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Protocol for a Pilot Study on the Neurocardiac Mechanism of an Interoceptive Compassion-Based Heart-Smile Training for Depression

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Abstract

Background: Heart-Smile Training (HST) is an interoceptive compassion-based behavioral intervention that in case reports has been beneficial for depression. Interoception refers to the awareness and regulation of physiological signals from inside the body. Depressed patients often have diminished interoceptive awareness and often experience disconnection from bodily needs and sensations. In addition to interoceptive dysfunction, depression often involves negative self-evaluation and self-critical rumination. HST is a compassion-based meditation training program that explicitly cultivates interoceptive awareness of the heart area. This study aims to investigate the possible neurocardiac mechanisms engaged through HST for depression patients.
Methods: We plan to enroll 50 subjects to be randomized into a 4-week HST intervention group and a waitlist group. A battery of psychological questionnaires will be administered at baseline and post-intervention timepoints, and electroencephalography (EEG) will be collected during compassion meditation guided by pre-recorded audio. The primary clinical outcome measures are on the feasibility of the intervention and research procedures, the primary mechanistic outcome measure is the post-intervention change in Heartbeat Evoked Potential (HEP) amplitude. Secondary outcome measures include changes in depression severity and EEG gamma spectral activity. Exploratory outcome measures include effects of HST on skin conductance response, heart rate variability, EEG spectral properties in other frequency bands, as well as a list of psychological questionnaires that measure depression and anxiety symptoms, emotion regulation, mindfulness, interoceptive awareness, self-compassion, gratitude, sleep quality, quality of life and social connectedness.
Results: Results not yet available.
Conclusion: This is the first study on the feasibility and interoceptive neurocardiac mechanism of HST. Our findings will provide frontier knowledge on the physiological working mechanism of behavioral interventions with an interoception-based meditative approach. https://clinicaltrials.gov/study/NCT05564533.

Keywords

interoception, compassion, depression, loving-kindness, neural, heart smile training

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Introduction

Compassion-based meditation training programs, recognized as an evolution of secular contemplative practices, integrate mindfulness with the development of prosocial mental states and attitudes. These programs have increasingly being acknowledged by researchers, clinicians, and the general public[1] for their ability to engender positive emotional states and trait changes in participants,[2] such as heightened positive affect and reduced negative affect,[3] enhancement in social connectedness,[4] potential attenuation of the physiological and subjective effects of stress,[5,6] as well as increased activity in brain regions associated with emotion processing and empathy.[7,8] Compassion-Based Interventions (CBIs) are related to Mindfulness-Based Interventions (MBIs),[9,10] except that the focus of the meditation training is on cultivating compassion towards self[11] or others.[12]

Over the past decades, multiple evidence-based CBIs have been developed, including include Cognitive-Based Compassion Training (CBCT),[13] Compassion Cultivation Training (CCT),[12] Mindful Self-Compassion (MSC),[11] and Compassion Focused Imagery (CFI).[14] The Heart-Smile Training (HST) program uniquely emphasizes the importance of cultivating embodiment through explicitly teaching practitioners to become aware of the body sensations and warm feelings, such as compassion, acceptance and gratitude in the heart area.[15] HST uses an iterative, integrative approach to combine focused attention and interoceptive awareness with core, intrinsic capacities of compassion, loving-kindness, and empathy. HST involves giving and receiving of compassion as well as cultivating wisdom and gratitude, while emphasizing heightening interoceptive awareness through body scans and interoceptive awareness during sound meditation.[15]

Originating from Korea and grounded in Mahayana Buddhism,[16] HST is designed to offer a holistic approach to improving mental health outcomes[15] through cultivating interoceptive awareness as the base for development of compassion and loving kindness.[17] Various formats that balance longer, more intensive practice sessions with shorter, weekly practice sessions have been experimented with for delivering HST.[18] Our prior qualitative research[18,19] used the NIH Stage Model[20] to compare the 3-day format with an 8-week group format that included a 1-day retreat, which revealed similar effects for depression and anxiety symptoms, with the 8-week format being more effective for cultivating interoceptive awareness.[18] During the Covid-19 pandemic, we developed a version of the HST that combines a 3-day online retreat with 4 weekly online sessions, called Intensive Introduction Program (HST-IIP), which we adapted for use in the current study. HST-IIP has been used in Korea for the general public,[15] but this is the first time it will be delivered in English for depression treatment. According to the NIH stage model,[20] the HST intervention is at Stage 1B, because it has developed the fundamental framework and core content of the intervention program and is currently being tested in a research setting with respect to its feasibility and neurophysiological mechanisms, which are the primary objectives of this study.

Depression is characterized by interoceptive dysfunction[21,22] with diminished interoceptive awareness, impacting body trust, responsiveness to bodily signals, self-regulation, and emotional awareness within the body.[23] Depression is linked to a disconnection from bodily sensations[24] and an impaired neural representation of interoceptive body states, particularly in the insular cortex.[25] The reduced insular activation observed during depressive episodes appears to recover after individuals emerge from the episode.[26] This diminished interoceptive awareness of internal bodily states carries significant implications for an individual's mental health and overall well-being, and may also be a mechanism impacting appetite loss[27] and alexithymia.[28,29] Therefore our hypothesis is that HST-IIP will improve interoceptive awareness for depressed patients, as measured by changes in Heartbeat-Evoked Potential (HEP)[30,31] from electroencephalography (EEG) and electrocardiogram (ECG), which will contribute to depression symptom improvement. We will test this hypothesis in this mechanistic pilot study with EEG, ECG and other physiological measures collected before and after the HST-IIP program compared to a waitlist control arm, combined with clinical and questionnaire assessments of symptom improvements.

Methods

Study Procedure

The study is approved by the Institutional Review Board (IRB) of Cambridge Health Alliance (CHA) (CHA-IRB-21-22-100) and has been registered at https://clinicaltrials.gov/study/NCT05564533. We propose a single-blinded randomized controlled trial with 2 arms: HST-IIP and waitlist control. The waitlist group will be asked not to participate in any mindfulness meditation programs until they complete all study procedures, and afterwards they will be given a code to enroll for free in a live-online mindfulness course routinely offered at the Center of Mindfulness and Compassion at CHA. All subjects will be instructed to continue their ongoing pharmacological and/or psychotherapy interventions (if applicable) concurrent to participating in this study and will be instructed to refrain from starting any new medications or psychotherapies during the study. A maximum of 50 eligible participants will be enrolled in the trial for 11 weeks (Figure 1).

Eligible subjects will be scheduled for a pre- and post-intervention EEG sessions at Mass General Brigham within the Spaulding Rehabilitation Hospital, during which EEG, ECG, galvanic skin response (GSR) and respiration signals will be collected. A battery of online self-report questionnaires will be administered within 24 h from each EEG visit, including Computerized Adaptive Testing–Depression

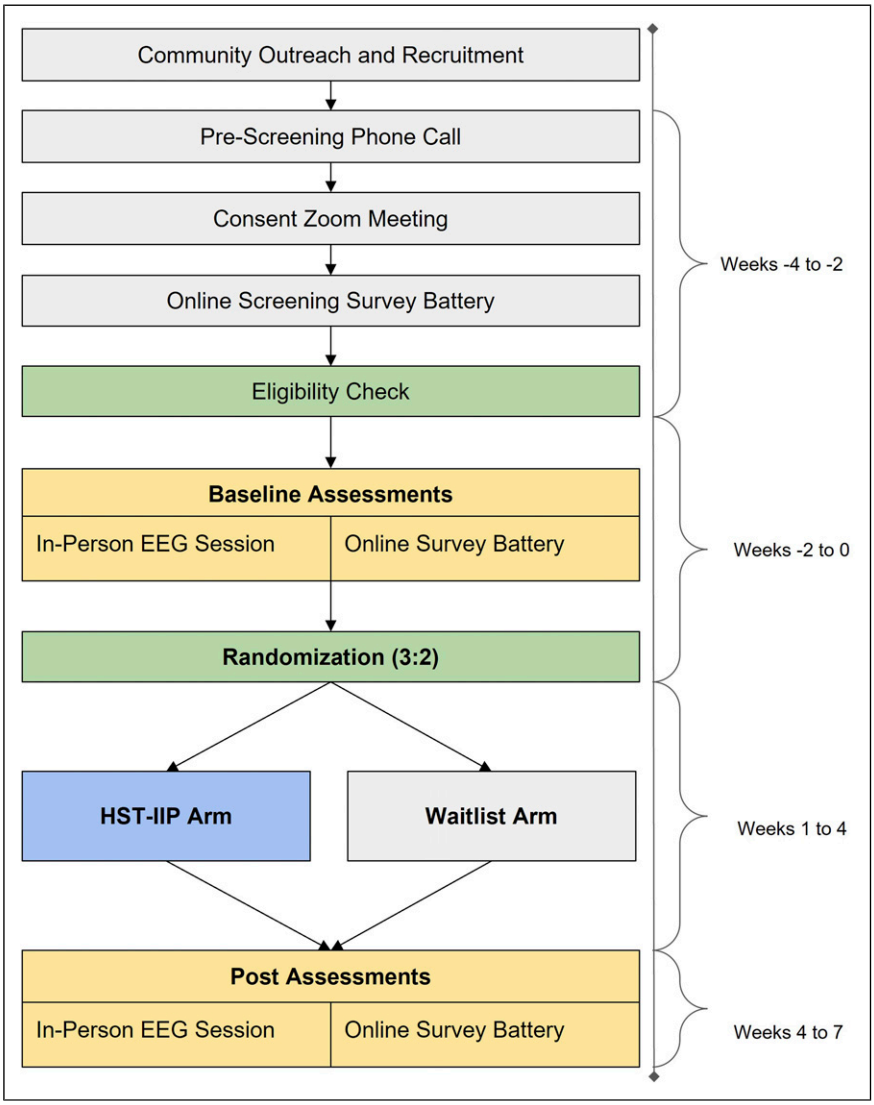

Figure 1. Overall study procedure schema.

Inventory (CAT-DI),[32] Computerized Adaptive Testing–Anxiety (CAT-ANX[33]), Depression Anxiety Stress Scale-21 (DASS-21[34]), 5 Facet Mindfulness Questionnaire (FFMQ[35]), Difficulties in Emotion Regulation (DERS[36]), Self-Compassion Scale (SCS[37]), Multidimensional Assessment of Interoceptive Awareness (MAIA-2[38]), Quality of Life Scale (QOLS[39]), Gratitude Resentment and Appreciation Test (GRAT[40]), Pittsburgh Sleep Quality Index (PSQI[41]), Social Connectedness Scale (SocCon[42]), Purpose In Life Test (PIL[43]). CAT-DI and CAT-ANX will be also collected weekly.

Subject Enrollment Plan and Eligibility Criteria

Participants will be recruited from the general public through advertising on social media platforms and posting on the website of Cambridge Health Alliance Center for Mindfulness and Compassion and Mass General Brigham clinical trials website for the public https://rally.massgeneralbrigham.org/. We will also receive referrals from a CHA mental wellness program that has accumulated a database of approximately 1500 people.[44,45] This study will enroll individuals of any gender and any demographic group who meet the eligibility criteria.

Subjects will go through 3 steps of screening: (1) initial phone pre-screening; (2) Zoom meeting with the subjects who pass the phone screening to review the consent form and conduct additional screening; and (3) a battery of online questionnaires administered via REDCap including a demographic survey, prior meditation and mindfulness experience survey, initial healthcare details survey and Computer Adaptive Tests for Mental Health (CAT-MH) to assess anxiety, psychosis, substance use, mania, PTSD, and social

determinants of health. Built-in data quality checks in REDCap and CAT-MH will be utilized for common data quality assurance such as value ranges, value format and data missingness.

Inclusion criteria include: (1) being 18-65 years old for the duration of the study[46]; (2) sufficient English fluency to understand procedures and questionnaires; (3) the ability to provide informed consent; (4) mild to moderately severe depression (as determined by a CAT-DI score of 35-75)[47,48]; those with severe depression (CAT-DI >75) will require further clinical evaluation to assess for symptoms of psychosis, amotivation or suicidality, and may be determined as eligible after ruling out those symptoms or risks.

Exclusion criteria include: (1) current participation in another research study; (2) unavailable or unable to participate in the planned dates for the HST-IIP sessions; (3) expected hospitalization during the study period, including second and third trimester pregnancy at screening; (4) previous experience with mindfulness or other mind-body practices, defined as more than 10 min of practice per day, more than 5 days a week for the past 6 months; participation in an 8-week mindfulness group program in the last 2 years, or participation in a meditation retreat longer than 1 day in the past 2 years; (5) anticipated inability to successfully complete in-person study sessions with EEG, ECG, respiration rate, and skin conductance response measurement; (6) anticipated inability to participate safely in the study intervention and without disrupting the group, due to any of the following criteria: (6.1) active psychosis defined by a PSY-S-CAT score >60 (from the CAT-MH assessment)[47]; (6.2) bipolar I disorder history or severe level of mania on CAT-MH (score >70)[47] OR current use of mood stabilizing medication for bipolar disorder; (6.3) acute suicidality or hospitalization for suicide attempt or self-harm within 3 months of the enrollment period; (6.4) moderate or severe substance use disorder; (6.5) use of illicit drugs (ie, cocaine, heroin, fentanyl, methamphetamine) or non-prescribed controlled medications (opioids, stimulants, or benzodiazepines) in the past 3 months at the time of screening.

Randomization Procedure

Randomization will be performed after subjects have completed baseline EEG and self-report assessments (Figure 1). A study staff member who is not involved in baseline assessments will randomize participants with their assigned study numbers using a computerized block randomization in blocks of 5 with a 3:2 allocation ratio such that 3 participants are randomized to the HST-IIP for every 2 participants randomized to the waitlist arm.

Participants will be called by phone and asked once more to confirm their availability to attend the scheduled dates and times of intervention sessions. Once confirmed, they will be informed about their group assignment by phone and will be sent a confirmation email. HST-IIP participants will also receive information about the start week for the HST-IIP group sessions and about the group structure and schedule. Participants on the waitlist will be required to not participate in any mindfulness programs until after completion of this study.

Blinding

This is a single-blinded study in which the PI, data analyst, statistician, and the EEG technician and analyst collecting and analyzing the physiologic data will be blinded to subject group assignments. Participants will be aware of the study arms once they are randomized. Research coordinators responsible for final determination of study eligibility will be blinded to the randomization sequence, but they will not be blinded to participant identity or allocation, because they will be responsible for informing participants of their scheduled group and study visits. There are a few circumstances where the blinding-criteria may be broken. For instance, the PI will be blinded, but if an unexpected serious adverse event related to intervention occurs, or if there is an important clinical decision to make related to a major protocol violation or unanticipated problem related to the intervention, then the PI may be informed.

Subject Engagement, Adverse Events Monitoring and Confidentiality

Research coordinators will send weekly follow-up emails and conduct engagement phone calls with anyone who missed a study testing or intervention session. An adverse event participant self-report form will be systematically collected at each in-person study visit (Baseline EEG visit and Post-Intervention EEG visit) and after each weekly intervention session in the HST-IIP arm. In addition, group leaders and research coordinators will be trained to identify and report any adverse events that occur or are reported during weekly group visits. All adverse events will be reviewed monthly by the PI, and serious adverse events will be reviewed within 24 h. This study has a research physician as an independent monitor who will monitor adverse events and data safety and conduct annual review of study progress. This study will have a data monitoring team, consisting of the principal investigator, a biostatistician, and a data coordinator, who will review data quality monthly. Any serious adverse events or major protocol deviations will be reported to CHA IRB within 72 h. Protocol modifications will be submitted as amendments to the CHA IRB. Personal information including Protected Health Information (PHI) will be stored in CHA's secure online platform of HIPAA-compliant Google G-Suite

Drive separately from research data. Alphanumeric codes will be generated as subject IDs and acrostics to protect subject confidentiality. Statistical analysis will be conducted on coded and/or deidentified data that do not contain PHI. Research data from this study is only accessible to approved CHA and Spaulding Hospital staff members as registered on the IRB. Research outcomes will be published in a peer-reviewed journal. Publications will only include congregated group results without any identifiable personal information. After publication of research results, de-identified data will be made available on the Harvard Dataverse or equivalent public-access data platform.

Intervention Program

The HST-IIP intervention will be taught by a lead teacher and an assistant teacher, supported by a coordinator. Originated from the Korean Seon Buddhist tradition,[16] HST-IIP is well-aligned with Mahayana Buddhism's core principles through emphasizing compassion and wisdom. The foundational philosophy and conceptual framework of HST are based on the Happiness-Mind Matrix model. This model integrates core virtues such as wisdom, gratitude, and focused attention with compassion, loving-kindness, and empathy. In this model, a focus on specific mental and interoceptive states accompany each meditation practice. For example, compassion is associated with a 'warm and gentle' state, wisdom with 'pure and serene,' flow with 'easy and calm,' and gratitude with 'happy and flourishing.' As practitioners embody the compassionate state of 'warm and gentle' through HST practices, they are guided to progressively integrate the other 3 states described in the Happiness-Mind Matrix. This structured approach allows for the holistic and iterative development of an individual's mental and emotional well-being, ultimately approaching a harmonious and flourishing life.

HST-IIP consists of one core practice, *Authentic Presence*, and multiple supplementary practices (Table 1). Authentic practice aims to provide individuals with the fundamental skills for expressing the compassion and loving-kindness that are inherently present within the body and mind. A defining feature of this practice is the action of genuinely smiling at oneself, with a focus on the heart area. To support and accelerate the cultivation of compassionate feelings through authentic practice, additional techniques are integrated, and the practitioner is supported to iteratively deepen the 4 states of the Happiness-Mind Matrix. These supplementary practices include fascia body scan, sound meditation, gratitude, and acceptance meditation, as well as gentle movement and walking meditations. Each of these practices is designed to warmly and gently enhance and nurture body awareness, thereby fostering a deeper sense of loving-kindness and compassion within the practitioner. This comprehensive approach aims to guide participants towards a harmonious integration of mind and body through facilitating a profound and lasting sense of heartfelt presence and well-being.

The HST-IIP program was developed based on the original 3-day retreat format in Korea[18] and adapted to integrate features of Mindfulness-Based Interventions (MBIs). The HST-IIP curriculum (Table 2) comprises a 3-day intensive retreat, followed by 4 weekly group meetings, and concludes with a 1-day retreat (for a total of 42 h of teaching). Each weekly session lasts 2.5 h. These meetings are designed to emphasize experiential practice and inquiry-based learning, with the aim of fostering deep insight.

Table 2 outlines the overall HST-IIP intervention procedure timeline and theme progression. The 3-day retreat (8 h per day) helps participants start their journey of getting to know and expressing authentic presence. Participants engage in the core and supplementary practices that provide basic skills for expressing compassion and loving-kindness. These practices cultivate awareness of 5 senses through fully embracing present moment interoceptive and exteroceptive experience. There is also time for self-reflection, sharing with other participants and the course instructor, and self-care in each session. The retreat is followed by the first regular weekly meeting (2.5 h), which teaches the core practice of HST-IIP and the Happiness-Mind Matrix Contemplation and focuses on the Happiness-Mind Matrix concept of gratitude to train the participants to gain full awareness with a clear mind, to embody authentic presence with gratitude, and to apply gentle attention to the present moment.

The second week focuses on the concept of flow in the Happiness-Mind Matrix, where participants engage in more practice of sensory awareness, relaxation and concentration while deepening the practice of authentic presence. Week 2 highlights the role of relaxation in achieving immersion in the present moment, through allowing thoughts to naturally flow while maintaining mindful body awareness. Week 2 introduces a tool for tracking and reflecting on interoceptive and exteroceptive experience and how they influence behavioral avoidance and valued action. Ultimately, the practice aims to guide participants to recognize when a sense of peace and happiness is present.

The third week focuses on the *compassion* concept of the Happiness-Mind Matrix. During this week, participants are supported to gain a clearer understanding of compassion and how it can be applied to real life. Through learning and practicing compassion, participants learn how to emotionally build empathy and affection towards suffering and failures. Week 3 also emphasizes the importance of compassion in fostering acceptance, inner peace and feelings of love and empathy.

The third week finishes with a 1-day retreat to integrate all knowledge learned in the past weeks and find connections.

Table 1. Core Practice and Supplementary Practices of the HST-IIP Intervention Program.

Core Practice	
Authentic presence	Authentic presence is the core practice of HST. This practice aims to provide the individual with basic skills for expressing compassion and loving-kindness, which are already present in the body and mind. This practice's main characteristic is the action of genuinely smiling at oneself, focusing on interoceptive sensation in the heart area.
Supplementary practices	
5 senses/tea meditation	This is a meditation that focuses on achieving full immersion of the self into the present moment, promoting groundedness, and cultivating awareness through engaging each of the 5 senses and fully embracing the sensory sensations of the here and now (eg, five senses tea meditation combines the 5 senses to cultivate mindfulness and establish a deeper connection to the present moment while enjoying tea or another beverage).
Internal body scan meditation	This is an interoceptive meditation technique that allows us to direct and shift our attention throughout different parts of the body and become aware of the ongoing sensations of tension and relaxation in that part. It is a technique that brings warmth and gentleness to the body and internal organs, which may eventually alleviate bodily tension.
Gratitude and love movement	This is a meditation that embodies feelings of gratitude and love, relaxation, and emptiness through gestures of accepting (thanks), sharing (love), and letting go (ease).
Gratitude-acceptance	Accept and appreciate the present state without rejecting or judging.
Fascia body scan	This is an interoceptive meditation technique, bringing awareness to the fascia, the tissue surrounding the body parts, while lying down or sitting. It is a form of relaxation meditation that promotes calmness and awareness of physical body sensations and allows for warm and gentle feelings of love and compassion to permeate the entire body.
Gratitude and love walking meditation	This is a mindful movement meditation that integrates the emotions of gratitude and love into mindful walking, allowing us to achieve higher consciousness and promote connection with ourselves, others, and our surroundings. This involves intentionally walking at a comfortable pace, focusing attention on the 5 senses of the present moment while embodying positive and uplifting emotions.
Happiness-mind matrix contemplation	This practice begins with being truly present in the current moment and fosters full awareness with a clear mind and gentle attention to the here and now. Through training, authentic presence can bring gentle warmth and comfort to the self and even reveal other virtues within the self. This practice employs a simple compassion meditation technique that can lead to happiness, calm, and contentment.
Interoceptive sound meditation	This is a meditation that awakens and encourages awareness of sensations, including any warm and kind feelings in the heart through the resonance of sound. This is mainly performed in connection with other meditations.
Journaling	Structured journal exercise supporting reflection on meaningful actions, experiential avoidance, and 5 senses awareness.
Others	Tongue stretching and eye massage to stimulate cranial nerves.

The objective of this week is to help participants understand the role of authentic presence in building compassion, which paves the path to achieving wisdom and a growth mindset.

In the last week, participants conclude with reviewing the program, and training in interconnecting gratitude and compassion to support wisdom and freedom from suffering. Through practicing all the meditations taught in the program, participants cultivate compassion and authentic presence, which may eventually enable them to develop the wisdom to lead a harmonious life.

Data Collection and Signal Processing

EEG data will be collected using a Geodesic EEG System (GES) 400 with Geodesic Sensor Nets (64 channels), and ECG, GSR, and respiration signals will be collected simultaneously using the same amplifier connected to different modules (AD Instruments, PowerLab, 8 channels), through a relay box that splits the trigger input equally into both GES and AD Instruments amplifiers. Because both the physiological data and EEG data amplifiers share the same trigger channel, all the acquired time series are synchronized, which ensures precise alignment of EEG and ECG data for accurate HEP analysis. A custom-made respiration belt will be placed around the chest to detect respiration patterns via air pressure transducer.[49] Both brain and autonomic physiological data will be acquired at rest (4 min with eyes open and 4 min with eyes closed) and during compassion meditation (15 min) instructed by pre-recorded audio provided by an HST-IIP instructor. All physiological data will be real-time monitored by experienced EEG technicians for data quality. Post-hoc data quality rating will be independently conducted by 2 EEG experts to decide whether some data need to be excluded from statistical analysis due to data quality issues.

EEG signals will be acquired with a sampling rate of 1000 Hz with a reference electrode placed at location Cz. The impedance of each electrode will be kept below 10 kΩ. After

Table 2. Overall HST-IIP Intervention Program Procedure Timeline and Theme Progression.

Session	Topic	Hours
Three-day intensive training at the beginning of week 1: day 1	Five senses tea meditation Why are you here – group go around introduction to happiness mind Matrix Deep fascia body scan Gratitude and love movement Mindful eating Introduction to *interoceptive sound meditation* and *authentic presence* Q&A and group sharing	8
Three-day intensive training at the beginning of week 1: day 2	Five senses tea meditation Gratitude and love movement Deep fascia body scan Interoceptive sound meditation and authentic presence Mindful eating Gratitude and love walking meditation Q&A and group sharing	8
Three-day intensive training at the beginning of week 1: day 3	Five senses tea meditation Gratitude and love movement Gratitude and acceptance meditation Deep fascia body scan Interoceptive sound meditation and authentic presence Mindful eating Empathy sharing Happiness mind matrix contemplation Applying HST in daily LIFE Q&A and group sharing	8
Regular weekly session of week 1	**Theme: gratitude** Group sharing Gratitude and love movement Didactic–happiness mind matrix Deep internal organ body scan Interoceptive sound meditation and authentic presence Journaling	2.5
Regular weekly session of week 2	**Theme: calm and ease** Gratitude and love movement Journaling group sharing Didactic: flow and relaxation Deep internal organ body scan Interoceptive sound meditation and authentic presence Q&A and group sharing	2.5
Regular weekly session of week 3	**Theme: loving-kindness and compassion** Gratitude and love movement Journaling group sharing Didactic– compassion, acceptance and Lovingkindness Deep internal organ body scan Interoceptive sound meditation and authentic presence Q&A and group sharing	2.5
Whole day retreat in week 3	Five senses tea meditation Gratitude and love movement Deep fascia body scan Interoceptive sound meditation and authentic presence Mindful eating Gratitude and love walking Gratitude and acceptance meditation Q&A and group sharing	8

(continued)

Table 2. (continued)

Session	Topic	Hours
Regular weekly session of week 4	**Theme: pure and serene** Gratitude and love movement Journaling group sharing Didactic–wisdom: cognitive defusion + contextual self + value seeking Deep internal organ body scan Interoceptive sound meditation and authentic presence Q&A and group sharing, closing	2.5
	Total hours	42

standard offline preprocessing, including downsampling, band-pass filtering (1-100 Hz), and ocular artifact removal by Independent Component Analysis (ICA),[50,51] EEG signal analysis will calculate HEP and Power Spectral Density (PSD) within standard EEG frequency bands. HEPs reflect the cortical processing of cardiac signals identified by changes in the amplitude (voltage) of the EEG time series time-locked to the ECG R-wave peaks.[30,31] For HEP analysis, the EEG time series will be downsampled from 1000 Hz to 400 Hz to match the sampling rate of the ECG data. For other EEG analyses, the EEG time series will be downsampled to 250 Hz to reduce data size and computational load while maintaining signal integrity, which is still sufficient to capture the relevant frequency components of the EEG signal according to the Nyquist theorem.[52] For offline R-wave peak detection, the open-source R-Deco software will be used.[53] Pre-processed EEG signals will then be segmented into windows around the R-wave peak (−200 to 800 ms). Finally, baseline correction will be performed using the pre-stimulus interval, and HEP values will be calculated following the averaging of these segmented time series across trials.[54] The standard EEG frequency bands (ie, Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-30 Hz), Gamma (30-100 Hz)) will be defined at single-subject level considering the Individual Alpha Frequency (IAF) estimated during the eyes-closed condition.[55] PSD will be computed using the Welch's method, which divides the signal into overlapping segments and applies the Fourier transform to each segment, thereby effectively break down the signal into its constituent frequency components, enabling a detailed analysis of the signal's spectral content.[56] After defining the range of frequencies for each band, PSD values will be averaged within each of them for further statistical analyses.

Instantaneous HRV estimates will be extracted from the ECG time series employing a point-process algorithm.[49,57] To evaluate the autonomic response to the intervention we will then extract specific time-varying parameters.[49,57] To account for the potential influence of breathing variations on HF-HRV, breathing rates will be used as a covariate for statistical analyses. HRV analyses will use a point-process method to estimate instantaneous HRV metrics, following the analysis protocols in our prior studies.[57,58] We will identify R-wave peaks through an automated, in-house peak detection algorithm, followed by expert manual verification to ensure data quality. Only artifact-free segments will be retained for further analysis. Following data cleaning and annotation, we will employ a point-process model to analyze the R-to-R interval (RRI) series and extract HRV-related measurements such as high frequency (HF) and low frequency (LF) powers.[57] Each RRI will be modeled using an inverse Gaussian probability function, characterizing the time interval before each successive heartbeat. The mean of this probability function will be determined using an autoregressive linear model of order k, capturing the dependence of each RRI on the last k beat-to-beat intervals. As a result of the time-varying point-process approach, we will obtain instantaneous spectral measures of HRV in canonical frequency bands, calculated continuously across the entire signal. For HF-HRV (0.15-0.40 Hz), which reflects parasympathetic (cardiovagal) modulation,[49,57] power values will be averaged over specific epochs of interest to assess changes relative to baseline. Given ongoing discussions in the literature regarding the interpretation of LF-HRV (0.04-0.15 Hz) as a marker of sympathetic activity,[59] we will consider it within the broader context of autonomic modulation, acknowledging both sympathetic and parasympathetic influences.

A GSR amplifier with low voltage, 75 Hz AC excitation and automatic zeroing, synchronized with milliseconds precision with brain and cardiac time series, will be employed to assess skin conductance changes over time. GSR data will first be preprocessed to remove artifacts and then segmented by the different phases of the experiment (ie, meditation task and resting state). Key features, such as Skin Conductance Level (SCL) and Skin Conductance Responses (SCR), will be extracted for further statistical analyses.

Outcome Measures

Primary Outcome Measures. The primary clinical outcome measure is the feasibility of the intervention and physiological assessments as measured by rates of participant completion and dropout, frequencies of study-related adverse events, and rate of subjects completing research procedures.

The primary neurophysiological outcome measure is the change in EEG HEP amplitude at post-intervention compared to pre-intervention (Post vs Pre). Our primary hypothesis is

that the HST-IIP group, compared to the waitlist group, will show a larger post-intervention increase in HEP amplitude during compassion meditation. HEP is emerging as a valuable heartbeat-linked electroencephalogram (EEG) measure to understand the altered body awareness associated with depression. HEP is a brain response to each heartbeat, which reflects cardiac signaling to the central autonomic nervous system; therefore, it is considered to be a biomarker of interoception.[60] Previous literature has established HEP as an effective neural measure of interoception in heartbeat detection tasks.[31,61,62] Compared to healthy controls, depressed patients have demonstrated less accurate detection of their own heartbeat (interoception accuracy).[21] This behavioral difference is also reflected in the analysis of HEPs, where depressed patients exhibit a significantly lower amplitude compared to healthy controls.[54] This reduced amplitude is indicative of diminished afferent signaling from the heart to the brain, possibly related to reduced interoceptive awareness of the heartbeat among individuals with depression. It is still unknown how a treatment designed to address symptoms of depression might influence HEP. A recent randomized clinical trial demonstrated interoceptive neural functions indexed by heartbeat evoked theta power enhanced by mindfulness training was a primary neural mechanism underlying PTSD symptom improvement.[63] Given these considerations, HEP is the primary neurophysiological outcome measure to investigate the effect of HST-IIP on interoceptive function. Though HEP has not been studied extensively in relation to contemplative interventions, HST-IIP is uniquely suited for this particular EEG neurocardiac measure. HST-IIP has a unique focus on cultivating interoceptive awareness in and around the region of the heart. Many of the HST-IIP practices are focused on the awareness of warmth from the heart or of the sensations from the heartbeat. Because awareness of the heart-mind connection is intrinsic to HST-IIP, HEP is an ideal EEG measure for determining the neural mechanisms and outcomes of HST-IIP, especially among depressed patients due to their diminished HEP signals.[23,54] By randomizing depressed patients to either HST-IIP or waitlist control, this pilot study will investigate HEP changes among depressed patients after HST. We also hypothesize that change in HEP will be associated with reduction in depression symptoms.

Secondary Outcome Measures. We will use CAT-DI as the main clinical outcome measure. Our hypothesis is that the HST-IIP group, compared to the waitlist control group, will show a larger post-intervention change (reduction) in CAT-DI scores.

Gamma oscillations in the EEG signal have been demonstrated to be a biomarker for major depression.[64] The gamma band of EEG signal (30-100 Hz) is also frequently reported as an indicator for compassion associated with meditation practices. For example, Tibetan Buddhist monks were found to self-induce sustained high-amplitude gamma-band oscillations and phase-synchrony during meditation.[65] A recent study showed elevated gamma power across different meditation traditions, supporting the use of EEG gamma power as a biomarker for meditation expertise.[66] Evidence from a neurophenomenological study indicates that, in advanced meditators (but not in untrained novices), gamma power in the posterior cingulate cortex is related to the subjective experience of effortless awareness in meditation.[67] The default mode network (DMN) is a key hub for self-regulation and self-awareness, and several midline DMN regions have been shown to be associated with self-criticism.[68] One study demonstrated elevated gamma power in the DMN as a result of meditation training.[69] Therefore, we will investigate the effect of HST-IIP on the gamma band of EEG signal as a secondary outcome measure.

EEG Gamma power is another secondary outcome measure. Based on prior literature on the influence of meditation on Gamma signal,[66] we hypothesize that the HST-IIP group, compared to the waitlist control group, will show a larger post-intervention increase in Gamma power during compassion meditation.

HRV will be used as another secondary outcome measure, because prior compassion meditation training studies have found increased HF-HRV was associated with clinical outcomes.[70-73]

Exploratory Outcome Measures. A group climate questionnaire and participant satisfaction surveys and follow-up interviews will also be administered to obtain quantitative and qualitative assessments of participant experience in the HST-IIP intervention groups. Prior research observed EEG prefrontal alpha-asymmetry to increase with more left prefrontal activity among previously depressed patients during guided LKM meditation, reflecting stronger analytical tendencies.[74] Therefore, we will also evaluate the effect of HST-IIP on alpha asymmetry as an additional exploratory outcome measure. Additional neurophysiological and psychological assessments will be analyzed as exploratory outcome measures, including PSDs of other EEG frequency bands (ie, Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), Beta (13-30 Hz)), skin conductance, as well as additional psychological measures including CAT-ANX, DASS-21, FFMQ, DERS, SCS, SocCon, MAIA-2, QOLS, GRAT, PSQI, and PIL.

Power Analysis and Sample Size Estimation

There has not been a prior study on the neurocardiac effect of HST. According to approximation recommendation for pilot studies, a sample size of 15-20 per arm is needed for the pilot study to be utilized to establish the power for a main trial designed to detect small to medium effect sizes with 90% power and two-sided 5% significance,[75] therefore we aim for a sample size of N = 21 for the HST-IIP arm and N = 14 for the waitlist group because we plan to randomize at 3:2 ratio.

A recent study on the effects of an 8-week MBI on neurocardiac interplay reported medium to large effect sizes (Cohen's d ~ .68-1.43),[76] based on which we have conducted exploratory power analysis and sample size estimation using GPower 3.1.9.7 as below. Assuming an effect size of Cohen's d = 1, at alpha level of .05, our planned sample size of 21 vs 14 will reach 80% power. If the effect size is as large as in the recent study with a Cohen's d = 1.43, at alpha level of .05, we will only need a total of 20 subjects (N = 12 for HST-IIP and N = 8 for waitlist) to reach 80% power.

To obtain a final sample size of 36, we expect we will need to enroll up to N = 50 subjects, with 10% anticipated attrition prior to the start of intervention, at which time N = 45 will be randomized in blocks of 5 in a ratio of 3:2 for HST-IIP and waitlist respectively, resulting in N = 27 in the HST-IIP group and N = 18 in the waiting list group. A dropout rate of 20% is anticipated during the course of intervention and possible lost-to-follow-up for post-intervention assessments, resulting in a total of 36 completers with 22 in the HST-IIP group and 14 in the control group.

Statistical Analyses Plans

No interim analysis is planned for this study. Primary and secondary outcomes will be analyzed using linear mixed effects model analyses with outcome measures as the dependent variables and predictors including time (pre- vs post-intervention) and group (HST-IIP vs waitlist). False Discovery Rate (FDR) procedure will be used to account for multiple comparison corrections.[77] All statistical analyses will be conducted with statistical software R.

For the primary feasibility outcome measures, the rates of subject dropout, intervention completion, adverse events, and research procedure completion will be calculated and compared between the HST group and the waitlist group. Dropout rates will be calculated as the proportion of subjects that have completed baseline assessments and are randomized to a group, but fail to provide post-intervention or post-waiting period assessments. Intervention completion rates will be calculated as the number of attended intervention hours with respect to the total number of intervention hours, and conclusion on intervention feasibility will be drawn if at least 70% subjects completed at least 70% of the intervention hours. Research procedure feasibility will be measured by proportion of subjects able to yield complete longitudinal research data from both pre- and post- intervention or waiting periods, and feasibility conclusion will be drawn if at least 70% patients assigned to a study group (HST vs waitlist) complete both pre- and post-intervention or waiting periods research data collection. To evaluate the acceptability and tolerability aspect of study feasibility, adverse events and serious adverse events will be monitored and we expect no serious adverse events related to study protocol in either group.

For the primary physiological outcome measure on EEG HEP amplitude during compassion meditation, first, linear mixed effects model analysis will be conducted with the "lme4" function of R[78] to test for effects of time, group and group by time interaction; then post- vs pre-intervention differences of HEP amplitude (ΔHEP) will be calculated for each subject, which will be used for group comparison with independent samples *t* test, to test the hypothesis that the HST-IIP group will have a larger increase in HEP amplitude compared to controls.

For the secondary clinical outcome measure CAT-DI, first linear mixed effects model analysis will be conducted with the "lme4" function of R[78] to test for effects of time, group and group by time interaction; then post- vs pre-intervention score difference (ΔCAT-DI) will be calculated for each subject, which will be used for group comparison with independent samples *t* test, to test the hypothesis that the HST-IIP group will have a larger score reduction.

For the secondary physiological outcome measure EEG Gamma power during compassion meditation, first Linear Mixed Effects model analysis will be conducted with the "lme4" function of R[78] to test for effects of time, group and group by time interaction; then post vs pre-intervention difference of Gamma power (ΔGamma) will be calculated for each subject, which will be used for group comparison with independent samples *t* test, to test the hypothesis that the HST-IIP group will have a larger post-intervention increase with ΔGamma.

Similar linear mixed effects model analyses and two-sample t-tests will also be conducted for all exploratory outcome measures. For example, Linear Mixed Effects model analysis will be conducted for the SCL and SCR feature of GSR data to test for effects of time, group, and group by time interaction, then post vs pre-intervention difference of SCL and SCR (ΔSCL, ΔSCR) will be calculated for each subject, which will be used for group comparison with independent samples *t* test.

In order to plan future studies, we will also conduct preliminary analyses to assess the effect size of the HST-IIP training on clinical improvement of patients with mild to moderately severe depression, as well as on the EEG characteristics across all frequency bands. To evaluate clinical survey outcomes, we will conduct a difference-in-differences, intent-to-treat, repeated measures analysis using linear mixed-effects models (mixed) to evaluate the factors time (pre- vs post-intervention), group (HST-IIP vs waitlist group) and the interaction of factors time × group. Mixed-effect models account for the clustering of multiple observations within participants. We will compute contrasts of predictive margins to test for significant within-group changes and difference-in-differences (between-group) estimates over time. Between-group and within-group effect size (Cohen's d) will be computed based on the predictive margins generated from the mixed models. Protocol non-adherence, such as dropouts or missing

intervention sessions, will be accounted for with the intent-to-treat analysis. Missing data will be handled based on the specific scenario of missingness that can involve excluding certain subjects from analysis (eg, missing all post-intervention assessments) or using multiple imputation (eg, missing an item on a questionnaire).

Results

Patient recruitment started in January 2023, and the study is still ongoing. Data analysis is expected to yield results for publication by the end of 2025.

Discussion

This is the first study to test the feasibility of the HST-IIP intervention program for patients with depression in the United States, as an important step in the development of this intervention which is currently at stage 1B of the NIH stage model.[20] It is also the first study on the interoceptive neurocardiac mechanism of HST, which will provide critical mechanistic insights for further development and validation of this intervention. Mechanistic discovery from this trial will also inform mechanistic investigation of other compassion-based interventions and the role of interoception in depression treatment.

This pilot study uses a Randomized Controlled Trial (RCT) design to compare HST with waitlist control, which is a proper first step in establishing the feasibility of this intervention. Recent meta-analyses[79,80] have demonstrated that research on MBIs over the past decades have shown MBIs only have superior clinical effects compared to passive controls such as waitlist, but without consistent advantage compared to active controls. While this is still an active area of research with regard to why MBIs do not always have advantage over active controls, future studies on HST will be thoughtful of this knowledge when designing an active control condition for HST. While there have been some case studies on HST,[81] there has not been a rigorous RCT to study its feasibility and mechanism, and this pilot study is an important step towards rigorous investigation of HST.

This pilot study focuses on depressed US adults as the target population out of several considerations: (1) Depressed patients have been known to have compromised interoceptive abilities[21,22] such as appetite changes[27] and alexithymia[28,29] with well-documented neural[25] and physiological representations,[24] therefore is an ideal condition for studying the feasibility of HST as an interoception based intervention, as well as for studying its neurophysiological mechanisms. (2) Because the HST intervention was originally developed in Korea, it is an important step to test its feasibility in an US based patient population to shed light on its cultural and linguistic adaptability as part of the feasibility research.

The choices of outcome measures on feasibility and neurophysiological mechanisms were made based on the design and objectives of the study. Feasibility will be measured by rates of participant completion and dropout, as well as frequencies of study-related adverse events; the feasibility for study completion also includes the component of completing the EEG data collection, which is informative for the future design and conduct of a full-scale clinical trial. The HEP measure from EEG was used as the primary mechanistic outcome measure based on prior research on HEP being a biomarker of interoception[60] and depressed patients demonstrating lower amplitudes of HEP compared to healthy controls,[21] therefore it is a proper measure for the mechanism of HST on improving interoceptive function. Additional metrics will also be analyzed from the EEG data as exploratory measures to understand other aspects of potential neurophysiological changes induced by the HST intervention.

There are several potential mechanisms for the HST intervention to influence HEP: First, meditation practices in HST include focused attention on the body's internal organs and especially around the heart area, and such focused interoceptive attention has been shown modulate HEP.[82] There are also other potential mechanisms for HST to influence HEP. For instance, the vocal sound during exhalation in HST practices creates internally propagating vibrations, which could potentially influence and refine interoceptive attention ability over time, eventually impacting HEP. Studies on vibroacoustic therapy[83] and whole body vibration[84] have shown that low-frequency vibrations can affect hemodynamic, neurological, and musculoskeletal responses in the human body,[85] which over time may contribute to improved interoceptive sensitivity. Alternatively, vagal nerve stimulation has been shown to modulate HEP,[86] therefore, mindfulness meditation, such as the inner silence following sound meditation in HST, can potentially increase vagal nerve activity and reduce sympathetic nervous system activity and physiological stress,[86] thereby modulating HEP.

A major limitation of the study design is the use of a waitlist control. The randomized controlled design with a waitlist control will allow us to control for the effects of time and regression to the mean, but it does not control for other nonspecific factors such as the effect of being part of a group, expectancy effects from belief in an intervention, time involved with the intervention, and positive influence of interacting with a compassionate instructor. Such limitations can be addressed in future studies by comparing HST to an active control group.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this

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Trial Registration

Trial registration https://clinicaltrials.gov/study/NCT05564533.

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References

1. Hofmann SG, Grossman P, Hinton DE. Loving-kindness and compassion meditation: potential for psychological interventions. *Clin Psychol Rev*. 2011;31(7):1126-1132.
2. Kirby JN, Tellegen CL, Steindl SR. A meta-analysis of compassion-based interventions: current state of knowledge and future directions. *Behav Ther*. 2017;48(6):778-792.
3. Jazaieri H, Jinpa GT, McGonigal K, et al. Enhancing compassion: a randomized controlled trial of a compassion cultivation training program. *J Happiness Stud*. 2013;14: 1113-1126.
4. Hutcherson CA, Seppala EM, Gross JJ. Loving-kindness meditation increases social connectedness. *Emotion*. 2008; 8(5):720-724.
5. Pace TW, Negi LT, Sivilli TI, et al. Innate immune, neuroendocrine and behavioral responses to psychosocial stress do not predict subsequent compassion meditation practice time. *Psychoneuroendocrinology*. 2010;35(2):310-315.
6. Pace TW, Negi LT, Dodson-Lavelle B, et al. Engagement with cognitively-based compassion training is associated with reduced salivary c-reactive protein from before to after training in foster care program adolescents. *Psychoneuroendocrinology*. 2013;38(2):294-299.
7. Klimecki OM, Leiberg S, Lamm C, Singer T. Functional neural plasticity and associated changes in positive affect after compassion training. *Cerebr Cortex*. 2013;23(7):1552-1561.
8. Mascaro JS, Rilling JK, Tenzin Negi L, Raison CL. Compassion meditation enhances empathic accuracy and related neural activity. *Soc Cognit Affect Neurosci*. 2013;8(1):48-55.
9. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol Sci Pract*. 2003;10(2): 144-156.
10. Zhang D, Lee EK, Mak EC, Ho CY, Wong SY. Mindfulness-based interventions: an overall review. *Br Med Bull*. 2021; 138(1):41-57.
11. Neff KD, Germer CK. A pilot study and randomized controlled trial of the mindful self-compassion program. *J Clin Psychol*. 2013;69(1):28-44.
12. Goldin PR, Jazaieri H. The compassion cultivation training (cct) program. *The Oxford handbook of compassion science*. 2017;1:237-246.
13. Ash M, Harrison T, Pinto M, DiClemente R, Negi LT. A model for cognitively-based compassion training: theoretical underpinnings and proposed mechanisms. *Soc Theor Health*. 2021; 19:43-67.
14. Rockliff H, Karl A, McEwan K, Gilbert J, Matos M, Gilbert P. Effects of intranasal oxytocin on'compassion focused imagery. *Emotion*. 2011;11(6):1388-1396.
15. Koleilat L. *Medicalizing Sŏn Meditation in Korea: An Interview with Venerable Misan Sŭnim. Buddhism and Medicine: An Anthology of Modern and Contemporary Sources*. New York, NY: Columbia University Press; 2019:215-220.
16. Kim Y. The spectrum of studies on the history of joseon buddhism and a new understanding of the Korean buddhist tradition. *The Review of Korean Studies*. 2022;25(1):71-106.
17. Kim WD, Kim JS, Cha SY, Lee JK, Park SH. *Compassion: a Seed or Fruit of Enlightenment*. Seoul, South Korea: Unjusa; 2015.
18. Kim E, Seo C, Gawande R, Giachos D, Kiley B, Schuman-Olivier Z, et al., eds. Development of compassion based intervention according to the NIH stage model: a case of heart-smile training. Contemplative Research Conference; November 5-8, 2020; Virtual.
19. Kim E, Schuman-Olivier Z, Kim B, Thein W, Kim MWD, eds. *Heart-centered, Interoceptive, Compassion-Based Intervention: Past, Present, and Future*. San Diego, CA: International Society for Contemplative Science; 2023.
20. Onken LS, Carroll KM, Shoham V, Cuthbert BN, Riddle M. Reenvisioning clinical science: unifying the discipline to improve the public health. *Clin Psychol Sci*. 2014;2(1):22-34.
21. Eggart M, Lange A, Binser MJ, Queri S, Müller-Oerlinghausen B. Major depressive disorder is associated with impaired interoceptive accuracy: a systematic review. *Brain Sci*. 2019;9(6): 131.
22. Harshaw C. Interoceptive dysfunction: toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychol Bull*. 2015;141(2):311-363.
23. Dunne J, Flores M, Gawande R, Schuman-Olivier Z. Losing trust in body sensations: interoceptive awareness and depression symptom severity among primary care patients. *J Affect Disord*. 2021;282:1210-1219.
24. Nummenmaa L, Glerean E, Hari R, Hietanen JK. Bodily maps of emotions. *Proc Natl Acad Sci U S A*. 2014;111(2):646-651.
25. Avery JA, Drevets WC, Moseman SE, Bodurka J, Barcalow JC, Simmons WK. Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biol Psychiatr*. 2014;76(3):258-266.
26. Wiebking C, de Greck M, Duncan NW, Tempelmann C, Bajbouj M, Northoff G. Interoception in insula subregions as a possible state marker for depression-an exploratory fmri study

investigating healthy, depressed and remitted participants. *Front Behav Neurosci*. 2015;9:82.
27. Simmons WK, Burrows K, Avery JA, et al. Depression-related increases and decreases in appetite: dissociable patterns of aberrant activity in reward and interoceptive neurocircuitry. *Am J Psychiatr*. 2016;173(4):418-428.
28. Scarpazza C, Zangrossi A, Huang Y-C, Sartori G, Massaro S. Disentangling interoceptive abilities in alexithymia. *Psychol Res*. 2022;86(3):844-857.
29. Gaggero G, Dellantonio S, Pastore L, Sng KH, Esposito G. Shared and unique interoceptive deficits in high alexithymia and neuroticism. *PLoS One*. 2022;17(8):e0273922.
30. Jones PT, Dear PH, Foote J, Neuberger MS, Winter G. Replacing the complementarity-determining regions in a human antibody with those from a mouse. *Nature*. 1986;321(6069):522-525.
31. Schandry R, Sparrer B, Weitkunat R. From the heart to the brain: a study of heartbeat contingent scalp potentials. *Int J Neurosci*. 1986;30(4):261-275.
32. Beiser D, Vu M, Gibbons R. Test-retest reliability of a computerized adaptive depression screener. *Psychiatr Serv*. 2016; 67(9):1039-1041.
33. Gibbons RD, Weiss DJ, Pilkonis PA, et al. Development of the cat-anx: a computerized adaptive test for anxiety. *Am J Psychiatr*. 2014;171(2):187-194.
34. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (dass) with the beck depression and anxiety inventories. *Behav Res Ther*. 1995;33(3):335-343.
35. Baer R, Smith G, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment*. 2006;13(1):27-45.
36. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. *J Psychopathol Behav Assess*. 2004;26:41-54.
37. Neff KD. The development and validation of a scale to measure self-compassion. *Self Ident*. 2003;2(3):223-250.
38. Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The multidimensional assessment of interoceptive awareness (maia). *PLoS One*. 2012;7(11):e48230.
39. Burckhardt CS, Anderson KL. The quality of life scale (qols): reliability, validity, and utilization. *Health Qual Life Outcome*. 2003;1(1):60-67.
40. Diessner R, Lewis G. Further validation of the gratitude, resentment, and appreciation test (grat). *J Soc Psychol*. 2007; 147(4):445-447.
41. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatr Res*. 1989;28(2): 193-213.
42. Lee RM, Robbins SB. Measuring belongingness: the social connectedness and the social assurance scales. *J Counsel Psychol*. 1995;42(2):232-241.
43. Crumbaugh JC. Cross-validation of purpose-in-life test based on Frankl's concepts. *J Indiv Psychol*. 1968;24(1):74-81.
44. Rosansky JA, Okst K, Tepper MC, et al. Participants' engagement with and results from a web-based integrative population mental wellness program (chamindwell) during the covid-19 pandemic: program evaluation study. *JMIR Ment Health*. 2023;10(1):e48112.
45. Lim CT, Fulwiler CE, Carson NJ, et al. Promoting population behavioral health in a safety-net health system during the covid-19 pandemic. *Psychiatr Serv*. 2021;72(10):1225-1228.
46. Jabès A, Klencklen G, Ruggeri P, Antonietti J-P, Banta Lavenex P, Lavenex P. Age-related differences in resting-state eeg and allocentric spatial working memory performance. *Front Aging Neurosci*. 2021;13:704362.
47. Achtyes ED, Halstead S, Smart L, et al. Validation of computerized adaptive testing in an outpatient nonacademic setting: the vocations trial. *Psychiatr Serv*. 2015;66(10):1091-1096.
48. Gibbons RD, Weiss DJ, Pilkonis PA, et al. Development of a computerized adaptive test for depression. *Arch Gen Psychiatr*. 2012;69(11):1104-1112.
49. Sclocco R, Garcia RG, Kettner NW, et al. The influence of respiration on brainstem and cardiovagal response to auricular vagus nerve stimulation: a multimodal ultrahigh-field (7t) fmri study. *Brain Stimul*. 2019;12(4):911-921.
50. James CJ, Hesse CW. Independent component analysis for biomedical signals. *Physiol Meas*. 2004;26(1):R15-R39.
51. Wang G, Teng C, Li K, Zhang Z, Yan X. The removal of eog artifacts from eeg signals using independent component analysis and multivariate empirical mode decomposition. *IEEE J Biomed Health Inform*. 2015;20(5):1301-1308.
52. Landau H. Sampling, data transmission, and the nyquist rate. *Proc IEEE*. 1967;55(10):1701-1706.
53. Moeyersons J, Amoni M, Van Huffel S, Willems R, Varon C. R-DECO: an open-source Matlab based graphical user interface for the detection and correction of R-peaks. *PeerJ Comput Sci*. 2019;5:e226.
54. Terhaar J, Viola FC, Bär KJ, Debener S. Heartbeat evoked potentials mirror altered body perception in depressed patients. *Clin Neurophysiol*. 2012;123(10):1950-1957.
55. Klimesch W. Eeg alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Rev*. 1999;29(2-3):169-195.
56. Welch P. The use of fast fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms. *IEEE Trans Audio Electroacoust*. 1967;15(2):70-73.
57. Barbieri R, Matten EC, Alabi AA, Brown EN. A point-process model of human heartbeat intervals: new definitions of heart rate and heart rate variability. *Am J Physiol Heart Circ Physiol*. 2005;288(1):H424-H435.
58. Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain correlates of autonomic modulation: combining heart rate variability with fmri. *Neuroimage*. 2008; 42(1):169-177.
59. Reyes del Paso GA, Langewitz W, Mulder LJ, Van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis

on a reanalysis of previous studies. *Psychophysiology*. 2013; 50(5):477-487.
60. Kumral D, Al E, Cesnaite E, et al. Attenuation of the heartbeat-evoked potential in patients with atrial fibrillation. *JACC Clin Electrophysiol*. 2022;8(10):1219-1230.
61. Pollatos O, Schandry R. Accuracy of heartbeat perception is reflected in the amplitude of the heartbeat-evoked brain potential. *Psychophysiology*. 2004;41(3):476-482.
62. Schandry R, Montoya P. Event-related brain potentials and the processing of cardiac activity. *Biol Psychol*. 1996;42(1-2):75-85.
63. Kang SS, Sponheim SR, Lim KO. Interoception underlies therapeutic effects of mindfulness meditation for posttraumatic stress disorder: a randomized clinical trial. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2022;7(8):793-804.
64. Fitzgerald PJ, Watson BO. Gamma oscillations as a biomarker for major depression: an emerging topic. *Transl Psychiatry*. 2018;8(1):177.
65. Lutz A, Greischar LL, Rawlings NB, Ricard M, Davidson RJ. Long-term meditators self-induce high-amplitude gamma synchrony during mental practice. *Proc Natl Acad Sci U S A*. 2004;101(46):16369-16373.
66. Braboszcz C, Cahn BR, Levy J, Fernandez M, Delorme A. Increased gamma brainwave amplitude compared to control in three different meditation traditions. *PLoS One*. 2017;12(1): e0170647.
67. Van Lutterveld R, Houlihan SD, Pal P, et al. Source-space eeg neurofeedback links subjective experience with brain activity during effortless awareness meditation. *Neuroimage*. 2017;151: 117-127.
68. Lutz J, Berry MP, Napadow V, et al. Neural activations during self-related processing in patients with chronic pain and effects of a brief self-compassion training–a pilot study. *Psychiatry Res Neuroimaging*. 2020;304:111155.
69. Berkovich-Ohana A, Glicksohn J, Goldstein A. Mindfulness-induced changes in gamma band activity–implications for the default mode network, self-reference and attention. *Clin Neurophysiol*. 2012;123(4):700-710.
70. Arch JJ, Brown KW, Dean DJ, Landy LN, Brown KD, Laudenslager ML. Self-compassion training modulates alpha-amylase, heart rate variability, and subjective responses to social evaluative threat in women. *Psychoneuroendocrinology*. 2014;42:49-58.
71. Tian S, Luo X, Che X, Xu G. Self-compassion demonstrating a dual relationship with pain dependent on high-frequency heart rate variability. *Pain Res Manag*. 2020;2020:3126036.
72. Lumma A-L, Kok BE, Singer T. Is meditation always relaxing? Investigating heart rate, heart rate variability, experienced effort and likeability during training of three types of meditation. *Int J Psychophysiol*. 2015;97(1):38-45.
73. Di Bello M, Carnevali L, Petrocchi N, Thayer JF, Gilbert P, Ottaviani C. The compassionate vagus: a meta-analysis on the connection between compassion and heart rate variability. *Neurosci Biobehav Rev*. 2020;116:21-30.
74. Barnhofer T, Chittka T, Nightingale H, Visser C, Crane C. State effects of two forms of meditation on prefrontal eeg asymmetry in previously depressed individuals. *Mindfulness*. 2010;1: 21-27.
75. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res*. 2016;25(3):1057-1073.
76. Gao J, Sun R, Leung HK, et al. Increased neurocardiological interplay after mindfulness meditation: a brain oscillation-based approach. *Front Hum Neurosci*. 2023;17:1008490.
77. Benjamini Y, Cohen R. Weighted false discovery rate controlling procedures for clinical trials. *Biostatistics*. 2017;18(1): 91-104.
78. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J stat softw*. 2015;67:1-48.
79. Goldberg SB, Tucker RP, Greene PA, et al. Mindfulness-based interventions for psychiatric disorders: a systematic review and meta-analysis. *Clin Psychol Rev*. 2018;59:52-60.
80. Goldberg SB, Riordan KM, Sun S, Davidson RJ. The empirical status of mindfulness-based interventions: a systematic review of 44 meta-analyses of randomized controlled trials. *Perspect Psychol Sci*. 2022;17(1):108-130.
81. Kim MWD, Min HJ. The heart-smile training: the compassion-based intervention program of Korean sŏn in the ai digital era. In: H Yi, DY Jin, eds. *Buddhism, Digital Technology and New Media in Korea: Ŭisang's Ocean Seal Diagram*. London, UK: Routledge; 2024:44-57.
82. Petzschner FH, Weber LA, Wellstein KV, Paolini G, Do CT, Stephan KE. Focus of attention modulates the heartbeat evoked potential. *Neuroimage*. 2019;186:595-606.
83. Skille O, Wigram T. The effect of music, vocalisation and vibration on brain and muscle tissue: studies in vibroacoustic therapy. In: *Art & Science of Music Therapy*. London, UK: Routledge; 2013:23-57.
84. Wong A, Figueroa A. Effects of whole-body vibration on heart rate variability: acute responses and training adaptations. *Clin Physiol Funct Imag*. 2019;39(2):115-121.
85. Bartel L, Mosabbir A, eds. *Possible Mechanisms for the Effects of Sound Vibration on Human Health. Healthcare*. Basel, Switzerland: MDPI; 2021.
86. Donelli D, Lazzeroni D, Rizzato M, Antonelli M. Silence and its effects on the autonomic nervous system: a systematic review. *Prog Brain Res*. 2023;280:103-144.