficiency, %					
Baseline	62.16±15.66	63.95±14.50	−0.489	0.626	0.119 (−0.357, 0.595)
Post-treatment	68.29±12.85	76.75±11.10*	−2.910	0.005	0.705 (0.214, 1.195)
Sleep Latency, min					
Baseline	44.55±27.07	40.83±22.24	0.620	0.537	0.150 (−0.326, 0.626)
Post-treatment	47.97±31.02	16.46±17.48*	5.120	<0.001	1.252 (0.732, 1.772)
WASO, min					
Baseline	151.88±58.23	135.91±49.91	1.216	0.228	0.294 (−0.184, 0.773)
Post-treatment	157.39±63.83	96.69±55.94*	4.177	<0.001	1.012 (0.507, 1.517)
W Bouts, n					
Baseline	40.64±19.22	38.06±23.13	0.498	0.620	0.121 (−0.355, 0.597)
Post-treatment	37.76±19.47	30.17±10.09	2.000	0.051	0.489 (0.007, 0.972)
Arousal Index, events/h					
Baseline	14.83±6.81	13.53±6.25	0.821	0.415	0.199 (−0.278, 0.676)
Post-treatment	10.88±4.95*	6.93±3.92*	3.654	0.001	0.883 (0.385, 1.382)
REM Latency, min					
Baseline	99.85±65.28	87.57±55.68	0.836	0.406	0.202 (−0.274, 0.679)
Post-treatment	85.73±69.72	96.26±60.45	−0.667	0.507	0.161 (−0.315, 0.638)
PSG Sleep Architecture					
N1, %					
Baseline	16.62±8.32	14.02±6.98	1.401	0.166	0.339 (−0.140, 0.818)
Post-treatment	13.56±5.54	10.42±4.81*	2.494	0.015	0.604 (0.118, 1.090)
N2, %					
Baseline	41.52±10.43	45.99±10.51	−1.761	0.083	0.427 (−0.054, 0.908)
Post-treatment	46.28±7.47	43.82±9.25	1.202	0.234	0.292 (−0.186, 0.771)
N3, %					
Baseline	20.60±10.29	23.26±7.37	−1.232	0.222	0.298 (−0.181, 0.776)
Post-treatment	24.54±11.35	29.61±7.27*	−2.181	0.034	0.532 (0.049, 1.016)
REM, %					
Baseline	22.65±12.38	18.76±11.47	1.345	0.183	0.326 (−0.153, 0.805)
Post-treatment	18.13±7.74	16.02±7.30	1.156	0.252	0.280 (−0.198, 0.758)

Notes: Data was presented as Mean±SD. Comparisons with baseline within the same group: *$P < 0.05$.

higher levels of both biomarkers in the RA group ($P < 0.05$) (Table 5). The 5-HT and BDNF data were complete with no missing values, directly supporting the reliability of the observation effect.

Sensitivity Analysis

To assess the robustness of the primary findings, we performed sensitivity analyses comparing results before and after imputation of missing values. Since missing data predominantly occurred at the week 12 follow-up, we focused our sensitivity analysis on this time point. The comparisons of ISI, PSQI, SAS, and SDS scores at week 12 (the final follow-up) between the RA and SA groups are presented in Table 6. For the ISI score, statistically significant differences between groups were observed both after imputation ($P = 0.002$) and before imputation ($P = 0.001$). Similarly, SAS scores showed significant group differences in both analyses ($P = 0.007$ for both). PSQI and SDS scores remained non-significant regardless of imputation status ($P > 0.05$ for all comparisons). The standardized mean differences and their confidence intervals showed substantial overlap between pre- and post-imputation analyses for all outcomes, indicating that missing data did not materially influence the effect estimates. These findings support the robustness of the study conclusions, suggesting that the handling of missing data had minimal impact on the overall results.

Safety Assessments

Adverse events (AEs) were systematically collected throughout the study period. At each visit, participants were asked a non-leading question ("Have you experienced any discomfort since the last visit?") and were also instructed to record any symptoms in a daily diary. All AEs were assessed for severity (according to CTCAE 5.0 criteria), duration, and causal relationship to the intervention (assessed as definitely related, probably related, possibly related, or unrelated). During the

Table 5 Comparison of Serum 5-HT and BDNF Levels in the SA Group and RA Group

Outcomes	SA (n=38)	RA (n=38)	*t*	*P*	SMD (95% CI)
5-HT, ng/mL					
Baseline	76.16±15.89	77.06±24.59	−0.181	0.857	0.044 (−0.432, 0.519)
Post-treatment	87.07±6.03*	101.91±16.99*	−4.854	<0.001	1.164 (0.650, 1.678)
BDNF, ng/mL					
Baseline	23.32±4.28	23.81±6.24	−0.376	0.708	0.092 (−0.384, 0.568)
Post-treatment	24.78±5.14	38.18±7.47*	−8.658	<0.001	2.090 (1.499, 2.681)

Notes: Data was presented as Mean±SD. Comparisons with baseline within the same group: *$P < 0.05$.
Abbreviations: 5-HT, 5-hydroxytryptamine; BDNF, brain-derived neurotrophic factor.

Table 6 Sensitivity Analysis Comparing Results Before and After Imputation of Missing Data

Outcomes	Mean ± SD		Group Difference		SMD (95% CI)
	SA Group	RA Group	*t*	*P*	
ISI Score					
After imputation	20.15±3.71	17.26±3.77	3.190	0.002	0.774 (0.281, 1.267)
Before imputation	20.43±3.54	17.12±3.82	3.558	0.001	0.899 (0.380, 1.418)
PSQI Total Score					
After imputation	15.06±2.81	16.11±3.37	−1.397	0.167	0.340 (−0.139, 0.819)
Before imputation	15.27±2.82	16.12±3.47	−1.067	0.290	0.270 (−0.226, 0.767)
SAS Score					
After imputation	45.18±7.33	40.66±6.12	2.769	0.007	0.670 (0.181, 1.159)
Before imputation	45.40±7.36	40.64±6.30	2.767	0.007	0.695 (0.186, 1.205)
SDS Score					
After imputation	47.52±10.42	45.29±11.67	0.829	0.410	0.201 (−0.275, 0.678)
Before imputation	47.27±10.59	45.06±11.86	0.776	0.441	0.196 (−0.299, 0.692)

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Table 7 Blinding Assessments

Guess	Treatment Assignment	
	RA (n=38)	**SA (n=38)**
RA	14 (40.00%)	10 (30.30%)
SA	9 (25.71%)	8 (24.24%)
Uncertain	12 (34.29%)	15 (45.45%)
BBI (95% CI)	0.143 (−0.126, 0.413)	−0.077 (−0.446, 0.292)

Note: Data was presented as number (%).
Abbreviations: BBI, Bang's Blinding Index; CI, Confidence Interval.

study, 9 participants experienced skin bruising, all of which occurred in the RA group. All cases were classified as mild in severity, required no medical intervention, and resolved completely within 2 weeks. Participants with bruising were instructed to apply ice packs within the first 24 hours and warm compresses thereafter to promote resolution. No bruising was classified as serious or led to participant withdrawal. All cases were assessed as definitely related to the acupuncture procedure. No other adverse reactions (bleeding, infection, dizziness, needle allergy, or syncope) were observed in any participant during or after the treatment and throughout the follow-up period. The safety assessment was graded as level 1.

Blinding Assessments

The Bang's index was 0.143 for the RA group and −0.077 for the SA group, indicating successful blinding in both groups (Table 7).

Discussion

This randomized, sham-controlled trial demonstrates that the Sancai acupoint matching method is an effective and safe intervention for primary insomnia. The protocol not only produced sustained improvements in subjective sleep quality but also brought about objective normalization of sleep progression and architecture as measured by PSG. Furthermore, the clinical benefits were associated with significant upregulation of peripheral serum 5-HT and BDNF levels, offering a plausible biochemical correlate for its mechanism of action.

Acupuncture, a complementary and alternative therapy, offers distinct advantages for insomnia treatment, including rapid onset, sustained efficacy, non-dependence, and absence of side effects. Meta-analyses indicate its efficacy is superior to pharmacotherapy.[30] Current clinical studies confirm that acupuncture significantly improves sleep quality in individuals with insomnia, enhancing sleep efficiency and total sleep time, while also alleviating anxiety and depression,[31–33] consistent with the findings of this study. Within the TCM framework, insomnia is closely linked to dysfunction of the heart, liver, and spleen, which are the core organs for mental activities, emotional regulation, and nutrient transformation respectively.[34] The core pathogenesis is "Liver depression, Spleen deficiency, and malnourishment of the Heart spirit", which is caused by chronic emotional stress ("Liver depression") and irregular lifestyle impairing digestive function ("Spleen deficiency"), ultimately leading to failure of the Heart to house the mind. Our Sancai protocol was designed to address this core dysfunction holistically. The Heaven domain (GV20, GV24) directly calms the mind, promote sleep and regulates cerebral function. This is supported by neurobiological evidence demonstrating that cranial acupuncture can alleviate affective disorders by regulating central neurotransmitters.[35] The Human domain (BL15 and CV17) harmonizes the Heart and chest Qi to relieve emotional distress. The Earth domain (LR3 and SP3) fortify the body's physical foundation by mitigating stress responses and enhancing digestive function. Collectively, this multi-tiered approach provides a comprehensive regulatory framework that concurrently targets the intertwined physiological and emotional dimensions of insomnia.

This study evaluated the clinical efficacy and related peripheral biomarker changes of the Sancai acupoint matching method in patients with insomnia. Clinically, the RA group achieved not only statistically significant but also clinically meaningful improvements. After treatment, the mean reduction in ISI score was 13.04 points in the RA group, which exceeded the predefined MCID of 4 points.[29] This degree of improvement corresponded to a shift from moderate insomnia to no clinically significant insomnia. Objectively, polysomnography revealed a significant increase in N3 slow-

wave sleep that further supporting the clinical relevance of the intervention, given that impaired N3 sleep represents a core pathophysiological feature of insomnia.[36] These objective findings were consistent with the subjective improvements in ISI and PSQI scores. In contrast, the SA group showed only transient subjective relief and a mild reduction in the micro-arousal index, without any favorable changes in sleep architecture. This dissociation between subjective perception and objective physiology indicates that non-specific effects may provide short-term psychological comfort, but cannot reverse the fundamental physiological abnormalities underlying insomnia. The marked differences between groups strongly support the presence of specific therapeutic effects of the active acupuncture protocol.

In line with clinical outcomes, the RA group exhibited significant post-intervention increases in serum 5-HT and BDNF levels. The SA group showed a mild elevation in 5-HT but no change in BDNF. As a monoamine neurotransmitter involved in sleep–wake regulation, the increased peripheral 5-HT may reflect altered tryptophan metabolism. However, serum 5-HT cannot directly represent central serotonergic activity in the brainstem or hypothalamus, which is an inherent limitation of peripheral measurements. The rise in 5-HT in both groups suggests a partial non-specific effect, whereas the markedly greater increase in the RA group implies a specific treatment component. Notably, only the RA group showed a selective increase in BDNF, a key molecule involved in neuronal plasticity, stress resilience, and emotional regulation.[37] Although the exact mechanism by which acupuncture upregulates peripheral BDNF remains unclear, this change provides a plausible biological basis for the improved mood symptoms (reduced SAS/SDS scores) observed in the RA group. The absence of a BDNF response in the SA group further distinguishes the specific biological impact of verum acupuncture.

Notably, all indicators measured in this study are peripheral biomarkers; thus, conclusions regarding central nervous system mechanisms remain speculative. Despite the close interaction between 5-HT and BDNF systems,[38,39] the present data do not allow definitive inferences about central synaptic plasticity, neurogenesis, or direct modulation of sleep-regulating circuits. Further studies using cerebrospinal fluid analysis or neuroimaging are warranted to clarify whether these peripheral changes reflect central functional alterations.

Collectively, the SA group displayed some short-term subjective improvements and a mild increase in 5-HT, which underscores the contribution of non-specific effects including placebo response, therapeutic attention, and treatment ritual inherent to complex interventions such as acupuncture.[40] Nevertheless, the RA group achieved more pronounced, sustained, and objectively confirmed benefits, accompanied by a unique BDNF response. These results provide robust evidence that the Sancai acupoint matching method yields specific and clinically meaningful therapeutic effects beyond non-specific influences.

A growing body of research indicates that neurotransmitter changes should be interpreted within the framework of large-scale brain network dysfunction induced by insomnia. The severity of insomnia may result from neural exhaustion or reduced metabolic efficiency due to chronic hyperarousal, rather than mere excessive neural activity.[41] This functional decline disrupts the dynamic balance among the default mode network (DMN), salience network (SN), and executive control network (ECN),[42,43] thereby impairing sleep-wake transition function. Multiple fMRI studies confirm that patients with insomnia, especially those comorbid with depression or anxiety, exhibit enhanced functional connectivity and overactivity in the SN, which is consistent with the hyperarousal state.[44,45] This aligns with the core manifestations of qi stagnation, emotional constraint, and hypervigilance in patients with insomnia related to TCM liver depression.[46] Resting-state fMRI shows abnormal internal functional connectivity of the DMN and reduced metabolism in some patients with spleen deficiency syndrome, which is consistent with the TCM description of insufficient qi-blood production due to spleen deficiency causing inadequate brain nourishment and subsequent fatigue, inattention, and cognitive impairment.[47,48] The present study observed improved sleep and mood following Sancai acupuncture, particularly an increase in serum BDNF levels. BDNF is critical for neural plasticity and has been confirmed to regulate large-scale brain networks related to sleep and mood;[49] although peripheral BDNF levels do not directly reflect central nervous system activity,[50] its increase provides a theoretical basis for exploring central correlations via neuroimaging techniques.

Future research could employ multimodal neuroimaging techniques (e.g., resting-state fMRI, task-state fMRI) to address key questions: 1) whether increases in peripheral 5-HT and BDNF correspond to changes in the activity or connectivity of brain regions involved in sleep-wake regulation and emotional processing; and 2) whether imaging biomarkers can predict treatment response and identify optimal candidates for the Sancai acupoint matching method. Such integrative research is feasible.

Limitations

Several limitations should be considered. First, the sample size may have limited subgroup analyses. Second, as noted in the discussion, the lack of neuroimaging data precludes conclusions regarding central mechanisms; hypotheses concerning brain network effects require direct testing. Third, while participants, outcome assessors, and data analysts were blinded, the acupuncturists could not be masked due to the nature of the intervention. Although a validated sham acupuncture procedure was employed, this may have introduced performance bias. Fourth, although the 12-week follow-up provides valuable preliminary data on treatment durability, with sustained improvements in ISI and SAS scores, the trend toward baseline regression in PSQI scores at week 12 suggests that certain components of sleep quality may deteriorate following treatment cessation. This precludes definitive conclusions regarding long-term durability. These findings underscore the need for extended follow-up studies to fully assess long-term efficacy and to explore optimal maintenance strategies, such as booster sessions or combined behavioral interventions.

Conclusion

In summary, this study demonstrates that the 8-week Sancai acupoint matching method is an effective and safe intervention for primary insomnia. The treatment produced significant and clinically meaningful improvements across multiple dimensions: sustained relief of insomnia severity (ISI) and anxiety symptoms (SAS) lasting up to 12 weeks post-treatment, improvements in objective sleep parameters (including increased N3 slow-wave sleep and total sleep time, reduced sleep latency and WASO, and upregulation of peripheral 5-HT and BDNF levels. Notably, the magnitude of ISI reduction exceeded the predefined minimal clinically important difference, confirming the clinical relevance of the intervention. However, the partial relapse in PSQI scores at week 12 suggests that while core insomnia and anxiety symptoms remain improved, overall sleep quality may require additional attention. These findings support the integration of the Sancai acupoint matching method into clinical practice for insomnia and highlight the need for future research investigating maintenance strategies, such as booster sessions or combination with behavioral interventions, to sustain long-term therapeutic benefits.

Clinical Trial Registration

This study followed the Consolidated Standards of Reporting Trials (CONSORT) and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA). Additionally, and was registered with Chinese Clinical Trial Registry (ChiCTR2300072229).

Abbreviations

5-HT, 5-hydroxytryptamine; BBI, Bang's Blinding Index; BDNF, brain-derived neurotrophic factor; CBT-I, cognitive behavioral therapy for insomnia; DMN, Default Mode Network; ECN, Executive Control Network; HPA axis, hypothalamic-pituitary-adrenal axis; ISI, Insomnia Severity Index; PI, primary insomnia; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RA, real-acupuncture; REM SL, Rapid Eye Movement sleep latency; SA, sham-acupuncture; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; SE, sleep efficiency; SL, sleep latency; SN, Salience Network; TCM, Traditional Chinese Medicine; TST, total sleep time; W Bouts, wake bouts; WASO, wake after sleep onset.

Data Sharing Statement

The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All participants provided written informed consent and the protocol was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (No. 2022–113).

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Author Contributions

NZ – Conceptualization, Funding acquisition, Formal analysis and Writing-Review & Editing. QW – Formal analysis, Visualization and Writing-Original Draft. WY – Data curation, Methodology and Writing-Review & Editing. YC – Resources and Writing-Review & Editing. LL – Investigation and Software. LT – Investigation and Project administration. XY – Software and Supervision. JL – Investigation and Validation. RL – Project administration and Writing-Review & Editing. HC – Investigation and Writing-Review & Editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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