



Augmentation of Positive Valence System Focused Cognitive Behavioral Therapy by Inaudible High-Frequency Sounds for Anhedonia : A Trial Protocol for a Pilot Study

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journal or publication title	JAMA Network Open
volume	2
number	11
page range	e1915819
year	2019-11
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URL	http://hdl.handle.net/2241/00161471

doi: 10.1001/jamanetworkopen.2019.15819





Original Investigation | Psychiatry

Augmentation of Positive Valence System-Focused Cognitive Behavioral Therapy by Inaudible High-Frequency Sounds for Anhedonia

A Trial Protocol for a Pilot Study

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Abstract

IMPORTANCE Recent conceptualizations in Research Domain Criteria have indicated that anhedonia, 1 of 2 core symptoms of depression, which can be treatment resistant, is associated with deficits in the positive valence system, and inaudible high-frequency sound therapy has been shown to enhance reward-related brain circuitry. Hence, cognitive behavioral therapy focusing on the positive valence system enhanced with sound therapy could have a synergistic effect on anhedonia.

OBJECTIVE To test the augmentation effect of inaudible high-frequency sounds on the efficacy of positive valence system-focused cognitive behavioral therapy to treat anhedonia.

DESIGN, SETTING, AND PARTICIPANTS In this individual-level allocation, exploratory, single-center randomized superiority pilot trial, patients, therapists, and evaluators will be masked to intervention or placebo assignment. The trial will take place at a national psychiatric referral hospital in Tokyo, Japan, among 44 adult patients with clinically significant anhedonia and moderate to severe depression. Outcomes will be analyzed following the intent-to-treat principle using a repeated-measures mixed model.

INTERVENTION The intervention group will participate in 8 weekly sessions of positive valence system-focused cognitive behavioral therapy with in-session exposure to an inaudible high-frequency sound; the comparison group will undergo cognitive behavioral therapy with in-session exposure to a placebo sound.

MAIN OUTCOMES AND MEASURES The primary outcome is anhedonia assessed using the self-reported Snaith-Hamilton Pleasure Scale. The secondary outcome is anhedonia assessed using the clinician-administered version of the Snaith-Hamilton Pleasure Scale.

DISCUSSION Recruitment for this study began in May 2018, and the projected date of final allocation is January 2020. A total of 21 eligible patients were registered for participation as of May 30, 2019. To date, treatments for depression do not guarantee clinically successful outcomes. This pilot trial will provide preliminary evidence of the augmentation effect of high-frequency inaudible sounds on cognitive behavioral therapy for anhedonia. Overall, exposure to an inaudible high-frequency sounds does not require attentional or cognitive effort from either patients or therapists; therefore, results from a future confirmative trial could indicate that cognitive behavioral therapy can be augmented in an effortless manner.

(continued)

Key Points

Question Can inaudible high-frequency sounds augment the efficacy of cognitive behavioral therapy for anhedonia?

Findings This trial protocol describes a placebo-controlled, randomized clinical pilot study testing the augmentation effect of inaudible high-frequency sounds on positive valence system-focused cognitive behavioral therapy among patients with clinically significant anhedonia and depression. The sound presentation system is designed to optimize exposure to inaudible high-frequency sounds during face-to-face cognitive behavioral therapy sessions.

Meaning The preliminary results of this pilot study could contribute to the design of confirmatory randomized clinical trials that will examine the augmentation effect of inaudible high-frequency sounds on the treatment of anhedonia.

+ Supplemental content

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Abstract (continued)

TRIAL REGISTRATION [umin.ac.jp/ctr](https://www.umin.ac.jp/ctr) Identifier: [UMIN00031948](https://www.umin.ac.jp/ctr)

JAMA Network Open. 2019;2(11):e1915819. doi:[10.1001/jamanetworkopen.2019.15819](https://doi.org/10.1001/jamanetworkopen.2019.15819)

Introduction

Mental disorders cause devastating effects at both the individual and societal level. Among these disorders, major depressive disorder is the leading cause of the global disease burden.¹ According to treatment guidelines and systematic reviews, cognitive behavioral therapy (CBT) is recommended for patients with depression who experience moderate to severe symptoms.² Nevertheless, the therapies available to treat depression can be improved. A 2010 meta-analysis³ showed that the standardized mean effect size of CBT for depression was low ($d = 0.22$) in a high-quality randomized clinical trial. A 2008 meta-analysis⁴ reported that 50% of patients relapsed after completing CBT, and 50% of those who did respond to treatment relapsed within 2 years. To overcome these situations, translational research bridging neuroscience and CBT has focused on developing novel CBT approaches or techniques that augment traditional CBT.⁵⁻⁷ Among them, we focused on the following 2 noninvasive interventions: (1) positive valence system-focused CBT (PoCot) and (2) inaudible high-frequency sounds. These interventions target the common neurological underpinnings of anhedonia.

Anhedonia, 1 of 2 cardinal depression symptoms, is known to be less responsive to both CBT and pharmacotherapy than other depressive symptoms.^{8,9} Anhedonia is the loss of interest or pleasure associated with deficits in reward-related brain circuitry.¹⁰⁻¹² Dysfunction of this circuitry includes blunted activation of the striatal regions and orbitofrontal cortex as well as blunted mesolimbic dopamine pathways.^{11,13} It has been suggested that major depressive disorder is characterized by an underestimation of reinforcements received, a reduced expectation of future rewards, less frequent endorsement and recall of positive traits in self-referential tasks, a diminished ability to modulate behavior as a function of reinforcement history, a reduced willingness to make efforts to gain rewards, and an inability to couple the hedonic impact of stimuli and reward assumption.¹³ According to Research Domain Criteria,¹⁴ anhedonia reflects disturbances of the positive valence system.^{15,16}

The positive valence system has been largely neglected in traditional psychotherapeutic techniques, including CBT.¹⁷ Findings in the field of neuroscience have led to the development of a CBT approach that directly targets the positive valence system; studies have demonstrated the efficacy of this novel CBT approach.¹⁸⁻²¹ It requires patients with depression to engage in activities that are designed to enhance the subconstructs of positive valence systems (eg, behavioral activation for improving motivation, positive awareness training for improving sensitivity to rewarding stimuli, and savoring training for the loss of pleasure). Craske et al²² reported that this positive affect training was more effective for improving anhedonia (ie, increasing positive affect) and reducing a patient's negative affect and suicidality than more conventional types of CBT (ie, CBT approaches targeting negative affect). Therefore, we believe that the PoCot approach may improve the efficacy of traditional CBT approaches for anhedonia.

The second approach that targets the positive valence system focuses on the hypersonic effect of inaudible high-frequency sounds. Hypersonic effect refers to the whole-body response following exposure to inaudible high-frequency sounds via deep brain activity activation, including reward-related neural circuitry.²³ Using inaudible high-frequency sounds recorded in a tropical rain forest, our research group previously demonstrated this phenomenon using various noninvasive brain function imaging and physiological measures.²³ For example, our positron emission tomography study²³ with healthy control participants demonstrated that inaudible high-frequency sounds, compared with high-cut placebo sounds, increased blood flow in the reward circuit and affected

related circuitry, including monoaminergic projections distributed across the brain stem, thalamus, and prefrontal region.

Inaudible high-frequency sounds have also been shown to produce higher electroencephalographic (EEG) alpha-band (ie, 8-13 Hz) power.²³ In addition, in a 2013 study with healthy controls,²⁴ simultaneous EEG and functional magnetic resonance image acquisitions indicated that the slow fluctuation component of EEG alpha power was positively associated with blood oxygen level-dependent signal changes in the brain stem, medial thalamus, and anterior cingulate cortex, all of which can be considered part of the reward-related neural circuitry. This observation again suggested that the changes in EEG alpha power induced by inaudible high-frequency sounds may correspond to the activation of reward-related circuitry. Moreover, inaudible high-frequency sounds have been reported to promote approach behavior²⁵; this may reflect reward-system activation (eg, better subjective mood or choosing higher levels of sound volume). Overall, inaudible high-frequency sounds have been shown to robustly enhance the subjective experience of sound quality and comfort and to promote approach behavior. Regarding the underlying physiological mechanisms, our previous study²⁶ demonstrated that the hypersonic effect may be induced not through the auditory system but through the body's surface. Although the underlying physiological mechanisms remain unclear, the overall accumulated evidence robustly suggests that inaudible high-frequency sounds enhance the reward system.

We hypothesized that the combination of the PoCot approach and inaudible high-frequency sounds would have a synergistic effect on anhedonia. Although, to our knowledge, no previous direct findings support this idea, PoCot is designed to enhance the brain reward circuitry,^{18,20} while inaudible high-frequency sounds increase blood flow.²³ In addition, reward circuitry activation via inaudible high-frequency sounds leads to a relaxed attentional state.²⁷ Considering that CBT is a learning process²⁸ and positive emotions enhance the learning process,²⁹ it is expected that a positive emotional state induced by inaudible high-frequency sounds will facilitate the learning process in CBT. Furthermore, inaudible high-frequency sounds are expected to enhance learning via EEG alpha-band power activation. The alpha-band frequency range inhibits activity in task-irrelevant brain regions, enabling effective task-irrelevant disengagement for information processing.³⁰ In addition, inhibiting task-irrelevant memories coupled with alpha-band activity is believed to enhance semantic orientation, allowing individuals "to selectively access stored information that represents the meaning of sensory information and 'higher order information,' such as language, mathematics, and geography."^{31(p613)} Hence, we expect that inaudible high-frequency sounds will augment the learning process of CBT via an induced relaxed attentional state and alpha band brain activity.

Methods

Trial Design

This trial was designed with an individual-level allocation with a 1:1 ratio. It is an exploratory, randomized clinical superiority phase II trial. Therapists, patients, and evaluators will be masked to allocation. The trial protocol appears in [Supplement 1](#). This report followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guideline.

Study Setting

This study will be conducted at the National Center of Neurology and Psychiatry (NCNP) Hospital in Tokyo, Japan. Patients who are nonresponsive to primary care in their local clinic or hospital are commonly referred to the NCNP Hospital. A detailed description of the setting appears elsewhere.³²

Eligibility Criteria

The inclusion criteria are as follows: patient (1) has anhedonia symptoms (Snaith-Hamilton Pleasure Scale [SHAPS] score ≥ 20), (2) has mild to severe depressive symptoms (GRID-Hamilton depression

rating scale score ≥ 8),³³ and (3) is aged 18 years or older. The exclusion criteria are as follows: patient has (1) current psychotic disorder, (2) current manic episodes, (3) severe substance use disorder, (4) serious suicidal ideation, (5) severe or unstable physical disorder or major cognitive deficit, and (6) other problems that may present serious obstacles regarding CBT. Exclusion criteria, except for items 5 and 6, will be assessed using the Mini-International Neuropsychiatric Interview version 7.0.2.³⁴

Interventions

Positive Valence System-Focused CBT

Both the intervention and control group will participate in PoCot, which will be conducted in a face-to-face, individualized format. Weekly sessions lasting 50 to 60 minutes will be conducted in a room with sound equipment. This intervention was developed using CBT advances that focus on the positive valence system,¹⁸⁻²¹ positive psychological interventions,³⁵ positive emotion regulation interventions,³⁶ traditional Japanese psychotherapy that emphasizes positive affect and reward,^{37,38} and findings from neuroscience and emotion research mentioned in the introduction.^{29,39} Biological and theoretical background information and details of the intervention are provided in the eAppendix and eTable in [Supplement 2](#).

Early PoCot sessions will include psychoeducation that emphasizes the importance of the positive valence system for anhedonia treatment. The participants will then begin to practice savoring positive sensations and emotions and attentively monitoring positive events in daily life. Participants will be asked to identify thoughts that interrupt their mindful acceptance of positive sensations and emotions and to examine alternative thoughts. In parallel, the participants will be encouraged to identify their strengths and try to use them in daily life. To help identify strengths, participants will be asked to identify past positive memories.

The focus of the program will then gradually shift from enhancing the patient's acceptance of short-term positive experiences (ie, short-term reward) to engaging longer-term, goal-directed, and more effortful behavior. Psychoeducation on the temporal discounting of rewards in anhedonia will be provided. The participants will be asked to identify longer-term goals or values in their lives. These goals will then be divided into smaller steps, and patients will be encouraged to engage in easier behaviors. Furthermore, patients will be asked to monitor events they are grateful for in daily life and to practice receiving and providing compliments to enhance positive interpersonal experiences. In the final session, participants will review the skills they acquired during the program and discuss how to maintain a positive lifestyle.

Sound Material and Presentation System for Inaudible High-Frequency and Placebo Sounds

The intervention group will be exposed to inaudible high-frequency sounds during PoCot sessions. Rainforest sounds, a natural sound source containing the richest amount of high frequencies with a conspicuously fluctuating structure, were chosen as the sound source for this trial. Sounds containing inaudible high-frequency components (HFCs), referred to as *full-range sounds*, were recorded in the rainforest of Borneo from 2004 to 2009 using a high-speed, 1-bit coding signal processor in a direct stream digital format at a sampling frequency of 5.6 MHz. The electrical signal contains a wealth of HFCs (ie, >100 kHz). The sounds include animal and bird calls, insects chirping, and wind. The track is 47 minutes long and will be presented on repeat.

We selected PoCot without inaudible high-frequency sounds (ie, placebo sounds) as the comparator because previous studies successfully used placebo sounds as a comparator.^{23,26} There was almost no difference in the subjective experience of sound quality between inaudible high-frequency sounds and the placebo sounds. To generate placebo sounds, the inaudible HFCs were excluded from the original sound material using a low-pass filter (digital finite impulse response filter; cutoff frequency, 27 kHz; allowable passband ripple, 0.5 dB; stopband, 28 kHz-150 dB) using the MATLAB signal processing toolbox (MathWorks, Inc).

The level of audible sounds should not disturb conversations during PoCot, and the preferred sound level may vary depending on individual participants and therapists. Conversely, the inaudible

HFCs should be presented equally to all participants in the intervention group. To this end, we constructed an original sound presentation system whereby the sound source signals recorded in a digital audio player (MR-2000S; KORG) can be divided into 2 pathways by a splitter with an independent volume control for each pathway (Behringer MX882; Behringer Music Group) (Figure 1). Using this presentation system, the fixed level of HFCs can be determined regardless of the audible low-frequency component level.

As the study will use a short-term intervention, all participants will be asked to participate in all 8 sessions. If participants must cancel a scheduled session, an alternative date will be scheduled immediately. Participants will be exposed to their assigned audio track during the entire PoCot session. The sound volume will be set in advance at approximately 55 dB. Participants will sit 2 m away from 2 fixed speakers and tweeters (eFigure 1 and eFigure 2 in Supplement 2).

Objectives

Primary Objective

The primary objective of this trial is to compare the efficacy of PoCot with in-session exposure to inaudible high-frequency sounds vs PoCot with in-session exposure to placebo sounds on anhedonia symptoms. Anhedonia symptoms will be assessed by 44 patients who have been diagnosed with clinically significant anhedonia symptoms using the SHAPS.⁴⁰

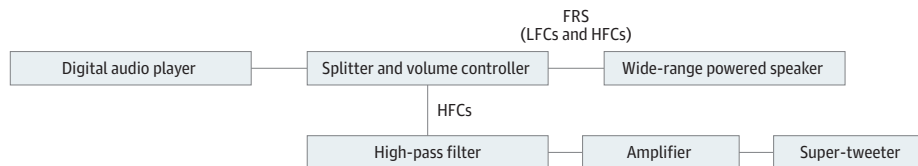
Secondary Objectives

The key secondary objective is to evaluate the severity of anhedonia symptoms using the clinician-rated version of the SHAPS (SHAPS-C).⁴¹ Additional outcome variables, including depression, positive emotion, negative emotion, satisfaction with life, and psychological well-being will also be assessed. In addition, a moderation and mediation analysis will be performed using the following 2 measures, which are relevant to the treatment mechanism: (1) perception of environmental rewards and (2) effort-based decision-making. Perception of environmental rewards will be assessed by the Environmental Reward Observation Scale.⁴² Based on behavioral theory, this brief scale was developed to subjectively evaluate environmental reward as an important treatment mediator of traditional and new behavioral activation techniques. Effort-based decision-making will be assessed using the Effort-Expenditure for Rewards Task.⁴³ Also, the relationship between the treatment process (eg, homework adherence) and outcomes will be examined.

Participant Timeline

The timeline is depicted in Figure 2. During the study period, all patients will continue treatment as usual.

Figure 1. Sound Presentation System



In the higher pathway, full-range sound (FRS) sources, which contain high-frequency components (HFCs) and low-frequency components (LFCs), are sent to wide-range, powered speakers (Oohashi Monitor Op. 7; Action Research Co) through a volume controller. In the lower pathway, HFCs are extracted from the sound source after passing through an independent volume controller using Butterworth Bessel high-pass filters

(cutoff frequency, 40 kHz, -48 dB per octave) and sent to super-tweeters (PT-R9; Pioneer Co) through a power amplifier (Cerenate; Fidelix). Audible LFCs and HFCs are transmitted via the first pathway, while the inaudible HFCs are presented via the second pathway.

Sample Size

It is difficult to estimate the necessary sample size because previous studies have not directly tested our hypothesis. Among the most studied augmentation strategies of CBT is the effect of D-cycloserine on CBT for anxiety disorders; a meta-analysis⁴⁴ reported that the standardized effect size of the augmentation on various outcomes ranged from 0.07 to 0.58. Based on this range, we conservatively selected a relatively low effect size to assess the augmentation effect of inaudible high-frequency sounds on CBT efficacy. We set a standardized effect size of 0.2 to 0.3 as the clinically significant minimum level. To detect the effect size, a sample size of 344 to 786 participants is needed for the main trial. For this pilot trial, we used the approach that was proposed specifically for calculating sample size for a randomized clinical pilot trial.⁴⁵ Using this strategy, 32 to 72 individuals are needed. Hence, a sample size of 40 is sufficient for this trial. Assuming a 12% dropout rate, we included a total of 44 patients. Before starting the main pilot trial, we will conduct an external preliminary trial on 3 patients to examine the trial's feasibility.

Assignment of Interventions

Allocation

The research coordinator will register the participants using an electronic data capture system (HOPE eACReSS version 5; Fujitsu). Sequences will be generated by this system before the patients begin the trial (ie, allocation concealment by central registration). The allocation staff will set the audio track (inaudible high-frequency sounds vs placebo sounds) in accordance with the generated sequences. Block randomization without stratification will be used.

Masking

All therapists, patients, evaluators, statisticians, and research coordinators will be masked to the allocation. Masking will be checked using the modified version of the Independent Evaluator Knowledge of Outcome⁴⁶ assessment, which was successfully used in a large-scale clinical trial involving CBT.⁴⁷ Using the data, we will calculate the blinding index.⁴⁸

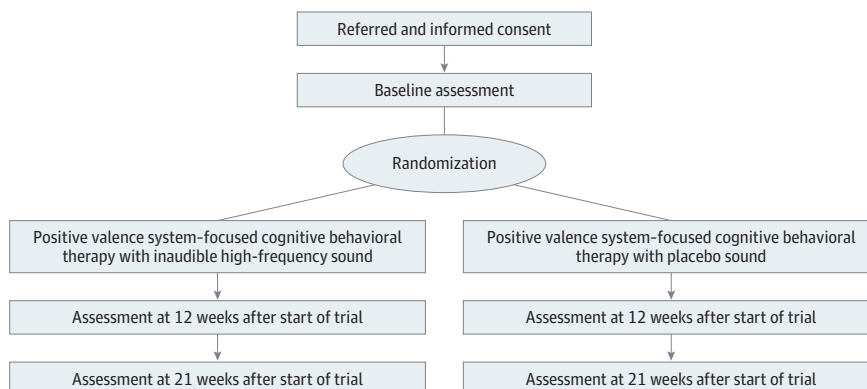
Data Collection, Management, and Analysis

The **Table** shows an overall description of the assessment during each visit. Assessment tools include the SHAPS, the SHAPS-C, the GRID-Hamilton Rating Scale, and the Beck Depression Inventory-II.

Primary Outcome

The SHAPS is a 14-item self-report questionnaire used to assess the presence and severity of anhedonia.^{40,49} Each item is answered by different 4-point Likert anchors. Following methods used in previous studies,^{50,51} the total score will be used. A higher score implies more severe anhedonia

Figure 2. Study Flow Diagram



symptoms, and a total score greater than 20 is interpreted as having anhedonia. Importantly, the reliability of the Japanese version of the SHAPS has been demonstrated (ie, $\alpha = 0.90$).⁴⁹

Key Secondary Outcome Measure

The SHAPS-C offers improved instructions and anchors compared with the original SHAPS.⁴¹ Similar to the SHAPS, the SHAPS-C consists of 14 items on a 4-point Likert scale. The SHAPS-C has been reported to have sufficient reliability ($\alpha = 0.90$) and validity (concurrent validity with SHAPS, $r = 0.85$; $P < .001$).⁴¹ We translated the English version of the SHAPS-C to Japanese using a rigorous back translation procedure.^{52,53}

Measures of Eligibility, Other Outcomes, Treatment Mechanisms, and Treatment Processes

The Mini-International Neuropsychiatric Interview³⁴ will be used to assess eligibility. The GRID-Hamilton depression rating scale,^{33,54,55} Beck Depression Inventory-II,⁵⁶ Positive and Negative Affect Schedule,⁵⁷ Satisfaction With Life Scale,⁵⁸ and Psychological Well-being Inventory⁵⁹ will be used to evaluate the other outcomes. The Environmental Reward Observation Scale⁴² and Effort-Expenditure for Rewards Task⁴³ will be used to assess treatment mechanisms, and the Homework Compliance Scale⁶⁰ will be used to assess treatment adherence. Detailed information on these assessments appears in [Supplement 1](#).

Statistical Analysis

Outcome Analysis | A mixed model for repeated-measures analysis will be conducted to analyze the primary outcome. The dependent variables in this model will be the participants' SHAPS scores, assessed during 8 visits from weeks 1 to 11 (ie, intervention period) and at week 12 (ie, postintervention period). The fixed effects will be allocation, visit, allocation-by-visit interaction, and

Table. Study Measures and Points

Outcome	Tool	Method	Enrollment		Intervention									After Intervention	Follow-up	
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	
Week	NA	NA	-2	-1	0	1-11									12	21
Diagnosis	MINI	IE		X												
Primary outcome, anhedonia	SHAPS	PSR		X		X	X	X	X	X	X	X	X	X	X	
Key secondary outcome, anhedonia	SHAPS-C	IE		X										X	X	
Other outcomes																
Depression and anhedonia	GRID-HAMD	IE		X										X	X	
	BDI-II	PSR			X				X					X	X	
Secondary outcomes																
Emotion	PANAS	PSR			X	X	X	X	X	X	X	X	X	X	X	
Life satisfaction	SWLS	PSR			X				X					X	X	
Well-being	PWB	PSR			X				X					X	X	
Treatment mechanisms																
Anhedonia	EROS	PSR			X					X				X	X	
Anhedonia	EEfRT	PSR		X										X	X	
Safety	AE	TSR and EA				X	X	X	X	X	X	X	X	X	X	
Adherence	HCS	TSR					X	X	X	X	X	X	X			
Blinding	IEKNO	PSR, TSR, and EA				X								X	X	

Abbreviations: AE, adverse event; BDI-II, Beck Depression Inventory-II; EEfRT, Effort-Expenditure for Rewards Task; EROS, Environmental Reward Observation Scale; EA, evaluator assessment; GRID-HAMD, GRID-Hamilton Depression Rating Scale 17 Item; HCS, Homework Compliance Scale; IE, interview with evaluator; IEKNO, Independent Evaluator Knowledge of Outcome; MINI, Mini-International Neuropsychiatric Interview

version 7.0.2; NA, not applicable; PANAS, Positive and Negative Affect Schedule; PSR, participant self-report; PWB, Psychological Well-being Inventory; SHAPS, Snaith-Hamilton Pleasure Scale; SHAPS-C, Snaith-Hamilton Pleasure Scale, clinician administered; SWLS, Satisfaction With Life Scale; TSR, therapist self-report.

SHAPS score before the intervention (ie, week 0). Covariance will be specified as the unstructured structure. The treatment effects will be presented as the difference in adjusted means between the allocations at week 12 (ie, visit 12). The confidence interval will be estimated, and a *t* test will be conducted to determine the effects of treatment. The treatment effect at other weeks as well as the standardized treatment effect will also be analyzed. As a secondary outcome analysis, analysis of covariance, including baseline measures, will be conducted to test the intervention effects on SHAPS-C scores at week 12. The mixed model for repeated-measures analysis will be conducted for the other outcomes. Statistical significance will be set at $P < .05$, and all tests will be 2-tailed.

Analysis Population and Missing Data | The primary and secondary outcome analyses will be evaluated using the intent-to-treat principle. Our secondary outcome analysis will use all registered participants who do not meet the discontinuation criteria, as per the protocol set. The mixed model for repeated-measures analysis will be used to treat missing data. Details of the statistical analyses, including interim analysis and stopping guidelines, are described in the statistical analysis plan and trial protocol ([Supplement 1](#)).

Monitoring

Data Monitoring

The primary investigator, in collaboration with the research coordinator and data manager, will conduct on-site and central monitoring and will report the results to the members of the data and safety monitoring board. All registered cases will be subjected to central monitoring. On-site monitoring will be conducted for the first 3 registered cases, then for 3 random, preidentified cases thereafter.

Adverse Events

Adverse events will be assessed using the Common Terminology Criteria for Adverse Events.⁶¹ These include dry mouth, astringency, dysuria, vision dysregulation, orthostatic hypotension, sleepiness, fatigue, sleeplessness, anxiety or agitation, depression or anhedonia, lack of appetite, gain or loss of body weight, loss of sexual desire, palpitations, thrill, diaphoresis, headache, dizziness, and others.

Ethical Approval and Informed Consent

This study has been approved by the NCNP institutional review board. The initial protocol was approved on November 13, 2017, and the modified version was approved on March 5, 2019. Research coordinators will explain and obtain written informed consent from participants regarding the following items: objectives, reasons for enrollment, the methods and time period, potential burdens, predictable risks and benefits, handling of personal information, means for information storage and disposal, conflicts of interest, any potential invasiveness, and compensation for research-related injuries.

Confidentiality

The administrator of the patients' personal information will manage and store all research-related printed or electronic records with personal information, with a corresponding table of personal information and research identification numbers to prevent any information from being divulged, stolen, or lost. The details are described in [Supplement 1](#).

Discussion

This protocol described the design of our pilot study for testing the augmentation effect of inaudible high-frequency sounds on positive valence system-focused CBT. To date, treatments for depression and/or anhedonia do not guarantee clinically successful outcomes. In contrast to the studies of the augmentation effect of D-cycloserine on CBT for anxiety disorders,⁴⁴ augmentation studies for CBT

treatments of depression are limited. Exposure to inaudible high-frequency sounds does not require attentional or cognitive effort from either the patients or therapists; therefore, results from a future confirmative trial could indicate that cognitive behavioral therapy can be augmented in an effortless manner.

Limitations

Our trial design has several limitations. First, this pilot trial aims to evaluate the potential efficacy of augmenting PoCot with inaudible high-frequency sounds. Because of its preliminary nature, this study only provides information regarding whether it is appropriate to proceed with a larger, definitive trial. Since our sample size calculation is specifically designed to obtain this information, the results of this trial should be cautiously interpreted. Second, considering the limited efficacy of traditional CBT approaches (eg, behavioral activation) and a promising novel neuroscience-driven treatment for anhedonia, we developed PoCot. However, the efficacy of this intervention has not been proven as a stand-alone treatment for anhedonia. Thus, further evidence is needed to test PoCot as a stand-alone treatment for anhedonia. A factorial design would be among the best methods to accomplish this because the use of inaudible high-frequency sound also has limited evidence for its efficacy as a stand-alone treatment for anhedonia. Third, we will not control for patient medications because this would present a potential recruitment barrier. Fourth, we included various outcome and process measures to evaluate the intervention from multiple perspectives; these evaluations should be interpreted as exploratory. Fifth, this trial cannot evaluate or offer detailed information for the following important aspects of the intervention: optimal doses or timing of PoCot and inaudible high-frequency sounds, the augmentation effect in each module of PoCot, specific subgroups that are responsive to PoCot and/or inaudible high-frequency sounds, and the influence of inaudible-high frequency sounds on several distinct reward processes.

Conclusions

This trial is expected to provide initial findings on the synergistic effect of psychological interventions that target the positive valence system and use inaudible high-frequency sounds. The combination of CBT and sound therapy could have a synergistic effect on anhedonia.

ARTICLE INFORMATION

Accepted for Publication: September 26, 2019.

Published: November 20, 2019. doi:[10.1001/jamanetworkopen.2019.15819](https://doi.org/10.1001/jamanetworkopen.2019.15819)

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Author Contributions: Dr Ito had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ito, Miyamae, Yokoyama, Yamashita, Maruo, Komazawa, Niwa, Honda, Horikoshi.

Acquisition, analysis, or interpretation of data: Yamashita, Ueno, Maruo.

Drafting of the manuscript: Ito, Yamashita, Maruo.

Critical revision of the manuscript for important intellectual content: Miyamae, Yokoyama, Yamashita, Ueno, Maruo, Komazawa, Niwa, Honda, Horikoshi.

Statistical analysis: Maruo.

Obtained funding: Ito, Miyamae, Honda, Horikoshi.

Administrative, technical, or material support: Ito, Miyamae, Yokoyama, Yamashita, Ueno, Komazawa, Honda, Horikoshi.

Supervision: Ito, Honda, Horikoshi.

Conflict of Interest Disclosures: Dr Horikoshi reported receiving grants and personal fees from Mitsubishi Tanabe Pharma Corporation outside the submitted work. No other disclosures were reported.

Funding/Support: Mr Miyamae was supported by a Public Health Research Foundation research grant for stress management in the field of stress science. Dr Horikoshi was supported by grants 17lk0310033h0001, 18lk0310046h0001, and 19lk0310063h0001 from the Japan Agency for Medical Research and Development Research Project for Improving Quality in Healthcare and Collecting Scientific Evidence on Integrative Medicine.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Naotsugu Hirabayashi, MD, PhD (National Center of Neurology and Psychiatry, Kodaira, Japan), Fumi Imamura, MA (National Center of Neurology and Psychiatry), Ayako Kanie, MD, PhD (National Center of Neurology and Psychiatry), and Aiichiro Nakajima, MD (National Center of Neurology and Psychiatry), helped develop the recruitment strategy. They were not compensated for their time. Norie Kawai, PhD (Department of Research and Development, Foundation for Advancement of International Science, Tsukuba, Japan), Emi Nishina, PhD (Department of Liberal Arts, The Open University of Japan, Chiba, Japan), and Tsutomu Oohashi, PhD (Department of Research and Development, Foundation for Advancement of International Science), contributed to the development of the sound presentation system. They were not compensated for their time. Naoko Kamimura (Tokyo, Japan) and Hiroko Nozaki (Tokyo, Japan) contributed to the development of the workbook of positive valence system-focused cognitive behavioral therapy for anhedonia. They were compensated for their time.

REFERENCES

1. World Health Organization. *Depression and Other Common Mental Disorders: Global Health Estimates*. Geneva, Switzerland: World Health Organization; 2017.
2. National Collaborating Centre for Mental Health (UK). *Depression: The Treatment and Management of Depression in Adults (Updated Edition)*. Leicester, UK: British Psychological Society; 2010.
3. Cuijpers P, van Straten A, Bohlmeijer E, Hollon SD, Andersson G. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychol Med*. 2010;40(2):211-223. doi:10.1017/S0033291709006114
4. Cuijpers P, van Straten A, Andersson G, van Oppen P. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *J Consult Clin Psychol*. 2008;76(6):909-922. doi:10.1037/a0013075
5. Wilkinson ST, Holtzheimer PE, Gao S, Kirwin DS, Price RB. Leveraging neuroplasticity to enhance adaptive learning: the potential for synergistic somatic-behavioral treatment combinations to improve clinical outcomes in depression. *Biol Psychiatry*. 2019;85(6):454-465. doi:10.1016/j.biopsych.2018.09.004
6. Goodwin GM, Holmes EA, Andersson E, et al. From neuroscience to evidence based psychological treatments: the promise and the challenge, ECNP March 2016, Nice, France. *Eur Neuropsychopharmacol*. 2018;28(2):317-333. doi:10.1016/j.euroneuro.2017.10.036
7. Holmes EA, Ghaderi A, Harmer CJ, et al. The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. *Lancet Psychiatry*. 2018;5(3):237-286. doi:10.1016/S2215-0366(17)30513-8
8. Boumparis N, Karyotaki E, Kleiboer A, Hofmann SG, Cuijpers P. The effect of psychotherapeutic interventions on positive and negative affect in depression: a systematic review and meta-analysis. *J Affect Disord*. 2016;202:153-162. doi:10.1016/j.jad.2016.05.019
9. McCabe C, Mishor Z, Cowen PJ, Harmer CJ. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biol Psychiatry*. 2010;67(5):439-445. doi:10.1016/j.biopsych.2009.11.001
10. Stanton CH, Holmes AJ, Chang SWC, Joormann J. From stress to anhedonia: molecular processes through functional circuits. *Trends Neurosci*. 2019;42(1):23-42. doi:10.1016/j.tins.2018.09.008
11. Berridge KC, Kringelbach ML. Pleasure systems in the brain. *Neuron*. 2015;86(3):646-664. doi:10.1016/j.neuron.2015.02.018
12. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev*. 2011;35(3):537-555. doi:10.1016/j.neubiorev.2010.06.006

13. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annu Rev Clin Psychol*. 2014;10:393-423. doi:10.1146/annurev-clinpsy-050212-185606
14. Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748-751. doi:10.1176/appi.ajp.2010.09091379
15. Dillon DG, Rosso IM, Pechtel P, Killgore WD, Rauch SL, Pizzagalli DA. Peril and pleasure: an RDoC-inspired examination of threat responses and reward processing in anxiety and depression. *Depress Anxiety*. 2014;31(3):233-249. doi:10.1002/da.22202
16. Lambert C, Da Silva S, Ceniti AK, Rizvi SJ, Foussias G, Kennedy SH. Anhedonia in depression and schizophrenia: a transdiagnostic challenge. *CNS Neurosci Ther*. 2018;24(7):615-623. doi:10.1111/cns.12854
17. Dunn BD, Widnall E, Reed N, et al. Evaluating Augmented Depression Therapy (ADepT): study protocol for a pilot randomised controlled trial. *Pilot Feasibility Stud*. 2019;5:63. doi:10.1186/s40814-019-0438-1
18. Craske MG, Meuret AE, Ritz T, Treanor M, Dour HJ. Treatment for anhedonia: a neuroscience driven approach. *Depress Anxiety*. 2016;33(10):927-938. doi:10.1002/da.22490
19. Taylor CT, Lyubomirsky S, Stein MB. Upregulating the positive affect system in anxiety and depression: outcomes of a positive activity intervention. *Depress Anxiety*. 2017;34(3):267-280. doi:10.1002/da.22593
20. Alexopoulos GS, Raue PJ, Gunning F, et al. "Engage" therapy: behavioral activation and improvement of late-life major depression. *Am J Geriatr Psychiatry*. 2016;24(4):320-326. doi:10.1016/j.jagp.2015.11.006
21. Henje Blom E, Tymofiyeva O, Chesney MA, et al. Feasibility and preliminary efficacy of a novel RDoC-based treatment program for adolescent depression: "Training for Awareness Resilience and Action" (TARA): a pilot study. *Front Psychiatry*. 2017;7:208. doi:10.3389/fpsy.2016.00208
22. Craske MG, Meuret AE, Ritz T, Treanor M, Dour H, Rosenfield D. Positive affect treatment for depression and anxiety: a randomized clinical trial for a core feature of anhedonia. *J Consult Clin Psychol*. 2019;87(5):457-471. doi:10.1037/ccp0000396
23. Oohashi T, Nishina E, Honda M, et al. Inaudible high-frequency sounds affect brain activity: hypersonic effect. *J Neurophysiol*. 2000;83(6):3548-3558. doi:10.1152/jn.2000.83.6.3548
24. Omata K, Hanakawa T, Morimoto M, Honda M. Spontaneous slow fluctuation of EEG alpha rhythm reflects activity in deep-brain structures: a simultaneous EEG-fMRI study. *PLoS One*. 2013;8(6):e66869. doi:10.1371/journal.pone.0066869
25. Yagi R, Nishina E, Oohashi T. A method for behavioral evaluation of the "hypersonic effect." *Acoust Sci Technol*. 2003;24(4):197-200. doi:10.1250/ast.24.197
26. Yagi R, Nishina E, Honda M, Oohashi T. Modulatory effect of inaudible high-frequency sounds on human acoustic perception. *Neurosci Lett*. 2003;351(3):191-195. doi:10.1016/j.neulet.2003.07.020
27. Kuribayashi R, Nittono H. High-resolution audio with inaudible high-frequency components induces a relaxed attentional state without conscious awareness. *Front Psychol*. 2017;8:93. doi:10.3389/fpsyg.2017.00093
28. Bruijniks SJE, DeRubeis RJ, Hollon SD, Huijbers MJH. The potential role of learning capacity in cognitive behavior therapy for depression: a systematic review of the evidence and future directions for improving therapeutic learning. *Clin Psychol Sci*. 2019;7(4):668-692. doi:10.1177/2167702619830391
29. Shiota MN, Campos B, Oveis C, Hertenstein MJ, Simon-Thomas E, Keltner D. Beyond happiness: building a science of discrete positive emotions. *Am Psychol*. 2017;72(7):617-643. doi:10.1037/a0040456
30. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev*. 2007;53(1):63-88. doi:10.1016/j.brainresrev.2006.06.003
31. Klimesch W. α -band oscillations, attention, and controlled access to stored information. *Trends Cogn Sci*. 2012;16(12):606-617. doi:10.1016/j.tics.2012.10.007
32. Ito M, Okumura Y, Horikoshi M, et al. Japan Unified Protocol Clinical Trial for Depressive and Anxiety Disorders (JUNP study): study protocol for a randomized controlled trial. *BMC Psychiatry*. 2016;16:71. doi:10.1186/s12888-016-0779-8
33. Williams JB, Kobak KA, Bech P, et al. The GRID-HAMD: standardization of the Hamilton Depression Rating Scale. *Int Clin Psychopharmacol*. 2008;23(3):120-129. doi:10.1097/YIC.0b013e32829f48f5
34. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22-33.
35. Quoidbach J, Mikolajczak M, Gross JJ. Positive interventions: an emotion regulation perspective. *Psychol Bull*. 2015;141(3):655-693. doi:10.1037/a0038648

36. Weytens F, Luminet O, Verhofstadt LL, Mikolajczak M. An integrative theory-driven positive emotion regulation intervention. *PLoS One*. 2014;9(4):e95677. doi:10.1371/journal.pone.0095677
37. Morita S, Morita M. *Morita Therapy and the True Nature of Anxiety-Based Disorders (Shinkeishitsu)*. Kondo A, trans. Albany, NY: SUNY Press; 1998.
38. Kandabashi J. *Keys for Psychiatric Self-Care* [in Japanese]. Tokyo, Japan: Iwasaki Gakujuutsu Press; 2009.
39. Carl JR, Soskin DP, Kerns C, Barlow DH. Positive emotion regulation in emotional disorders: a theoretical review. *Clin Psychol Rev*. 2013;33(3):343-360. doi:10.1016/j.cpr.2013.01.003
40. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone: the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry*. 1995;167(1):99-103. doi:10.1192/bjp.167.1.99
41. Ameli R, Luckenbaugh DA, Gould NF, et al. SHAPS-C: the Snaith-Hamilton Pleasure Scale modified for clinician administration. *PeerJ*. 2014;2:e429. doi:10.7717/peerj.429
42. Armento ME, Hopko DR. The Environmental Reward Observation Scale (EROS): development, validity, and reliability. *Behav Ther*. 2007;38(2):107-119. doi:10.1016/j.beth.2006.05.003
43. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One*. 2009;4(8):e6598. doi:10.1371/journal.pone.0006598
44. Ori R, Amos T, Bergman H, Soares-Weiser K, Ipser JC, Stein DJ. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. *Cochrane Database Syst Rev*. 2015;(5):CD007803. doi:10.1002/14651858.CD007803.pub2
45. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. *J Clin Epidemiol*. 2013;66(2):197-201. doi:10.1016/j.jclinepi.2012.09.002
46. Roll D, Ray SE, Marcus SM, et al. Independent evaluator knowledge of treatment in a multicenter comparative treatment study of panic disorder. *Neuropsychopharmacology*. 2004;29(3):612-618. doi:10.1038/sj.npp.1300373
47. Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA*. 2000;283(19):2529-2536. doi:10.1001/jama.283.19.2529
48. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials*. 2004;25(2):143-156. doi:10.1016/j.cct.2003.10.016
49. Nagayama H, Kubo S, Hatano T, et al; Young Japanese Expert Group for Parkinson's Disease and Movement Disorders: YJ-EXPANDS. Validity and reliability assessment of a Japanese version of the Snaith-Hamilton pleasure scale. *Intern Med*. 2012;51(8):865-869. doi:10.2169/internalmedicine.51.6718
50. Franken IH, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). *J Affect Disord*. 2007;99(1-3):83-89. doi:10.1016/j.jad.2006.08.020
51. Liu WH, Wang LZ, Zhu YH, Li MH, Chan RC. Clinical utility of the Snaith-Hamilton-Pleasure scale in the Chinese settings. *BMC Psychiatry*. 2012;12:184. doi:10.1186/1471-244X-12-184
52. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976)*. 2000;25(24):3186-3191. doi:10.1097/00007632-200012150-00014
53. Wild D, Grove A, Martin M, et al; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health*. 2005;8(2):94-104. doi:10.1111/j.1524-4733.2005.04054.x
54. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62. doi:10.1136/jnnp.23.1.56
55. Tabuse H, Kalali A, Azuma H, et al. The new GRID Hamilton Rating Scale for Depression demonstrates excellent inter-rater reliability for inexperienced and experienced raters before and after training. *Psychiatry Res*. 2007;153(1):61-67. doi:10.1016/j.psychres.2006.07.004
56. Beck AT, Steer AR, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation; 1996.
57. Clark LA, Watson D. Mood and the mundane: relations between daily life events and self-reported mood. *J Pers Soc Psychol*. 1988;54(2):296-308. doi:10.1037/0022-3514.54.2.296
58. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. *J Pers Assess*. 1985;49(1):71-75. doi:10.1207/s15327752jpa4901_13
59. Ryff CD. Beyond Ponce de Leon and life satisfaction: new directions in quest of successful ageing. *Int J Behav Dev*. 1989;12(1):35-55. doi:10.1177/016502548901200102

60. Primakoff L, Epstein N, Covi L. Homework compliance: an uncontrolled variable in cognitive therapy outcome research. *Behav Ther*. 1986;17(4):433-446. doi:10.1016/S0005-7894(86)80073-9
61. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed October 10, 2019.

SUPPLEMENT 1.

Trial Protocol

SUPPLEMENT 2.

eAppendix. Biological and Theoretical Rationale and Treatment Descriptions of Positive Valence System-Focused Cognitive Behavioral Therapy

eFigure 1. Speaker and Super-Tweeter

eFigure 2. Layout of the Therapy Room

eTable. Description and Findings Related to Positive Valence System-Focused Cognitive Behavioral Therapy Treatment Modules for Anhedonia

eReferences.