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Cereset Research Standard Operating Procedures for Insomnia: A Randomized, Controlled Clinical Trial

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Abstract

Background: Interventions for insomnia that also address autonomic dysfunction are needed.
Objective: We evaluate Cereset Research™ Standard Operating Procedures (CR-SOP) in a pilot randomized, controlled trial. CR-SOP is a less operator-dependent, more generalizable innovation of HIRREM®, a noninvasive, closed-loop, allostatic, acoustic stimulation neurotechnology demonstrated to improve insomnia and autonomic function.
Methods: Adults with Insomnia Severity Index (ISI) scores of ≥8 were randomized to receive ten sessions of CR-SOP, with tones linked to brainwaves (LB, intervention), or a sham condition of random tones not linked to brainwaves (NL, control). Measures were collected at enrollment and 0-14 days and 4-6 weeks post-allocated intervention. The primary outcome was differential change in ISI from baseline to 4-6 weeks post-intervention. Secondary self-report measures assessed sleep quality65 and behavioral outcomes. Ten-minute recordings of heart rate and blood pressure were collected to analyze autonomic function (heart rate variability [HRV] and baroreflex sensitivity).
Results: Of 22 randomized, 20 participants completed the allocated condition. Intention to treat analysis of change from baseline to the 4-6 week outcome demonstrated mean ISI score reduction of 4.69 points among controls (SE 1.40). In the intervention group, there was an additional 2.58 point reduction in ISI score (SE 2.13; total reduction of 7.27, $P = .24$). Sleep quality and some measures of autonomic function improved significantly among the intervention group compared to control.
Conclusions: This pilot study compared use of a standardized, allostatic, acoustic neurotechnology intervention with a sham, active control condition. The magnitude of change in insomnia severity was clinically relevant and similar to the findings in a prior, fully powered trial, but the differential improvement observed was not statistically significant. Significant improvements were demonstrated in sleep quality and some autonomic function measures.

Keywords

insomnia, HIRREM, acoustic neuromodulation, autonomic, closed loop neurotechnology, allostasis, Cereset Research

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Introduction

Insomnia is a significant public health problem associated with dysfunction of multiple organ systems and various poor outcomes. Specifically, insomnia is associated with reduced work productivity, increased absenteeism, increased healthcare costs, and accident risk.[1,2] Epidemiological studies link insomnia to dysfunction across various organ systems (including adverse cardiovascular, neurological, and metabolic

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outcomes) and increased mortality.[3,4] The DSM-5 removed the distinction between primary and secondary insomnia to emphasize that insomnia should be a target for treatment, regardless of etiology.[5]

While cognitive behavioral therapy is an efficacious first line treatment[6] and psychopharmacological treatments and complementary and alternative medicine approaches are commonly used,[7] additional novel therapies for insomnia are needed. Limitations to current therapies include side effects, risk for dependence, time constraints, personal preference, or lack of efficacy. In addition to direct symptom relief, insomnia therapy may potentially have additional system wide benefit, given the links between insomnia and adverse outcomes across various organ systems. For example, investigators who studied an internet-based sleep support intervention raised questions about whether the intervention might potentially benefit hypertension in future studies.[8] Scientists are beginning to evaluate impact of sleep on disease states and more diffuse body functions including the autonomic nervous system.

Autonomic dysfunction in insomnia, especially increased sympathetic activity[3] could link this condition to adverse outcomes across various organ systems, and measurement of autonomic function during insomnia therapy may elucidate the relation between insomnia and autonomic function and potentially reveal a mechanism of therapy benefit. Heart rate variability (HRV) indicates the relative contribution of sympathetic vs parasympathetic influences in autonomic regulation. Prospective studies show that lower HRV is associated with increased cardiovascular and all-cause mortality.[9] Reduction in HRV has been observed with insomnia,[10] and is consistent with the hyperarousal theory, which has now been supported by polysomnographic and neuroimaging findings.[11,12] HRV may thus be a relevant biomarker for adverse effects of insomnia on the cardiovascular system.[13] Moreover, research suggests that improvement in HRV could be a marker of response to therapy for insomnia.[14]

In recent years, closed-loop technologies are under investigation as a precision-guided method to impact neural circuits involved in mental health and autonomic function.[15] Through repeated cycles of real time monitoring and calibrated intervention, closed-loop neurotechnologies have the potential to evaluate an individual's unique and changing patterns of brain activity, and to make dynamic therapeutic adjustments within milliseconds. High-resolution, relational, resonance-based electroencephalic mirroring (HIRREM®, registered trademark of Brain State Technologies, Scottsdale, AZ), is a closed-loop, acoustic stimulation neurotechnology based on the principle of allostasis.[16] Acoustic stimulation is an advantageous modality to echo brainwave information given the perceived effects of music on the autonomic nervous system, and the shorter processing time required as compared to visual feedback strategies.[17] Reduced insomnia symptoms and improved autonomic cardiovascular regulation were observed in a large open label series[18] and a randomized, placebo controlled trial among 107 adults comparing HIRREM to sham auditory stimulation.[19] Among a cohort with military-related post-traumatic stress, reduced self-reported insomnia, post-traumatic stress, depression, anxiety symptoms, and improved autonomic cardiovascular regulation, as well as significant changes in whole brain resting MRI network connectivity were demonstrated.[20] While the HIRREM intervention proved to be safe, effective and well-tolerated in the previous placebo-controlled trial of 107 adults with insomnia, the intervention was based on operator-dependent protocols and required significant participant time (10-20 sessions lasting 90-120 minutes each).[19]

An upgraded platform for medical research using a similar approach to HIRREM, of rapidly echoing brainwaves in real time as audible tones in a closed-loop paradigm, has been rebranded as Cereset Research™ (CR). Cereset is short for "cerebral reset." Cereset is currently offered commercially as a technique for relaxation, well-being, and stress management. Being a low risk general wellness device, Cereset is exempt from FDA regulation (personal communication, Brain State Technologies/Cereset). Application of CR using a standard operating procedures approach (CR-SOP), with every participant receiving an identical intervention, with similar times and locations for echoing, reduces operator dependence and improves scalability. In addition, smart protocols now leverage increased computer capability to actively manage the intervention delivery. This further reduces operator dependence and variability of the intervention, and may improve efficacy.

The objective of this study was to evaluate the feasibility and preliminary efficacy of this standardized, more scalable, less-time intensive version of this brainwave echoing technology (CR-SOP), and compare to a sham control condition. Specifically, in this pilot, randomized, controlled study of adults with insomnia symptoms, we compare 4-6 week post-intervention change in insomnia severity following 10 sessions of CR-SOP linked to brainwaves (intervention) to 10 sessions of auditory stimulation with a control condition (tones with random pitch). Additional objectives include exploring group differences in other behavioral symptoms and autonomic measures over the study period.

Methods

Study Participants

This single site, randomized, controlled trial was conducted in the Neurology Department at Atrium Health Wake Forest Baptist, an academic medical center in Winston-Salem, North Carolina. Participants had symptoms of insomnia persisting for at least 1 month based on Insomnia Severity Index ≥8, and this was not attributable to another known diagnosis (such as exclusions listed below that could cause sleep disturbance). Participants were recruited by community physician referral, word of mouth, and advertisement. Potential participants were excluded if they were unable, unwilling, or incompetent

to provide informed consent, or physically unable to attend study visits. Other exclusions were: known history of obstructive sleep apnea, periodic limb movements, seizures, urinary problems such as benign prostatic hypertrophy, severe hearing impairment, or ongoing need for treatment with opiates, benzodiazepines, antipsychotics, stimulants, thyroid hormone, antidepressants such as selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI) or tricyclics, or sleep medications such as zolpidem or eszopiclone. Those with anticipated, ongoing use of recreational drugs or alcohol, and those with weight over 285 pounds (chair limit for intervention and placebo administration) were excluded. Individuals participating in another active intervention study, and individuals with previous history of receiving HIRREM/Cereset Research intervention were also excluded. Participants were instructed to abstain from alcohol or recreational drugs during the intervention and until final data collection; whether participants adhered to this instruction was assessed by the study coordinator at each data collection visit. Participants were advised to suspend chiropractic, cranial-sacral therapy, and bioenergy work during the intervention, and for at least 3 weeks following, and to refrain from caffeine use after 1:00 pm. All participants were instructed to otherwise continue their ongoing care (any other medications or therapies, outside of those listed above as exclusions).

Study Design

This was a randomized, blinded, controlled trial. Study participants and all study personnel, except Technologists administering the intervention, remained blinded to group assignment. The protocol was approved by the Institutional Review Board at Wake Forest University Health Sciences, with full informed consent obtained from each participant. The 22 participants were randomly allocated 1:1 to intervention or a random tones control using blocked randomization with a block size of 4; these groups composed those analyzed in the intention-to-treat analyses. Standard intention-to-treat analysis is an approach in which all randomized participants are included in the statistical analyses even if they do not have follow-up data.[21] The randomization scheme and assignments were created independently by a team member who had no contact with the participants and were securely maintained in a password-protected Excel file accessed only by the unblinded Technologist (at the time of the first intervention/control session following enrollment). Group assignments were made independent of and concealed from the team member enrolling the participant and conducting follow-up outcome assessments; thus, outcome collection was blinded to group assignment. The study had been approved to enroll up to 24 participants in order to achieve a target goal of 20 to complete the intervention and enrollment ended once there were 20 completers.

Twenty-two participants were randomized to receive the CR-SOP intervention. Ten were assigned to receive tones linked to brainwaves (LB, intervention), while 12 were assigned to receive random tones not linked to brainwaves (NL, control), in addition to continued current care. Written informed consent and all baseline measures were obtained during an enrollment visit (V1). Figure 1 shows an overview of the study schedule and activities.

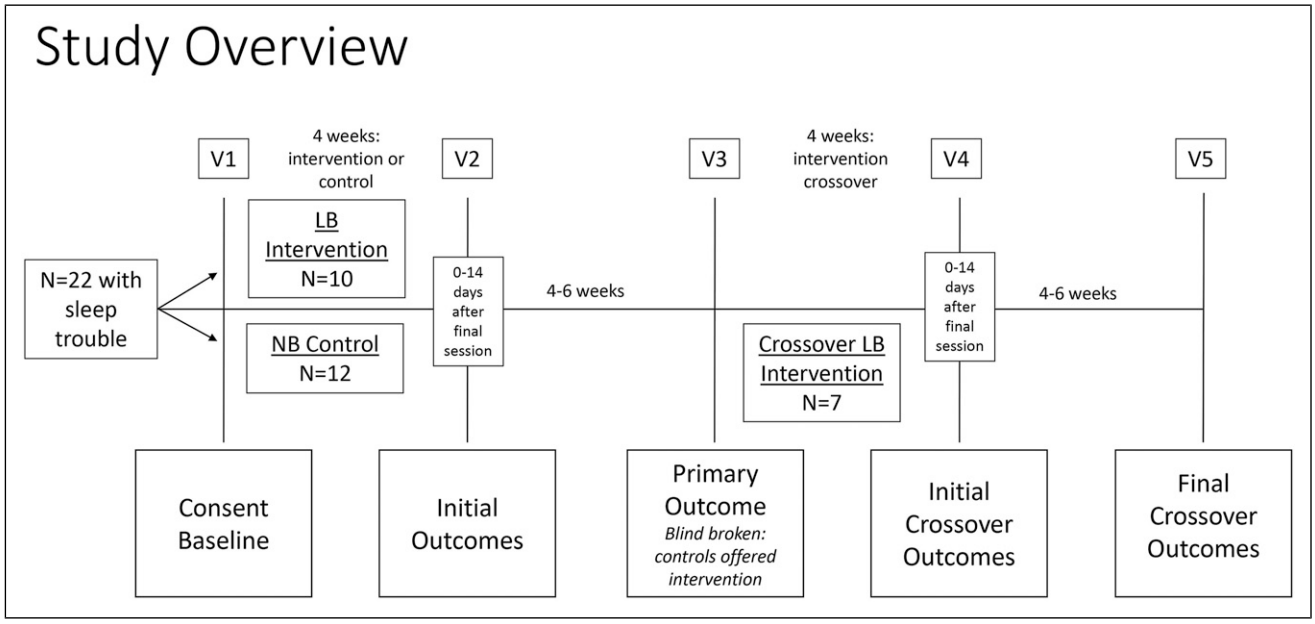

Figure 1. Study overview demonstrating timeline for visits, intervention/control delivery, and outcome collection during the randomized (V1-3) and crossover portions of the study (V4-5).

Sessions began 0-14 days following the V1 enrollment visit. Participants received 10 intervention/control sessions over a 4-week period (S1-S10). Participants received the first 2 sessions on consecutive days. Afterwards, participants could receive 2 intervention/control sessions during a half-day period with an hour break between sessions. Participants received the third session within the first 5 days. Participants were encouraged to complete the remainder of the 10 intervention/control sessions with no more than 5 days between sessions and were otherwise scheduled based on convenience and scheduling needs for the participant. The time of day was noted for both intervention/control sessions and data collections. Participants completed an expectation measure where they were asked to guess study group assignment prior to Session 5.

Zero to 14 days after the final intervention/control session there was a post-intervention/control data collection visit (V2). All measures were repeated. Four to 6 weeks after completion of the intervention/control sessions, there was another post-intervention/control data collection visit (V3), which served as the primary outcome for the study and all measures were repeated, including the expectation measure regarding group assignment. The blind was then broken following data collection at the V3 visit, and group assignment was shared with the participant. Although official involvement in the study was completed after V3, those who were in the control group were offered a crossover course of CR-SOP sessions.

Participants who chose to crossover completed intervention sessions within 3 months of V3. The same scheduling timeline and data collection plan was followed for crossover sessions. A data collection visit (V4) occurred 0-14 days after intervention completion. A final data collection (V5) was conducted 4 to 6 weeks after the last intervention crossover session.

Closed-loop Neurotechnology Intervention

All participants received a standard intervention protocol series of 10 sessions of 60-75 minutes in length, consisting of 4-6 individual protocols, each typically lasting from 6-20 minutes. Total intervention listening time was 536 minutes; additional session time included time for placement changes and Technologist check-in with the participant.

During sessions, with the participant comfortably at rest, sitting or reclining, paired sensors were placed over specific target areas on the scalp corresponding with brain regions/lobes to be observed. The Cereset Research (CR) system includes the use of 64-bit processing architecture for faster feedback than the prior HIRREM technology, 4 sensors, and more standard protocols (while retaining flexibility with length and sequencing of the standard protocols). All protocols were done with eyes closed. Four sensors (2, paired locations) are placed on the scalp at a time. However, only 1 pair of sensors are actively echoing feedback. The software automatically switches from 1 pair to the other between protocols. This reduces the number of sensor placement changes needed during a session by half compared to the prior HIRREM version of the technology, resulting in shorter session time and fewer interruptions. The CR intervention is limited to 4 paired protocols during sessions targeted the bilateral hemispheres according to the 10-20 International System at F3/F4 and P3/P4, FP1/FP2 and T3/T4, C3/C4 and O1/O2, and AFZ/POZ and CB1/CB2.

For those in the intervention group, software algorithms identified dominant frequencies as specific frequencies in the 0.5 Hz to 48.5 Hz range and translated each to an audible tone in real time. These selected tones were chosen from a set of engineered tones whose ADSR (attack, decay, sustain, release) envelopes were all exactly equal in length, to eliminate 1 tone having more influence than another lower or higher tone. Each chosen tone was echoed back to the participant via ear buds with as little as 4-8 millisecond delay (Personal communication, Brain State Technologies). The volume at which each note is played is the same, and is based on the comfortable volume setting indicated by each participant, since CR is working to echo the brain rather than being any type of operant conditioning intervention.

Participants were thus able to "listen to their brain," and figuratively speaking, to observe their brain pattern in an acoustic mirror, via tones linked in real time to the electroencephalographic pattern in the brain. CR-SOP software algorithms are intended to improve inflexible, potentially maladaptive patterns of cerebral activity. Particular attention is given to activity patterns suggesting dominant hemispheric asymmetries and/or suboptimal ratios of electrical amplitudes across the spectrum of frequencies.[16] Pilot data suggest correlation of brain pattern with autonomic cardiovascular regulation outcomes (heart rate variability, HRV), and that changes in asymmetry of frequencies and amplitudes may be observed from pre- to post-Cereset Research intervention.[18,22]

This closed-loop, recipient-unique, acoustic-stimulation brain feedback, or acoustic neuromodulation, supports the brain to auto-calibrate, self-adjust, relax, and to shift towards a more balanced state, often with reduced hyperarousal. This process is accomplished with no need for active, conscious, cognitive involvement by the participant, operant conditioning, or training the brain to accomplish anything.[16]

Those assigned to the control group received randomly generated tones during sessions, as a sham, active control intervention. All activities, procedures, and session times were similar to the intervention LB condition, with placement of sensors on various scalp locations. Sensors used for the control group had no active recording function and the tones were randomly generated, with no relationship to current brain activity.

All sessions (intervention or control) occurred with eyes closed, for which the participant was instructed to relax while sitting or reclining in a chair (Human Touch PC-6).

Data Management

Study data were collected and managed using REDCap electronic data capture tools hosted at Wake Forest School of Medicine.[23] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Outcome Measures

A series of measures were collected at the enrollment and follow-up visits, including self-report symptom questionnaires, and continuous recordings of BP and HR used to analyze measures of autonomic cardiovascular regulation. The primary outcome in this study was differential change in the score reported on the Insomnia Severity Index (ISI) from V1 to V3 (enrollment to 4-6 weeks post intervention/control completion, Figure 1).

Participants in the control group who chose to crossover to the linked to brainwave intervention also had 2 additional data collection visits as described above, V4 (0-2 weeks after active intervention completion) and V5 (4-6 weeks post-intervention completion). Other than the expectation measure, the measures collected at V4 and V5 were identical to V2 and V3.

Psychological and Psycho-Physiological Function

Insomnia and Sleep-Related Measures. The severity of insomnia symptoms was measured using the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS) self-report symptom inventories. The ISI (primary outcome) is a 7 question measure, with responses from 0-4 for each question, yielding scores ranging from 0-28.[24] The PSQI is a 19 item inventory that assesses sleep quality over a 1-month time interval.[25] Items are weighted on a 0-3 interval scale. A global PSQI score is calculated by totaling the 7 component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality. The ESS measures a person's general level of daytime sleepiness, or their average sleep propensity in daily life. The simple questionnaire is based on the likelihood of dozing off or falling asleep in a variety of different situations. Rated on a 4-point scale (0-3), it evaluates the chance of dozing off or falling asleep while engaged in 8 different activities. The ESS score (the sum of 8-item scores, 0-3) can range from 0 to 24.[26]

Depression

The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item survey assessing depressive symptoms to screen for depression.[27] Scores range from 0-60, with a score of 16 commonly used as a clinically relevant cut-off.[28]

Anxiety

The Generalized Anxiety Disorder-7 (GAD-7) is a 7 item screening tool for anxiety that is widely used in primary care. GAD-7 is a brief, reliable and valid measure of assessing generalized anxiety disorder.[29] The GAD-7 score (the sum of 7 items scores, 0-3) can range from 0 to 21.

Stress

The Perceived Stress Scale (PSS) is a ten-item psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to evaluate how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale, with answers rated from 0-4, also includes a number of direct queries about current levels of experienced stress.[29]

Expectation Measure

Participants were asked which group they believed they were assigned to, acoustic stimulation linked to brainwaves (LB, intervention), or non-specific acoustic stimulation (NL, control). This expectation measure regarding group assignment was obtained at V1, before the fifth session during the intervention period, and at the outcome visits. The second collection of the expectation measure, during the intervention period, but prior to anticipated meaningful benefit in the intervention group, allowed a realistic evaluation of the effectiveness of the blinding for the control intervention.

Blood Pressure (BP), Heart Rate (HR), Heart Rate Variability (HRV), Baroreflex Sensitivity (BRS), and Blood Pressure Variability (BPV)

Continuous BP and HR were acquired from noninvasive finger BP cuff for a minimum of 10 minutes, with subjects lying down quietly, supine. Systolic BP (SBP) and beat to beat, RR intervals (RRI) files were generated via the data acquisition system (BIOPAC Acknowledge 4.2, Santa Barbara, CA) and analyzed using Nevrokard BRS software (Medistar, Ljubljana, Slovenia) for measures of BRS, HRV and BPV as previously published[19] and described below.

Frequency Method. Power spectral densities of SBP and RRI were assessed over specified ranges (low frequency, LF: .04-.15 Hz; high frequency, HF: .15-.4 Hz). LF and HF alpha indices were calculated as measures of BRS. Power of RRI spectra in LF, HF range (LF_{RRI} and HF_{RRI}) were calculated as measures of HRV and the ratio of LF_{RRI}/HF_{RRI} is used as a measure of sympathovagal balance.[30]

Table 1. Participant Demographics and Clinical Characteristics.

Variable	Intervention Group (n = 10)	Control Group (n = 12)
Sociodemographics		
Age, mean (SD), years	58.6 (8.0)	54.7 (19.2)
Female, N (%)	7 (70.0)	9 (75.0)
white non-hispanic race/ethnicity, N (%)	9 (90.0)	11 (91.7)
Employment status, N (%)		
Employed	7 (70.0)	5 (41.7)
Retired	2 (20.0)	6 (50.0)
Other[a]	1 (10.0)	1 (8.3)
Self-reported comorbidities, N (%)**		
Depression	2 (20.0)	1 (8.3)
Vertigo	2 (20.0)	3 (25.0)
Hot flashes	3 (30.0)	2 (16.7)
Hyperlipidemia	2 (20.0)	3 (25.0)
Hypertension	2 (20.0)	3 (25.0)
Migraines or other headaches	1 (10.0)	2 (16.7)
Stress/anxiety	1 (10.0)	3 (25.0)
Other clinical characteristics		
Caffeine use before enrollment, N (%)	8 (80.0)	11 (91.7)
Alcohol use prior to enrollment, N (%)	5 (50.0)	7 (58.3)
Duration with sleep trouble, mean (SD), years	9.0 (10.4)	5.5 (4.2)
Hours of sleep per night	5.6 (1.2)	5.2 (1.6)

[a]This includes 1 part-time employed individual in the intervention group and 1 unemployed individual in the control group. **Comorbidities reported by 3 or more participants are shown here.

Time Domain Analysis was used to calculate BRS using sequence method as Sequence UP, DOWN and TOTAL. HRV was also measured as standard deviation of normal beat-to-beat interval (SDNN) and the root mean square of successive RRI (rMSSD). BPV was determined as the standard deviation of the mean arterial pressure (SDMAP).

Safety and Adverse Events

Participants were asked about any new or worsened symptoms at every data collection visit, and during Technologist check-ins prior to intervention/control sessions. Safety monitoring was conducted by the Principal Investigator and adverse events were reported to the Institutional Review Board using established protocols.

Statistical Analysis

Linear mixed models (LMMs) were used to contrast longitudinal changes in outcome measures between the intervention and control groups.[31] LMMs provide a natural mechanism to address correlations induced by repeated measurements on a single participant as well as the potential presence of incomplete data due to participants that are lost to follow-up. The primary analytic model included fixed effects corresponding to group assignment, measurement time point, and their interaction. Mean contrasts were used to compare the change for the outcome measures between groups from baseline to the follow up assessments at V2 (0-2 weeks after randomized intervention/control completion) and V3 (our primary test of efficacy for the primary ISI measure; 4-6 weeks after completion of randomized intervention/control sessions). Among those randomized to sham control who chose to crossover to intervention, linear mixed models were used to estimate mean changes in measures from baseline to each follow-up visit and changes from V3 to the V4 and V5 post-crossover intervention visits. Following recent practical guidelines for LMMs,[32] we used a combination of goodness-of-fit measures,[33] residual-based diagnostics, and outcome transformations to address important assumptions (homogeneity of the variance and normality for the model residuals) and specification of the covariance structure. The LMMs were fitted using PROC GLIMMIX in SAS. In addition to the primary intention-to-treat analysis, a per-protocol analysis was done as part of sensitivity analyses.

Results

A total of 148 individuals were assessed for eligibility, and 22 men and women age 18 or older were enrolled (mean age 56.5 +/- 15.0, 18 women); Table 1 and Figure 2. Demographic and clinical characteristics were similar between groups, except the intervention group had more employed individuals (vs. retired), and the intervention group had longer duration of sleep trouble (Table 1). None of the participants were taking beta blockers. The time over which the intervention and control sessions were

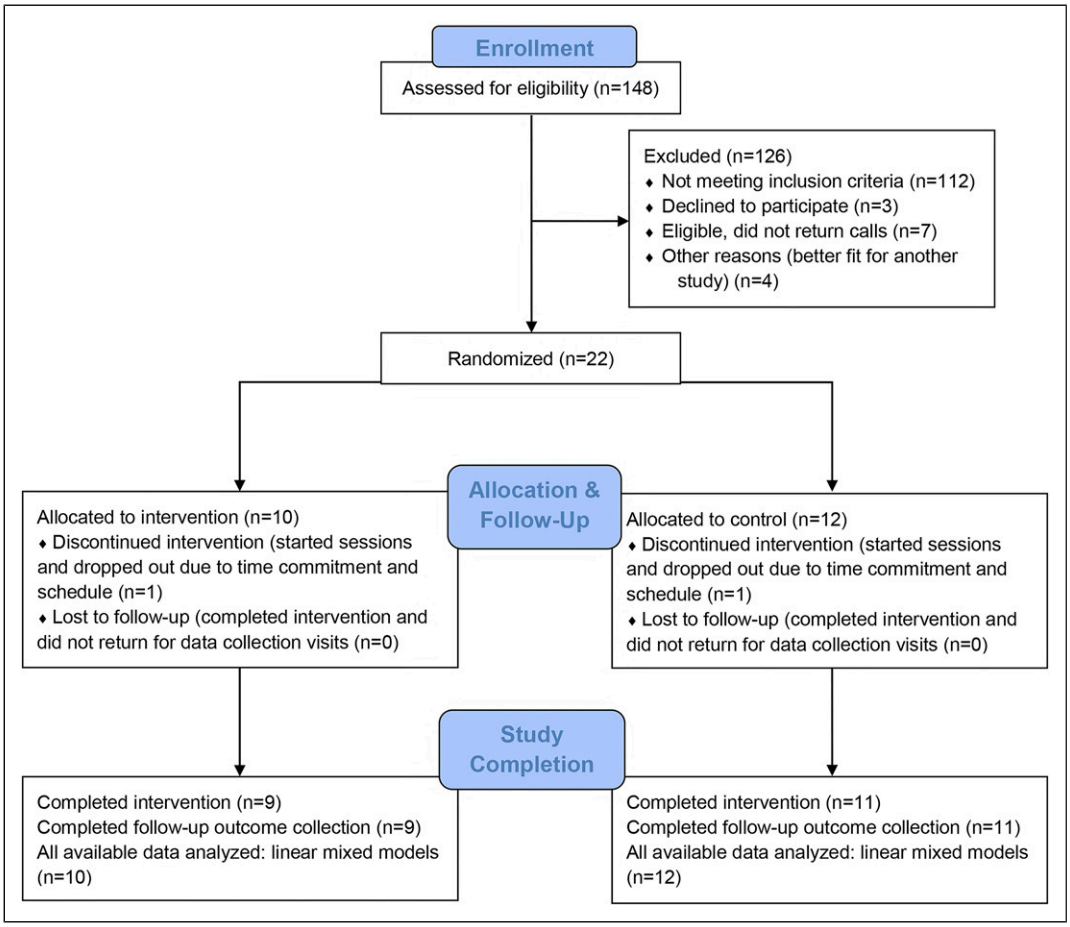

Figure 2. Consort diagram showing the flow of participants through the study for the groups receiving tones linked to brainwaves (LB, intervention), and tones not linked to brainwaves (NL, control).

received, and intervals to data collection time points were similar for both groups. There were no important differences between groups for the total days to receive allocated condition, in-office days receiving sessions, days between V1 and the start of sessions, or days between last session and V3. Of those randomized to control, 7 individuals initiated crossover sessions with tones linked to brainwaves a mean of 26.5 days (SD 32.4) after the V3 outcome visit. Six completed the intervention and V4 and V5 outcome assessments.

Participation and Adequacy of Blinding

Of the 22 participants enrolled and randomized, 10 were assigned to the intervention and 12 to the control group; all were included in intention-to-treat analyses. Of those assigned to intervention, 9 completed all sessions (1 discontinued after 6 sessions due to schedule conflicts). In the control group, 11 completed all 10 sessions (1 discontinued after 1 session due to schedule conflicts). Overall 10 participants (7 in control group) reported minor violations to the alcohol abstinence guidance during the study period (3 or fewer drinks total among 7 participants, occasional consumption among others). Across the various data collection time points, 56% to 70% in the control group and 44% to 78% in the intervention group reported they felt they were receiving active intervention on the expectation measure, indicating adequate blinding.

Sleep Outcomes

Raw values of the sleep measures at baseline and follow-up are demonstrated in Table 2. The primary outcome for this study was differential change in ISI scores from V1 to V3. Among all 22 randomized patients (intention to treat linear mixed model analysis using the GLIMMIX procedure, Figure 3A), in the control group there was a mean reduction of ISI score of 4.69 points (SE 1.40, $P = .003$) and in the intervention group there was a larger and clinically significant reduction in ISI score (7.27 points, SE 1.55, $P = .0002$). The change in ISI score in the intervention group was not significantly different from the control group ($P = .24$ for difference between groups, 95% CI: (-7.05, 1.88) points for difference between groups). Change in excessive daytime sleepiness (ESS) did not differ between randomized groups.

Table 2. Health outcome measures at baseline and follow-up: Raw Values.[a]

Measure Mean (SD)	Baseline (V1)	V2 (0-2 weeks Post Randomized condition)	V3 (4-6 weeks Post Randomized condition)	Crossover Intervention	
				V4 (0-2 wk Post intervention)	V5 (4-6 wk Post intervention)
Insomnia (ISI, Primary)					
Intervention	14.9 (4.7)	9.7 (4.9)	8.8 (5.5)		
Control	18.0 (3.1)	12.5 (5.6)	12.7 (5.0)		
Crossover N = 6	18.0 (4.1)	12.5 (7.1)	13.3 (6.5)	10.8 (5.8)	9.0 (7.6)
Sleep quality (PSQI)					
Intervention N = 9, 8[b]	7.8 (2.7)	7.0 (2.4)	4.9 (3.5)		
Control	10.3 (2.3)	7.5 (2.7)	8.0 (3.2)		
Crossover N = 6	10.5 (2.3)	7.2 (3.5)	7.7 (4.0)	7.3 (3.7)	6.8 (4.2)
Excessive daytime sleepiness (ESS)					
Intervention	5.1 (2.0)	4.1 (2.6)	4.7 (1.7)		
Control	6.2 (3.8)	5.5 (4.0)	5.2 (3.4)		
Crossover N = 6	5.8 (5.1)	3.7 (2.7)	4.2 (3.8)	4.8 (3.9)	4.3 (3.9)
Anxiety (GAD-7)					
Intervention	4.2 (6.2)	2.4 (3.3)	1.9 (3.9)		
Control	6.4 (5.3)	4.5 (4.5)	3.9 (4.8)		
Crossover N = 6	5.7 (2.8)	4.7 (3.4)	3.2 (4.1)	3.2 (3.0)	3.8 (3.1)
Depression (CES-D)					
Intervention	11.5 (13.9)	7.7 (9.6)	7.1 (11.3)		
Control	15.8 (11.2)	9.9 (9.4)	11.0 (9.8)		
Crossover N = 6	16.7 (9.9)	11.8 (11.7)	13.0 (10.7)	9.2 (7.0)	8.8 (9.7)
Perceived stress (PSS)					
Intervention	12.7 (7.0)	11.1 (7.5)	11.2 (7.9)		
Control	16.7 (7.6)	11.8 (6.1)	11.4 (6.6)		
Crossover N = 6	17.7 (5.0)	13.5 (6.2)	13.3 (5.6)	12.5 (6.7)	12.3 (7.5)

[a]N = 10 for intervention and N = 12 for control group at V1 and N = 9 for intervention and N = 11 for control at V2 and V3 unless otherwise noted.
[b]1 participant in intervention group omitted at all visits due to incomplete data preventing PSQI scoring.

Sleep quality significantly improved in the intervention group compared to controls at V3, with adjusted mean change of −5.74 points on the PSQI instrument in the intervention group compared to control (P = .0007).

In the crossover group, once these individuals received the intervention, many of the scores improved, including the ISI, with mean reduction in ISI score of 4.33 points (SE 1.11) in the linear mixed model analysis from end of control follow-up (V3) to 4-6 weeks after completion of linked to brainwave intervention (V5) P = .013 (Figure 3B). Sleep quality improved, with mean reduction in PSQI from baseline (V1) to V4 of 3.17 points and 3.67 points to V5 (P = .03 and .02 respectively; there had been a non-significant change from baseline to V3 in this group during the sham control condition: 2.83 points, P = .11).

Other Symptom Outcomes

Table 2 also demonstrates raw mean baseline and follow up scores for anxiety, depression, and perceived stress. Some reductions in anxiety, depression and perceived stress scores were observed during follow up in both randomized groups. Specifically, in linear mixed model analysis, the intervention group had 50.8% reduction in GAD-7 anxiety score from baseline to V3 (P = .005) and 56.6% reduction in CES-D depression score from baseline to V3 (P = .003). Reductions in the control group from V1 to V3 were 33.2% and 26.2% for the GAD-7 and CES-D respectively. Perceived stress scale scores improved in both groups from V1 to V3, by 2.3 points in the intervention group and 3.9 points in the control group; the difference was not statistically significant. Among those who crossed over to

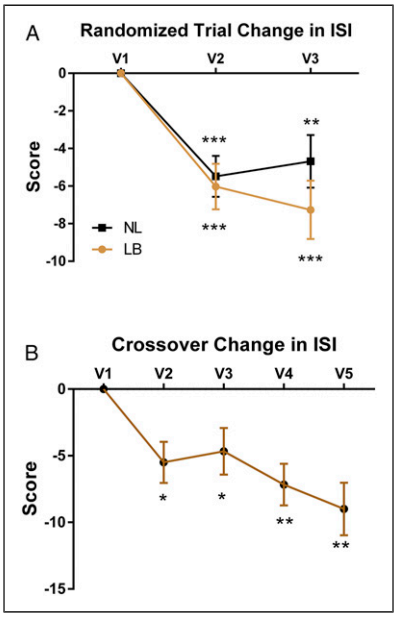

Figure 3. A. Intention to Treat outcomes for the Insomnia Severity Index (ISI) at baseline (V1), 0-14 days post randomized intervention/control (V2), 4-6 weeks after completion of randomized intervention/control (V3, primary outcome) for those receiving intervention (tones linked to brainwaves, LB) compared to control (tones not linked to brainwaves, NL) B. Crossover outcomes for ISI among N = 6 participants randomized to control who subsequently received active intervention. V4 occurred 0-14 days post active intervention completion and V5 occurred 4-6 weeks post active intervention completion (*$P \le .05$, **$P \le .01$, ***$P \le .001$ for comparison to V1 baseline value).

receive active intervention, only the CES-D demonstrated a statistically significant improvement from V3 to V5 ($P = .03$).

Autonomic Cardiovascular Regulation

Based on intention-to-treat analysis, significant interval improvements were observed across multiple measures of HRV (SDNN, and rMSSD) and BRS (Sequence ALL) at post intervention time points (V2, V3), compared to V1 in the intervention group (Figure 4A-C). The improvements in the intervention group were also significant when compared to outcomes in the NL control group at V2. In the control group, no significant changes were observed at V2 or V3 compared to V1 values. For those who participated in the crossover active intervention, measures of autonomic function then significantly improved at V5 compared to V3 (Figures 4D-F).

Safety and Adverse Events

There was 1 dropout per arm, due to scheduling constraints/time required for the intervention, as mentioned above. There were no serious adverse events and no study related adverse events. One participant reported tinnitus, hot flashes, and increased pulse, but this was felt to be due to a change in medication/diet rather than the intervention.

Discussion

In this randomized, blinded, controlled trial of a scalable, less operator-dependent innovation of a closed-loop neurotechnology, individuals with insomnia completed ten visits to receive acoustic stimulation within a relaxed study setting. The intervention group of interest listened to audible tones of variable pitch and timing linked to current brainwaves while relaxing in a zero-gravity chair. The tones were generated by software-guided, algorithmic analysis of their real time brain electrical activity (intervention), while the control group listened to non-specific, randomly generated tones. Upon session completion, and at 4-6 weeks after intervention, participants in the intervention group reported reduced insomnia symptoms. They also showed greater improvements in multiple measures of autonomic function, especially improvement in baroreflex sensitivity and HRV, indicating an enhanced parasympathetic tone in this group compared to those who received control (random tones not linked to brainwaves). The magnitude of insomnia symptom reduction was clinically meaningful in the intervention group at V2 and V3 (≥6 point drop in ISI), but not in the control group,[24] though the difference between groups in this small pilot study was not statistically significant. Sleep quality measured by the PSQI had a statistically significant improvement in the intervention group at V3 compared to control, and met clinically meaningful criteria (3 point drop).[34]

A unique feature of this study is that the control group was invited to cross over and receive the intervention with tones linked to brainwaves. Both the ISI and PSQI scores demonstrated statistically significant improvement from baseline after linked brainwave intervention in the crossover group. Both measures also surpassed thresholds for clinically meaningful change. By V5, or 4-6 weeks after intervention, the crossover group had significant improvements in the autonomic measures Seq ALL, rMSSD and SDNN.

The changes in autonomic function shown in the intervention group are consistent with our previous reports, where HIRREM intervention improved parasympathetic tone and reduced sympathetic tone, shifting the balance towards parasympathetic dominance.[18,19,22] The improvement in autonomic measures occurred only in the intervention group, which suggests that these physiological measures were not impacted by a placebo effect in the control group.

This study of the CR-SOP linked to brainwave intervention is consistent with existing literature demonstrating positive impact of a noninvasive, real time, recipient-unique closed-loop neuromodulation on insomnia and autonomic cardiovascular regulation. Findings are in line with a previous randomized, controlled trial for insomnia.[19] CR-SOP is designed to decrease participant time burden with shorter, standardized sessions, and utilizes a less technologist-dependent approach.

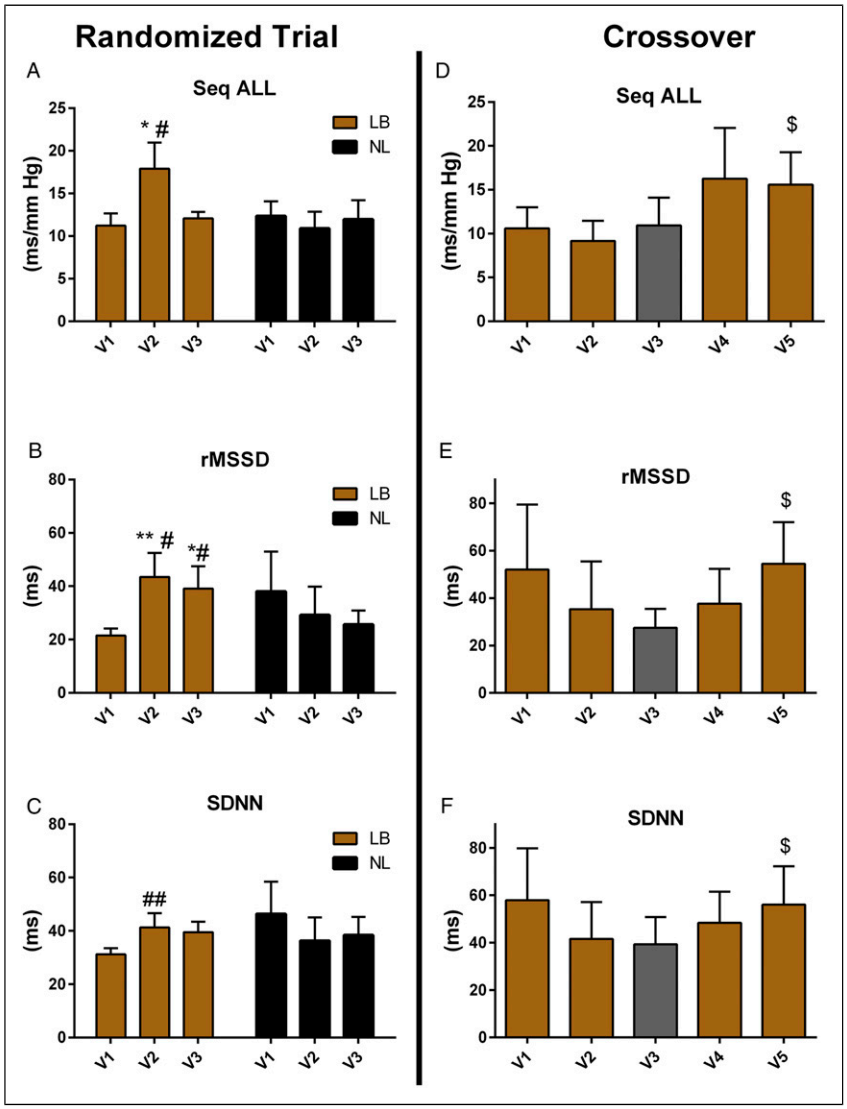

Figure 4. Panel of 3 autonomic function measures: Seq ALL, a measure of baroreflex sensitivity, and 2 heart rate variability outcome measures, rMSSD and SDNN. Results are shown for the randomized portion of the study (Figure 4A-C) and crossover portion (Figure 4D-F). Results shown include change within groups over time compared to V1 for those receiving tones linked to brainwaves (LB intervention) and tones not linked to brainwaves (NL control;. * = $P < .05$, ** = $P < .01$), differences between the 2 groups during the randomized portion of the study (# = $P < .05$, ## = $P < .01$), and difference from V3 in the crossover portion ($ = $P < .05$).

This study is an important step forward using a more reductionist approach that offers greater potential for scalability (ie less technologist training time and shorter participant listening time).

Disturbed synchronization of neural oscillations and suboptimal proportionation, or hyperarousal of electroencephalographic (EEG) signatures, are reported in insomnia.[35-37] The autonomic analysis fits with literature that reports dysregulation, as identified by measures of heart rate variability (HRV), with insomnia.[38,39] We have previously reported correlation of right dominant brain pattern with sympathetic dominant patterns of HRV.[40] This intervention supports shifts towards improved balance and reduced hyperarousal.[18] It should follow that downstream measures of HRV would also improve. This is consistent with the concept of allostasis: the brain (as the organ of central command) facilitates flexible orchestration of system functions to meet changing conditions and demands, and disease is associated with rigidification, or loss of dynamic range of response.[41]

We postulate that CR-SOP with tones linked to brainwaves allowed these neural networks to reset, with associated reduction of symptoms of insomnia and improved autonomics. This interpretation is consistent with secondary analysis of a placebo-controlled trial of vestibular therapy for insomnia, which found differential change in HRV distinguished responders from non-responders in the group

Table 3. Comparison of Relevant Non-Pharmacologic Interventions for Insomnia.

	Current Study of Cereset Research – Standard Operating Procedures	Music Therapy	White Noise Acoustic Stimulation	Vibroacoustic Stimulation	Cognitive Behavioral Therapy for Insomnia (CBT-I)
Citation	N/A	Jespersen KV, otto M, kringelbach M, van someren E, vuust P, 2019	Ebben MR, yan P, krieger AC, 2021	Zabrecky G, shahrampour S, whitley C, et al, 2020	Arnedt JT, conroy DA, mooney A, furgal A, sen A, eisenberg D, 2021
Study design	RCT	RCT	Within-subject ABA* design	Randomized, waitlist	Non-inferiority RCT
Number of subjects	22	57	10	30	65
Closed-loop approach	Yes	No	No	No	No
Duration of each session	60-75 min	30 min minimum	Overnight	24 min initially, then 60 min	30-60 min
Number of sessions	10 in office	21 at home	7 at home	1 in office, 8 at home	6 (with very experienced clinician)
Total listening time	536 min	630+ minute	Not reported	504 min	180-360 min
Intervention period	Mean 15.3 days	3 weeks	3 weeks	1 month	6 weeks
Outcome measures	ISI, PSQI, HRV	ISI, PSQI, pQoL, actigraphy	Actigraphy, sleep diary	ISI, actigraphy, fMRI	ISI, sleep diary
Significant change in ISI (absolute change)	Yes (−7.27 within group)	Yes, (−3.1 within group at 1 month)	ISI not used	Yes (−3.1 within group)	Yes Telemedicine (−8.9) Face-to-face (−9.3)
Clinically meaningful change in ISI	Yes	No	N/A	No	Yes
Significant change in ANS†	Yes	N/A	N/A	N/A	N/A

*ABA design – Subject has baseline, treatment phase, followed by another baseline (washout) period. †ANS – Autonomic Nervous System.

receiving the primary intervention.[14] Moreover, the HRV and BRS changes shown in the present study are consistent with the premise that successful allostatic therapeutics should be associated with healthful influence on peripheral ("downstream") organ system dysregulation.[41,42] Closed-loop therapies with real time monitoring for modulation of biological function offer a precision-guided, patient-centric strategy for brain-based therapies.[43] Very few other non-pharmacological modalities exist that are truly closed-loop and provide instant feedback.

Numerous other non-pharmacological strategies have been evaluated for use in patients with insomnia. Cognitive Behavioral Therapy for insomnia (CBT-I) is generally considered the first line therapy for primary and comorbid insomnia.[6] Of relevance to the current study, a handful of publications report the use of various types of acoustic stimulation in clinical trials for insomnia. This includes music,[44] white noise,[45] and vibroacoustic stimulation.[46] Table 3 provides an overview of similarities and differences between various aspects of these studies, and modalities. For perspective, a recent report using CBT-I is also included.[47] Several key differences between CR-SOP and these other approaches include the use of a closed-loop paradigm, a relatively brief intervention period, clinically meaningful change in the ISI outcome measure, and accompanying significant change in autonomic nervous system function. We recognize that there is limited data on closed-loop, non-pharmacological modalities for a true comparison to this study.

Strengths and Limitations

The current study successfully administered CR-SOP sessions within a randomized, controlled trial design and demonstrated feasibility and clinically relevant magnitude of improvement in insomnia and sleep quality for this less operator-dependent innovation of the HIRREM intervention. The intervention was well-tolerated and the blind was maintained with the revised control condition. This study provides foundational preliminary evidence that scalable innovations of the technology are feasible and likely effective.

Our study has the following limitations. Participants with any level of insomnia were enrolled (ISI ≥8), rather

than the more severe insomnia required for inclusion in our prior larger trial. While the magnitude of change in insomnia severity was similar in this small study compared to our prior larger study, and the confidence interval includes a clinically meaningful difference between groups, the confidence interval also includes smaller effects and no effect. Thus, reduced efficacy of the technique for milder insomnia has not been excluded. As this was a pilot study designed to demonstrate feasibility of the CR-SOP technique, and not a fully powered trial, it is not surprising that the primary outcome did not demonstrate a statistically significant difference between the intervention and control groups. However, the magnitude and direction of change in insomnia, sleep quality, and many of the autonomic measures were similar to the benefit demonstrated in our prior larger trial.[19]

Although heart rate variability and baroreflex sensitivity are objective outcome measures, this study did not collect direct measures of sleep such as polysomnography-based sleep stages and sleep spindles or slow-wave content, due to funding limitations. Within the growing non-pharmacological landscape for insomnia, there has been recent interest in using acoustic stimulation to enhance slow wave oscillations during sleep.[48] The oscillation literature suggests the pathophysiology of insomnia could be characterized by a lack of slow wave activity, thus measurement of slow wave sleep content would be beneficial in future studies.

No daily sleep diaries were required. Scores for depression and anxiety did not meet clinical criteria at baseline, so a floor effect may have affected those outcomes. Participants in this study had a mean age of >50 years, were mostly female, and of white, non-Hispanic ethnicity. This limits the generalizability of our findings, and future studies should include more diverse samples. More individuals in the intervention group were employed than in the control group; it is possible that job related impacts on sleep could have reduced the intervention's potential benefit for sleep relative to those who were not actively employed. The use of several commonly prescribed categories of medications was also an exclusion, limiting generalizability. Other questions not addressed by this study include the implications of the present findings for individuals using psychotropic agents since these were excluded. Future studies should be conducted with expanded scope, including larger samples, with objective sleep measures included. These future studies could include longer follow up periods and potentially follow-up intervention sessions to evaluate whether this would extend the period of benefit.

Conclusion

In conclusion, this pilot randomized, controlled study of the scalable CR-SOP noninvasive, closed-loop, allostatic, acoustic stimulation neurotechnology demonstrated statistically and clinically significant improvements in sleep quality, baroreflex sensitivity and heart rate variability. There was also a clinically relevant improvement in the primary insomnia outcome (though it was not statistically significant between the groups). The between-group differences for objective autonomic measures suggests that benefits were not likely due to a placebo/expectation effect, and they raise the possibility for healthful effect on physical comorbidities associated with insomnia. Future, fully powered studies are warranted to explore effects on other measures or mechanisms of sleep disturbance and in other populations.

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Author Contribution

Author contributions included conception and study design (CLT, HS, LG, and CHT), data acquisition (CLT, and HS), data preparation and analysis (CLT, HS, SLS, HMC, and CHT), and interpretation and reporting of data for this project (CLT, HS, HMC, LG, CHT). All authors have reviewed the manuscript and agreed to be accountable for all aspects of this work.

Declaration Conflicting of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors affiliated with the Wake Forest School of Medicine have no conflicts to report. Lee Gerdes is currently employed by Brain State Technologies, Scottsdale, AZ.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Registration

ClinicalTrials.gov - NCT03607994.

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