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A Three-Arm Randomized Controlled Trial of Cross-Modal Digital Health System Integrated with Cognitive Behavioral Therapy for Insomnia: Neurophysiological Mechanisms and Clinical Efficacy

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Abstract

INTRODUCTION: Insomnia Disorder is a global public health problem. Cognitive behavioral therapy for insomnia (CBT-I), as the gold standard for combating insomnia, still has limitations such as low patient adherence and inability to directly intervene in physiological hyperarousal. Traditional sensory interventions lack precise, mechanism-driven designs, making it difficult to effectively suppress this hyperarousal. This study aims to address these limitations by developing a non-pharmacological intervention based on predictive coding theory (PCT) and multi-sensory integration.
OBJECTIVES: This study developed a Cross-Modal Digital Health System (CMDH-I) that combines CBT-I principles with personalized, synchronized auditory, visual, and vibro-tactile stimulation, and dynamically modulates the intervention process through a closed-loop control mechanism driven by real-time heart rate variability (HRV) biofeedback. The primary objectives include evaluating the clinical efficacy of CMDH-I combined with CBT-I on objective sleep latency (SL) and subjective sleep quality (PSQI). Furthermore, the study aims to explore the underlying neurophysiological mechanisms, particularly the regulatory role of heart rate variability (HRV-RMSSD) and changes in electroencephalogram (EEG) power spectral density.
METHODS: A 6-week, double-blind, three-arm randomized controlled trial (RCT) was conducted on 90 patients with primary insomnia. Participants were randomly assigned to one of three groups: (1) CBT-I + True CMDH-I; (2) CBT-I + Sham CMDH-I (stimulus asynchrony); and (3) CBT-I standard control group. The primary outcomes were objective sleep latency (SL) and subjective sleep quality (PSQI). Secondary outcomes included neurophysiological parameters: electroencephalogram power spectral density (δ/σ wave) and heart rate variability (HRV-RMSSD).
RESULTS: The reduction in SL and PSQI scores in the True CMDH-I group was significantly greater than that in the other two groups, exceeding the lowest clinically significant difference (MCID) ($p < 0.001$). More importantly, mediation analysis showed that the improvement in HRV-RMSSD was one of the main mechanisms by which CMDH-I improved sleep quality, accounting for 58.1% of the total effect. In addition, the increase in frontal lobe EEG delta wave power was closely associated with the increase in HRV-RMSSD ($r=0.68$), which validated the hypothesis of the vagus-thalamus-cortex pathway proposed in this study.
CONCLUSION: CMDH-I is a closed-loop, cross-modal digital health system based on PCT. As a non-pharmacological intervention for sleep disorders, this system outperforms standard CBT-I in clinical efficacy. The research results provide empirical evidence that the system's therapeutic effect is achieved through enhanced parasympathetic activity (increased HRV-RMSSD), thus validating its precise neurophysiological mechanism of sleep regulation. This study establishes a clearly defined digital treatment system, providing objective physiological indicators for personalized sleep medicine and representing a significant advancement.

Keywords: cross-modal integration, predictive coding, CBT-I, insomnia disorder, neurophysiology.

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1. Introduction

Insomnia disorder is a global public health problem affecting up to 20% of the adult population [1] and has a significant socioeconomic burden due to decreased productivity and increased risk of chronic diseases [2]. Cognitive behavioral therapy for insomnia (CBT-I) has been established as the gold standard first-line treatment [3], but its efficacy is often limited by low patient compliance and the inability to directly regulate the underlying physiological hyperarousal state [4], which is currently considered the core mechanism of chronic insomnia [5]. This hyperarousal state, characterized by increased autonomic and cortical activity, requires interventions that can directly and precisely target the nervous system to promote successful sleep. Recent developments in wearable sensor technologies, including the use of photoplethysmography (PPG), have provided promising solutions for continuous, real-time monitoring of physiological states, such as heart rate variability, which is essential for understanding and intervening in the hyperarousal state associated with insomnia [6].

A key challenge in advancing insomnia treatment is bridging the gap between cognitive restructuring and direct physiological regulation. Traditional monomodal physiological interventions, while showing the potential to disrupt brain rhythms [7, 8], are usually limited in effect (approximately 0.3)[9]. However, current research lacks a unified theoretical and empirical framework that links the neural mechanisms of multisensory integration to the neurobiological hyperarousal model of insomnia [10]. In particular, there is a lack of empirical research based on closed-loop, cross-modal intervention, that is, using real-time physiological data (such as heart rate variability) to drive sensory input, thereby verifying the causal mechanism of sleep regulation from the peripheral to the central nervous system. To overcome this limitation, this study proposes a cross-modal digital health system (CMDH-I), which utilizes the principle of multi-sensory enhancement and predictive coding theory (PCT) to achieve a synergistic effect of sleep induction by inhibiting hyperarousal circuits. The design of such systems must consider the broader environmental and behavioral contexts, where sustainable health engineering and ecological co-creation design principles can optimize the interaction between individuals and their health environments, ensuring that interventions promote not only clinical efficacy but also long-term health behaviors and outcomes [11].

This study designed a rigorous three-group randomized controlled trial (RCT) to evaluate the clinical efficacy and mechanism of CMDH-I. On the one hand, this study evaluated the improvement effect of CMDH-I + CBT-I on objective (PSG) and subjective (PSQI) sleep indicators compared with the sham control group and the standard CBT-I control group; on the other hand, it explored the peripheral-central neurophysiological mechanism, focusing on the mediating role of HRV and the changes in EEG power spectral density. In this study, we proposed and validated the following hypotheses:

- H1 (Clinical Efficacy): Compared with the two control groups, CMDH-I + CBT-I resulted in a significantly greater reduction in SL and PSQI scores.
- H2 (Physiological Mechanism): Elevated HRV-RMSSD significantly mediated the improvement in PSQI scores in the CMDH-I group.
- H3 (Central Mechanism): Increased EEG δ power in the frontal lobe was positively correlated with HRV changes, confirming the vagus-thalamic cortex resonance mechanism.

2. Related Work

The core feature of chronic insomnia is physiological hyperarousal, manifested by increased activity of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis [12], including increased heart rate, elevated body temperature, and cortical activation. This hyperarousal state makes the process of falling asleep difficult. The vagus nerve, as a major component of the parasympathetic nervous system, plays a key role in regulating arousal levels. Increased vagal tone is usually measured by heart rate variability (HRV) indicators such as RMSSD and is associated with greater self-regulation and faster sleep onset [13]. Therefore, effective nonpharmacological interventions should aim to suppress sympathetic activity and enhance vagal function.

Predictive coding theory (PCT) provides an important perspective on sleep regulation [14, 15]. According to PCT, the brain continuously generates internal models to predict sensory input, and the process of falling asleep can be viewed as a process of minimizing prediction errors—that is, reducing the difference between the internal model and external sensory information. In a hyperarousal state, the brain's prediction errors increase significantly, leading to increased alertness [16]. A highly consistent and predictable sensory environment, coupled with a calm physiological state, can effectively reduce prediction errors, thereby promoting the inactivation of high-arousal circuits (such as the amygdala-locus pathway) and promoting sleep [17].

Although CBT-I remains the gold standard for insomnia treatment, its efficacy is often limited by accessibility and low patient compliance [4,18]. Digital CBT-I (dCBT-I) has become a scalable solution to improve access, and some studies have demonstrated its effectiveness [19, 20].

However, existing technological interventions, such as monomodal stimulation devices, are usually open circuits and cannot respond to individual physiological states in real time. Although promising, even closed-loop auditory stimulation designed to enhance slow waves tends to focus on a single modality rather than integrating biofeedback from the autonomic nervous system [21, 22, 23]. This lack of integration limits their ability to precisely reduce prediction errors or optimise vagal responses. Key gaps in current research include: First, a lack of mechanism integration; previous studies have not combined predictive coding theory (PCT) with multisensory integration to develop closed-loop interventions. Second, a lack of closed-loop biofeedback; previous sensory interventions could not be dynamically adjusted, while CMDH-I is the first to use real-time heart rate variability (HRV) feedback to regulate vibration stimulation, directly acting on the vagal pathway. Third, a lack of empirical validation; currently, there are no rigorous randomized controlled trials that simultaneously measure clinical outcomes (PSQI, sleep latency) and complete peripheral-central neurophysiological pathways.

Previous studies have shown that combining consistent auditory, visual and tactile inputs can produce a superadditive neural effect, that is, the combined response is greater than the sum of the individual modal responses [24]. The convergence of wearable technology and neuroscience has enabled the development of systems that can monitor and regulate physiological states in real time [25, 26]. Based on these studies, the CMDH-I proposed in this study applies three targeted interventions simultaneously to sleep induction: auditory rhythm induction through δ wave binaural beats to promote slow-wave sleep; visual rhythm induction through specific wavelengths and low-frequency modulation to act on endogenous photosensitive retinal ganglion cells and indirectly regulate the suprachiasmatic nucleus, thereby promoting relaxation; and tactile feedback based on real-time HRV, which provides non-invasive vagal nerve stimulation through vibration stimulation to enhance parasympathetic nerve activity. CMDH-I maximizes the multi-sensory synergistic (superadditive) effect by synchronizing these three sensory stimuli in real-time closed loop, creating a neural state with low prediction error, thereby rapidly inhibiting autonomic hyperarousal and promoting sleep preparation. To verify this mechanism, this study conducted a three-arm randomized controlled trial (RCT) to verify our hypothesis.

3. Methodology

This study protocol was designed as a 6-week, double-blind, three-arm randomized controlled trial (RCT) to evaluate the efficacy and neurophysiological mechanisms of the CMDH-I and CBT-I. The study protocol was reviewed and approved by the Guangzhou Wanqu Cooperative Institute of Design Ethics Committee (ID: YJY-EC-2025-101), and all procedures complied with the Declaration of Helsinki. Written informed consent was obtained from all participants.

3.1 Study Design and Participants

3.1.1 Participants and Recruitment

The study screened 105 potential participants who met the DSM-5 diagnostic criteria for primary insomnia, defined as an independent sleep disorder not caused by other medical conditions, medications, or psychological disorders. Based on statistical power analysis (G* power: ANOVA, effect size f = 0.35, significance level α = 0.05, test power Power = 0.85), 90 participants were required for randomization, with 30 participants in each group. To address an expected dropout rate of approximately 15%, the initial screening of participants was slightly higher than the required sample size. The recruitment, randomization, and follow-up process for participants is shown in the CONSORT flowchart (Figure 1).

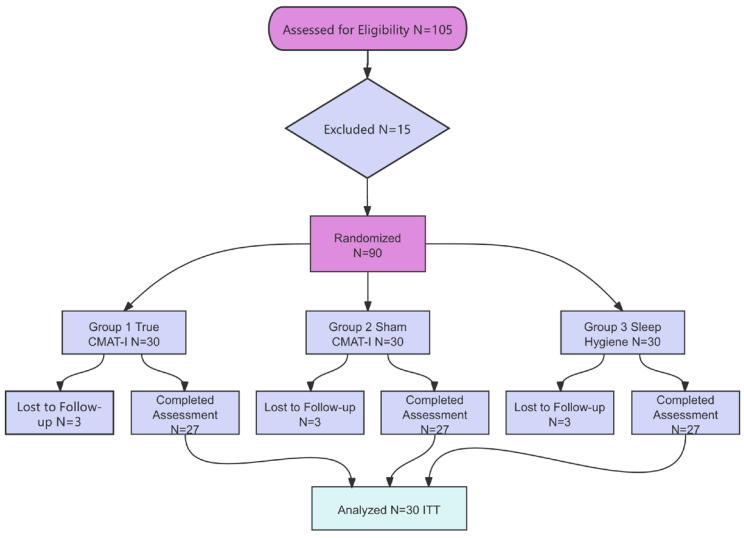

Figure 1. CONSORT Flowchart of the Three-Arm Randomized Controlled Trial

3.1.2 Randomization and Blinding

This study employed a double-blind design, ensuring that outcome evaluators and data analysts were unaware of the group allocation. Participants were informed that all devices were for neuromodulation, guaranteeing they were blinded to the "real" or "sham" nature of the CMDH-I devices. Eligible participants were randomly assigned to three groups using block randomization (block size 6) in a 1:1:1 ratio.

- Experimental Group (True CMDH-I): Standard CBT-I + True CMDH-I (synchronized stimulation).
- Active Control Group (Sham CMDH-I): Standard CBT-I + Sham CMDH-I (desynchronized stimulation, identical appearance).
- Standard Control Group (CBT-I): Standard CBT-I (time-matched control).

3.2 The Cross-Modal Digital Health System (CMDH-I)

CMDH-I is a hardware and software system based on PCT that provides consistent, synchronized, and personalized sensory stimulation. By combining digital health with a closed-loop biofeedback mechanism, the system minimizes brain prediction errors, effectively suppressing high arousal states and promoting sleep. The system architecture is shown in Figure 2.

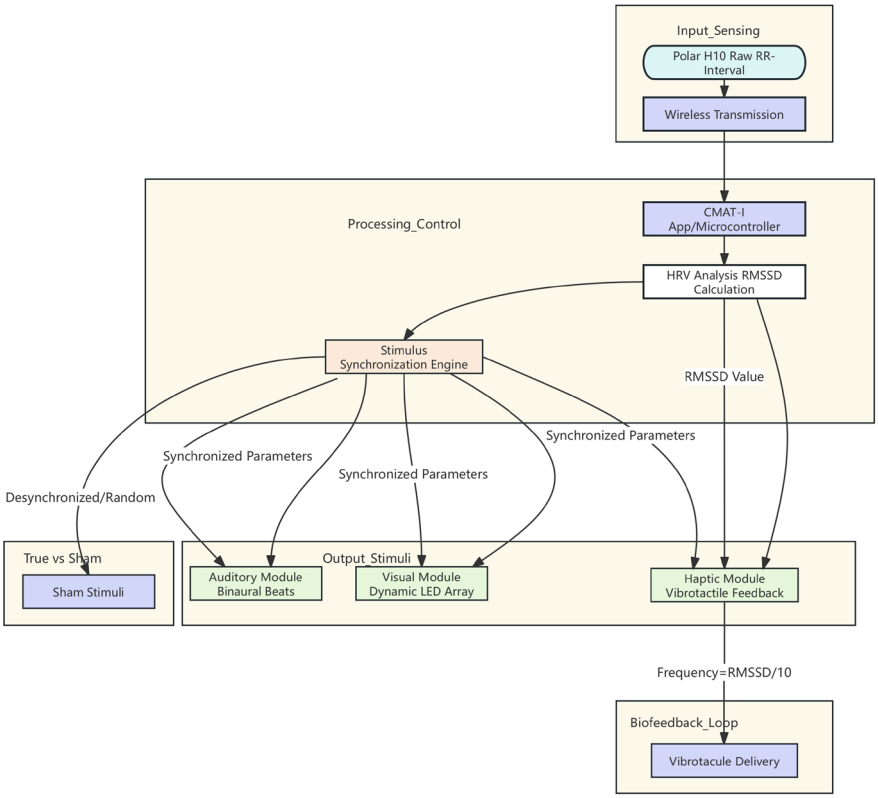

Figure 2. CMDH-I System Architecture and Stimulus Parameter

3.2.1 System Architecture and Biofeedback Loop

The system operates a closed-loop control based on real-time heart rate variability (HRV) data. Raw RR interval data is acquired via a Polar H10 chest strap and wirelessly transmitted to the CMDH-I application. The HRV analysis module in the application calculates the root mean square (RMSSD) of the continuous heart rate difference in real time. Subsequently, this RMSSD value drives the tactile module through a biofeedback loop, where the vibration frequency is set proportionally to the RMSSD (Frequency $\propto$ RMSSD/10). This design directly acts on the vagus nerve pathway, promoting a parasympathetic dominant state.

To ensure temporal alignment of the three sensory modalities, the CMDH-I system employs a centralized timing controller within the mobile application. All stimulus outputs are synchronized to a common 1000 Hz master clock. Laboratory verification tests using a multi-channel oscilloscope and photodiode / microphone / accelerometer sensors confirmed that the onset delay between modalities was consistently below 5 milliseconds (average inter-modal delay: 2.6 ± 0.7 milliseconds), within the temporal binding window for multisensory integration (typically 50-200 milliseconds).

Under the pseudo-CMDH-I condition, stimuli were deliberately desynchronized by introducing random time delays between modality onsets (range: 200-800 ms), and stimulus parameters were randomized (see Table 1), thus disrupting temporal consistency and increasing prediction error. This design ensured that the sham condition controlled for sensory exposure while eliminating synchronization, which is theoretically crucial for minimizing prediction error.

Table 1. The three synchronized sensory stimulation modalities

Modality	Parameter	True CMDH-I	Sham CMDH-I	Rationale
Auditory	Carrier Frequency (Left)	200 Hz	200–500 Hz (randomized)	Delta-frequency binaural beats (3.4 Hz) target slow-wave sleep oscillations
	Carrier Frequency (Right)	203.4 Hz	203.4–503.4 Hz (randomized)	Consistent binaural beat frequency promotes thalamocortical entrainment
	Binaural Beat Frequency	3.4 Hz (δ-wave)	Variable (0.5–15 Hz, randomized)	Synchronized δ-frequency reduces prediction error
	Volume	50 dB SPL	50 dB SPL	Comfortable listening level, non-disruptive
	Delivery	Stereo headphones	Stereo headphones	Ensures binaural beat perception
	Temporal Pattern	Continuous, synchronized	Asynchronous with visual/haptic (200–800 ms delay)	Temporal coherence critical for multi-sensory integration
Visual	Wavelength	460 nm (blue)	460–650 nm (randomized)	Targets intrinsically photosensitive retinal ganglion cells (ipRGCs)
	Modulation Frequency	0.1 Hz (sinusoidal)	0.1–5 Hz (randomized)	Slow modulation promotes relaxation and circadian alignment
	Luminance Range	10–50 lux	10–50 lux	Low intensity to avoid alerting effects
	Display	Smartphone screen	Smartphone screen	Accessible, portable delivery method
	Temporal Pattern	Synchronized with auditory	Asynchronous (200–800 ms delay)	Synchronization minimizes prediction error
Haptic	Vibration Frequency	HRV-RMSSD / 10 (Hz)	10–30 Hz (randomized, not	Real-time biofeedback enhances vagal tone
	Frequency Range	10–50 Hz (adaptive)	10–30 Hz (fixed, randomized)	Adaptive frequency provides personalized stimulation
	Amplitude	0.5 g (constant)	0.5 g (constant)	Perceptible but non-disruptive vibration intensity

Modality	Parameter	True CMDH-I	Sham CMDH-I	Rationale
	Delivery	Wrist-worn vibrotactile device	Wrist-worn vibrotactile device	Non-invasive, comfortable placement
	Biofeedback Source	Real-time HRV-RMSSD (Polar H10)	None (open-loop)	Closed-loop control targets parasympathetic activation
	Temporal Pattern	Synchronized with auditory/visual	Asynchronous (200–800 ms delay)	Temporal synchronization critical for prediction error reduction
Session	Duration	30 minutes	30 minutes	Sufficient time for physiological adaptation
	Frequency	Nightly (before	Nightly (before bedtime)	Consistent timing supports circadian regulation
	Synchronization	All modalities synchronized (<5 ms latency)	Intentionally desynchronized (200–800 ms random delays)	Synchronization is the key experimental manipulation

3.2.2 Stimuli Modalities and Parameters

The three synchronized sensory stimulation modalities provided by CMDH-I are shown in Table 2. The True CMDH-I group received calibrated stimulation parameters to ensure consistency and predictability, thereby promoting sleep-related brainwave rhythm induction and enhancing parasympathetic activation by minimizing prediction error. The Sham CMDH-I group served as an active control, receiving stimulation of the same modality but with asynchronous and randomized parameters. This was designed to control for non-specific sensory exposure and participants' psychological expectations (placebo effect), thus ensuring that the effects of the experimental groups primarily stemmed from genuine neural mechanism modulation.

3.2.3 Theoretical Basis of Multimodal Collaboration

CMDH-I system integrates three sensory modalities, each with different but complementary mechanisms for sleep induction:

- Auditory Component (Binaural Beats): δ frequency (3.4 Hz) binaural beats directly carry thalamocortical oscillations, promoting slow-wave activity characteristic of deep sleep. This auditory rhythm acts as a temporal scaffold for cortical synchronisation.
- Visual Component (Blue Light Modulation): 460 nm blue light modulated at 0.1 Hz targets intrinsically photosensitive retinal ganglion cells (ipRGCs), which project to the suprachiasmatic nucleus (SCN). This pathway indirectly regulates circadian rhythm by reducing alertness, promoting physiological relaxation.
- Tactile Component (HRV-driven Vibration): Real-time vibratory tactile stimulation, proportional to HRV-RMSSD, provides non-invasive vagus nerve stimulation through mechanoreceptors and C-fibre activation. This directly enhances parasympathetic tone, creating a physiological basis for sleep onset.

According to predictive coding theory (PCT), the brain constantly generates predictions for incoming sensory information. When multiple sensory modalities simultaneously deliver synchronous and highly predictable signals, predictive errors are minimised across multiple processing streams. This cross-modal consistency produces a "superadditive" effect—the combined neural response exceeds the sum of individual modal responses. In cases of insomnia, hyperarousal is characterised by elevated predictive errors in multiple neural circuits (e.g., amygdala-locus coeruleus pathway), and synchronous multimodal stimulation provides a stronger mechanism to suppress arousal than any single modality.

Furthermore, closed-loop biofeedback ensures that the tactile component dynamically adapts to the individual's real-time physiological state (HRV), while the auditory and visual components maintain consistent temporal patterns. This design creates a personalised yet predictable sensory environment, minimising predictive errors while enhancing vagal tone—addressing both cognitive and autonomic mechanisms.

Table 2. The three synchronized sensory stimulation modalities

Modality	True Stimulus Parameters	Sham Stimulus Parameters	Theoretical Basis
Auditory	Binaural Beats δ frequency: 3.4Hz (δ wave)	Random broadband noise (200-800Hz, no beat)	Thalamocortical Rhythm Entrainment
Visual	Dynamic LED Array: 460nm Blue Light, 0.1Hz sinusoidal modulation	Fixed White Light, 100 lux, no modulation	ipRGC Activation Curve
Haptic	Vibrotactile: Frequency = Real-time HRV-RMSSD/10 (Biofeedback Loop)	Random Vibration: Frequency 5-30Hz random switching	Mechanoreceptor C-fiber Response

3.3 Procedures and Interventions

The intervention lasted for 6 weeks. Participants in the CMDH-I groups (Ture and Sham groups) were instructed to use the device for 30 minutes each night before their scheduled bedtime. All three groups received the standard CBT-I curriculum, ensuring that the only variable difference was the CMDH-I intervention. Figure 3 illustrates the standardized nighttime protocol schedule for the cmdh-1 intervention. Each session followed a structured sequence to ensure consistency across participants and nights. Based on the initial sleep assessment, participants were instructed to begin the experiment 30 minutes before their scheduled bedtime.

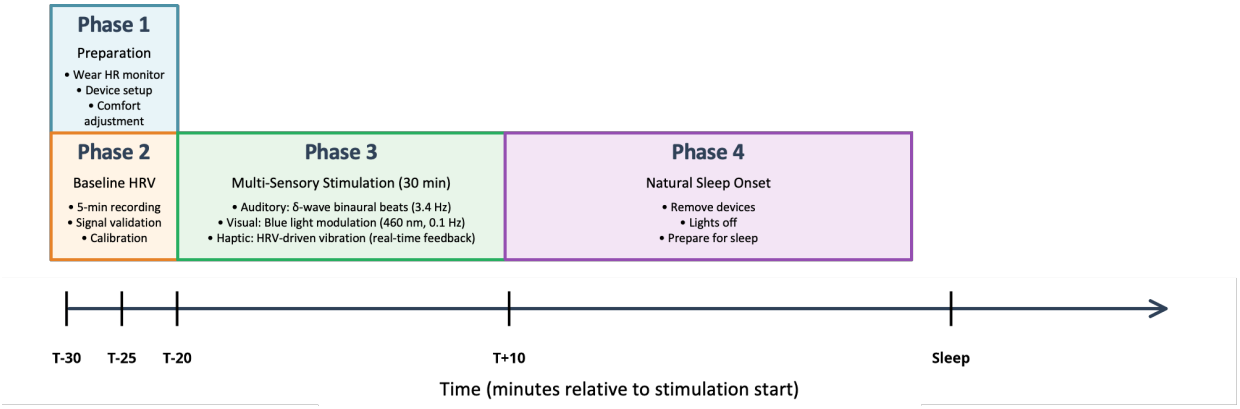

Figure 3. Schematic Timeline of Nightly CMDH-I Protocol

Notes: Each session followed a structured 40-minute sequence from preparation to natural sleep onset. The 30-minute stimulation phase (Phase 3) delivered synchronized multi-sensory inputs with real-time HRV biofeedback.

3.4 Device Implementation and User Training

3.4.1 User Training Protocol

All participants in CMDH-I Group (True and Sham groups) received a standardized 30-minute individual training session before the intervention period. The training included: (1) device setup and Bluetooth pairing with the smartphone app (5 minutes); (2) correct placement of the Polar H10 chest strap and verification of heart rate signal acquisition (5 minutes); (3) adjustment of visual display brightness and haptic vibration intensity to a comfortable level (10 minutes); (4) real-time feedback-guided exercises (10 minutes). Participants demonstrated their capability by successfully completing a full 30-minute session under supervision. A quick start guide and video tutorials were provided for reference

3.4.2 Fault Modes and Troubleshooting

CMDH-I system incorporates several safeguards to ensure reliable operation: 1. Bluetooth disconnection: If the heart rate monitor disconnects from the app for more than 10 seconds, the system automatically pauses haptic stimulation and displays a reconnection prompt. Auditory and visual stimulation continue at baseline parameters until reconnection is established. Usage logs show disconnection events occurred in less than 3% of sessions, with an average reconnection time of 19±6 seconds. 2. Sensor error: The app continuously monitors HRV signal quality. If physiologically unreasonable values are detected (for example, RR intervals < 300 ms or more than 5 consecutive > 2000 ms), the system flags the data as potentially erroneous and restores haptic stimulation to the default frequency (15 Hz) until a valid signal is regained. Participants are instructed to readjust the chest strap when an error prompt appears. 3. Battery management: When device battery falls below 20%, the system provides a low battery warning to ensure sessions are not interrupted. Participants are instructed to charge the device daily.

3.4.3 Adaptive Stimulation Parameters

Although core stimulation parameters remain unchanged throughout the intervention to maintain predictability, the haptic vibration frequency is adjusted in real time based on HRV-RMSSD, using the formula:

$$\text{Vibration Frequency (Hz)} = \text{RMSSD (ms)}/10 \quad (1)$$

This adaptive mechanism ensures that as parasympathetic tone increases during each session (reflected by rising RMSSD), the haptic vibration frequency increases proportionally, providing continuous positive biofeedback. During the 6-week intervention, participants in the True CMDH-I group showed gradually increasing baseline RMSSD values at the start of treatments (Week 1: 28.3±5.1 ms; Week 6: 42.7±6.8 ms), indicating sustained enhancement of vagal tone. Apart from real-time HRV-driven adaptation, the system does not employ nighttime parameter adjustments.

The intervention lasted for 6 weeks. Participants in the CMDH-I groups (Ture and Sham groups) were instructed to use the device for 30 minutes each night before their scheduled bedtime. All three groups received the standard CBT-I curriculum, ensuring that the only variable difference was the CMDH-I intervention.

3.5 Measurement and Data Acquisition

3.5.1 Primary Outcomes

The primary outcomes were assessed at week 6 of the intervention and included objective sleep latency (SL) measured by polysomnography (PSG) and subjective sleep measured by the Pittsburgh Sleep Quality Index (PSQI).

3.5.2 Secondary Outcomes

(i) Objective Sleep (PSG): Total Sleep Time (TST), Waiting-After-Sleep Awakening (WASO), and Arousal Index.

(ii) Neurophysiology: Electroencephalogram (EEG) power spectral density (PSD) analysis (δ/σ waves) and heart rate variability (HRV) indicators (RMSSD, LF/HF ratio).

(iii) Psychological: Insomnia Severity Index (ISI), Generalized Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9).

(iv) User Experience and Usability: At the end of the 6-week intervention, participants in both CMDH-I groups completed a customized user experience questionnaire, assessing: (1) ease of device setup and use; (2) comfort during treatment; (3) perceived sleep benefits; (4) likelihood of continued use; and (5) open-ended feedback on device improvements.

3.5.3 Quality Control

PSG data were scored by two independent sleep technicians who maintained blinding on experimental group assignment (kappa agreement > 0.85). EEG data were preprocessed using EEGLAB in MATLAB. Initially, the raw EEG signals were band-pass filtered (0.5–45 Hz) and all electrodes were re-referenced to the average. Independent Component Analysis (ICA) was conducted using the extended Infomax algorithm to identify and remove artefactual components. Components were classified as artefacts if they met at least one of the following criteria: (1) spatial topography consistent with eye movements (frontal distribution) or muscle activity (temporal/peripheral distribution); (2) spectral power concentrated above 20 Hz (indicative of muscle artefact); (3) temporal dynamics displaying stereotypical artefact patterns, such as blinking or saccades. All components were reviewed by two independent EEG analysts, yielding a inter-rater agreement. Continuous impedance monitoring ensured that electrode impedance remained below 5 kΩ throughout the recording.

3.6 Statistical Analysis

Preliminary analysis used a linear mixed-effects model (LMEM) to test the Group×Time interaction on SL and PSQI scores. The model is as follows:

$$Y_{ij} = \beta_0 + \beta_1(Group_i) + \beta_2(Time_j) + \beta_3(Group_i \times Time_j) + b_{0i} + b_{1i}(Time_j) + \varepsilon_{ij} \quad (2)$$

where represents the outcome variable for participant i at time point (SL or PSQI); is the fixed intercept; β_1, β_2, and are the fixed effects of group, time, and their interaction, respectively; represents the random intercept for participant i; b_{1i}denotes the random slope of time for participant i; and is the residual term. Random effects are assumed to follow a bivariate normal distribution with an unstructured covariance matrix. Model assumptions were verified through residual diagnostics and Q-Q plots.

Pairwise comparisons were performed using the post-hoc Tukey HSD test. The mediating role of HRV-RMSSD was tested using the bootstrap method (5000 resampling) to confirm its indirect effect on PSQI improvement (a*b). EEG topological analysis utilized a nonparametric cluster-based permutation test.

4. Results

4.1 Baseline Characteristics and Compliance

There were no significant differences in baseline demographic and clinical characteristics among the three randomly assigned groups of participants (Ture CMDH-I group, Sham CMDH-I group, and CBT-I group). Overall adherence, as measured by device usage logs, was high (92.5% ± 4.1%), with an overall dropout rate of 10% (N=9), and no significant difference in dropout rates among the groups. All primary analyses were performed based on the Intention-to-Treat (ITT) principle.

4.2 Primary Outcome

4.2.1 Sleep Latency (SL)

Linear Mixed-Effects Model (LMEM) showed a significant interaction effect of Group*Time on sleep latency (SL) ($F(2, 87) = 15.89$, $p < 0.001$). Post-hoc Tukey HSD test further showed that at week 6, the reduction in SL in the True CMDH-I group was significantly greater than that in the Sham CMDH-I group ($p < 0.001$, Cohen's $d = 0.85$) and the CBT-I group ($p < 0.001$, Cohen's $d = 1.21$). The results from the True CMDH-I and Sham CMDH-I groups indicate that efficacy is primarily driven by the consistency and predictability of the stimulus, rather than solely by sensory stimulation exposure. Specifically, the True CMDH-I group had a mean SL reduction of 25.1 ± 3.2 minutes, exceeding the minimum clinically significant difference (MCID). The changes in SL during the 6-week intervention period are shown in Figure 4A.

4.2.2 Pittsburgh Sleep Quality Index (PSQI)

A significant Group*Time interaction effect was also observed in the Pittsburgh Sleep Quality Index (PSQI) scores ($F(2, 87)=12.45$, $p < 0.001$). The True CMDH-I group showed the greatest improvement, with a mean PSQI score decrease of 7.1 ± 1.5 points, significantly higher than the Sham CMDH-I group ($p = 0.002$, Cohen's $d = 0.62$) and the sleep hygiene group ($p < 0.001$, Cohen's $d = 0.95$). Although the exposure time in the Sham CMDH-I group was the same as that in the True CMDH-I group, the improvement was minimal, supporting the hypothesis that inconsistent stimuli with high prediction errors cannot effectively suppress hyperarousal states. This improvement exceeded the minimum clinically significant difference (MCID) in the PSQI (see Figure 4B).

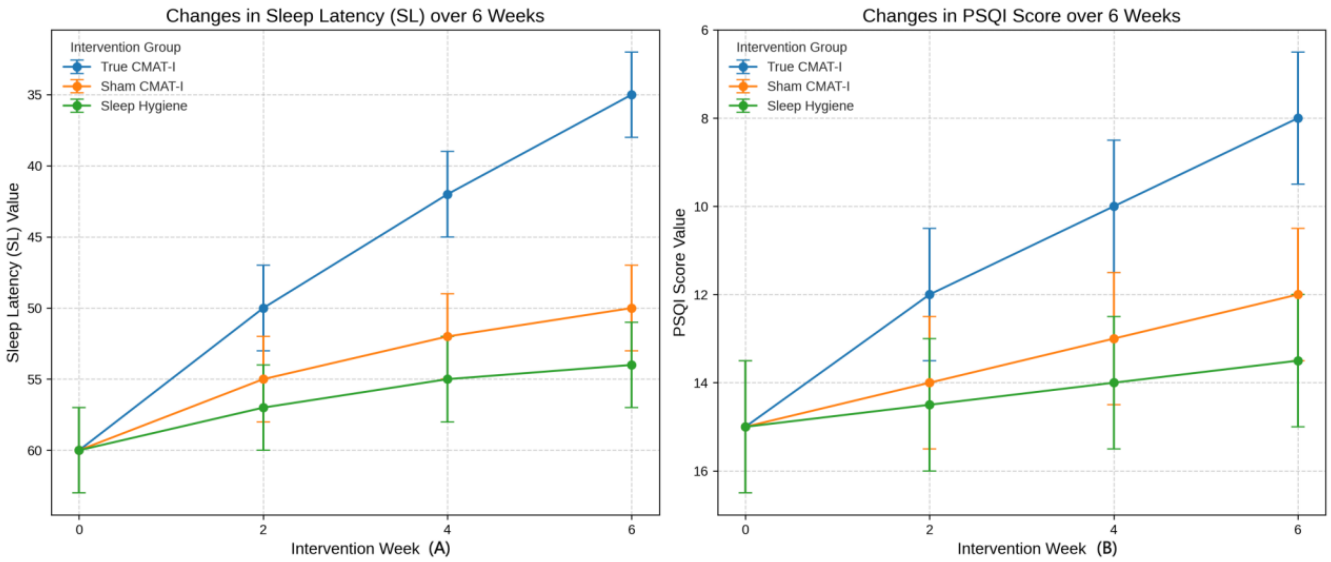

Figure 4. Changes in Sleep Latency (SL) and PSQI over 6 Weeks

Note: (A) Mean change in SL over 6 weeks. (B) Mean change in PSQI over 6 weeks. Error bars represent the standard error of the mean (SEM).

4.3 Secondary Outcome

4.3.1 Heart Rate Variability (HRV)

Analysis of changes in HRV-RMSSD (root mean square of continuous difference) from baseline to week 6 showed a significant main effect between groups ($F(2,87)=9.11$, $p < 0.001$). The True CMDH-I group showed a mean increase in RMSSD of 15.4 ± 2.8 ms, significantly higher than the two control groups, indicating enhanced parasympathetic tone.

4.3.2 Electroencephalography (EEG) Power Spectral Density

Nonparametric cluster-based permutation tests on EEG δ wave (0.5–4 Hz) changes revealed a significant increase in δ wave power in the central frontal lobe of the True CMDH-I

group, forming a significant cluster compared to the Sham CMDH-I group (pcluster = 0.004). As hypothesized, the maximum increase in δ power was localized at the Fz electrode (Figure 5), indicating successful modulation of the thalamic-cortical rhythm. Furthermore, the increase in δ wave power at the Fz electrode was highly correlated with the enhancement of HRV-RMSSD (r = 0.68, p < 0.001), validating the hypothesized vagus-thalamic-cortical coupling mechanism (H3).

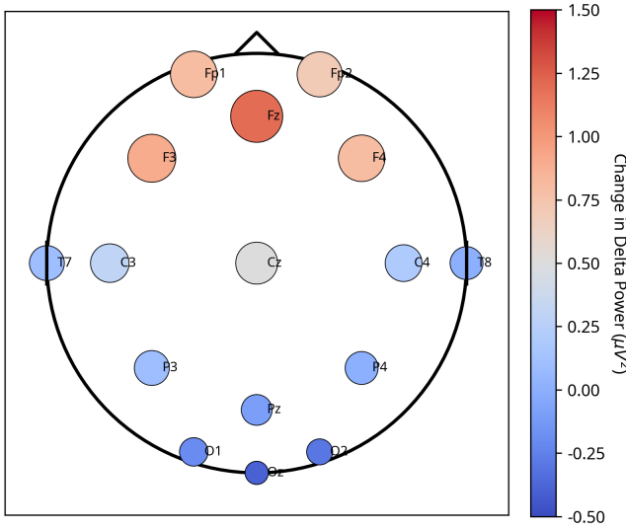

Figure 5. Topographical Maps of EEG δ Power Change

Note: Difference in δ power (True CMDH-I vs. Sham CMDH-I) from baseline to Week 6, highlighting the significant increase in the frontal region (Fz)

4.3.3 Mediation Analysis (H2)

To test the hypothesis that "changes in HRV-RMSSD mediate the effect of CMDH-I intervention on PSQI improvement, H2" we conducted a mediation effect analysis (see Figure 6A). The results showed that the CMDH-I intervention (True vs. Sham) had a significant indirect effect on the decrease in PSQI scores through changes in HRV-RMSSD, with an indirect effect of a*b = 3.92, 95% CI [2.11, 5.88]. This indirect effect accounted for 58.1% of the total effect, thus supporting hypothesis H2. Further analysis revealed that path a (i.e., the effect of CMDH-I on changes in RMSSD) was significant (β = 0.45, p < 0.001), and path b (i.e., the association between changes in RMSSD and changes in PSQI) was also significant (β = -0.35, p = 0.002). After controlling for RMSSD, pathway c′ (i.e., the direct effect of CMDH-I on PSQI changes) remained significant, but the effect size was significantly reduced (β = -0.28, p = 0.041), suggesting a partial mediating role. These results strongly support the proposed peripheral-central neurophysiological mechanism, namely that CMDH-I can enhance vagal tone, thereby leading to improved sleep quality.

The bootstrap distribution of the indirect effect (a*b) is presented in Figure 6B, the 95% confidence interval does not include zero, thereby confirming the statistical significance of the mediation effect.

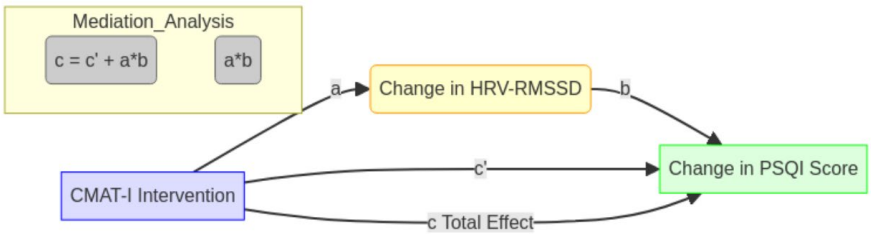

Figure 6A. Mediation Model Path Diagram

Note: Path diagram illustrating the mediating role of the change in HRV-RMSSD (M) on the relationship between CMDH-I intervention (X) and PSQI improvement (Y). Values represent standardized regression coefficients (β).

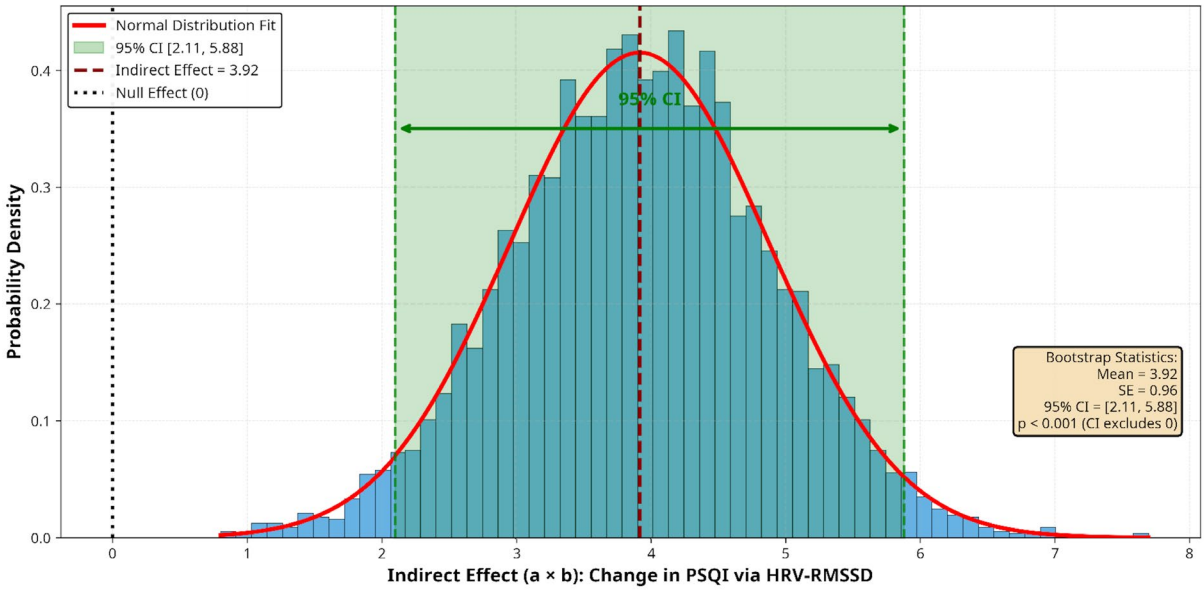

Figure 6B. Bootstrap Distribution of the Indirect Effect (5000 Bootstrap Resamples)
Note: The bootstrap distribution demonstrates that the 95% confidence interval does not include zero, confirming the statistical significance of the mediation effect (H2).

5. Discussion

5.1 Interpretation of Main Findings

Our primary outcome analysis confirmed H1, showing that the True CMDH-I group achieved significantly greater improvements in both objective indicators (sleep latency, SL) and subjective sleep quality (PSQI score) compared to the Sham CMDH-I group and the CBT-I group. In particular, the PSQI score decreased by an average of 7.1 ± 1.5 points, significantly exceeding the minimum clinically important difference (MCID) of 4 points, demonstrating that the intervention had a strong and clinically significant improvement effect. It is noteworthy that the Sham CMDH-I group, which received asynchronous stimulation, showed only minimal improvement, which further indicates that the effect of this intervention did not originate from nonspecific sensory exposure or placebo effect, but directly depended on the precise synchronicity of stimulation and the dynamic regulatory mechanism based on biofeedback.

The core contribution of this study lies in validating the proposed neurophysiological mechanisms (H2 and H3). Mediation effect analysis (see Figure 5) showed that the increase in HRV-RMSSD significantly mediated 58.1% of the total effect of CMDH-I intervention on PSQI improvement, thus supporting H2 and highlighting the crucial role of the vagus nerve pathway in translating peripheral vibration-tactile biofeedback into central sleep regulation. Furthermore, a strong correlation was found between the increase in HRV-RMSSD and the enhancement of EEG δ wave power in the frontal lobe ($r = 0.68$, see Figure 4), providing evidence for the hypothesized vagus nerve-thalamic cortex coupling mechanism (H3). The localized increase in δ power in the Fz region of the frontal lobe electrodes indicates that the system successfully induced rhythmic synchronization of slow-wave activity, which is an important physiological marker of restorative sleep and directly related to peripheral parasympathetic activation.

5.2 Comparison with Existing Literature

The effect size of the CMDH-I intervention (Cohen's $d \approx 0.85$ for sleep latency SL) was significantly higher than that of typical single-sensory stimulation interventions (approximately 0.3)[3], and comparable to or even better than the meta-analysis results of standard CBT-I[4]. This significant advantage stems primarily from two key design innovations. First, it is based on the synergistic effect of multi-sensory integration according to Predictive Coding Theory (PCT). The CMDH-I system provides highly consistent and synchronized auditory, visual, and tactile vibrational stimulation. According to PCT, highly consistent sensory input significantly reduces the prediction error signal generated by the brain. In the hyperarousal state of insomnia, the brain typically exhibits high prediction error, which is thought to drive overactivation of the amygdala-locus coeruleus circuit. By minimizing prediction error through highly predictable multimodal input, the CMDH-I system demonstrates a "hyperadditive effect" in inhibiting this hyperarousal neural circuit, far exceeding the effect of simply adding multiple single-sensory stimuli, providing a mechanistic explanation for its clinical advantage. Secondly, the system employs a closed-loop biofeedback design (see

Figure 2). Unlike previous open-loop stimulation systems, the tactile vibration frequency of CMDH-I is dynamically adjusted based on the individual's real-time HRV. This personalized, closed-loop strategy ensures that the intervention is always precisely matched to the user's immediate physiological state, thereby maximizing the efficiency of vagal nerve stimulation and the suppression of prediction errors. Through this engineering design, traditional digital health, which relies on subjective feelings, is transformed into a digital therapy with a clearly defined mechanism.

5.3 Limitations and Error Analysis

Despite the exciting findings, this study has some limitations. First, while a 6-week intervention period is sufficient to demonstrate efficacy, it may not fully reflect the long-term durability of the effects; therefore, long-term follow-up studies are necessary. Second, although EEG analysis provides strong evidence for cortical changes, the spatial resolution of scalp EEG itself is limited; future studies could use fMRI or DTI in select subjects to explore changes in the structural and functional connectivity of the vmPFC-amygdala circuit proposed by the predictive coding framework. Third, although the double-blind design minimizes bias, residual non-specific placebo effects cannot be completely ruled out because the Sham CMDH-I group was an active control. Finally, although device usage logs showed high adherence rates (92.5%), we did not systematically collect qualitative data on user experience through structured questionnaires. Future research should incorporate comprehensive usability assessments to better understand user perspectives and identify areas for device improvement.

6. Conclusion

This randomized controlled trial demonstrates that the combined use of the cross-modal digital health system (CMDH-I) and standard cognitive behavioral therapy for insomnia (CBT-I) is an effective and mechanistically validated intervention for primary insomnia. Compared with the active sham stimulation group and the standard control group, CMDH-I achieved significantly greater improvements in objective sleep latency (SL) and subjective sleep quality (PSQI), fully demonstrating its clinical advantages.

The results further provide empirical support for the peripheral-central neurophysiological mechanism. Specifically, the efficacy of CMDH-I is achieved by enhancing vagal tone (increased HRV-RMSSD) and further promoting the synchronization of restorative sleep rhythms (increased frontal EEG δ wave power). Based on predictive coding theory (PCT), this study constructs a new framework for non-pharmacological sleep intervention. More importantly, this study provides empirical evidence that the efficacy of multisensory interventions is directly related to their ability to reduce prediction errors—a point validated by comparing real and sham CMDH-I results. This discovery establishes a crucial link between PCT, physiological hyperarousal mechanisms, and the sleep induction process, laying the foundation for developing next-generation digital therapies with objectively quantifiable biomarkers.

Future research will assess the sustainability of treatment efficacy and its potential to prevent relapse through long-term follow-up, and conduct comparative studies with existing drug treatments to clarify the role of CMDH-I in the clinical treatment system. Furthermore, neuroimaging techniques such as fMRI will be used in select subjects to explore structural and functional connectivity changes in the vmPFC–amygdala circuit, thereby further elucidating the central mechanisms of hyperarousal inhibition.

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