Effects of Self-Focused Emotion Regulation Interventions Embedded in a Mobile Healthcare App on Resting-State Brain Functional Connectivity in Individuals with High Levels of Anxiety and Depression

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ABSTRACT

Effects of Self-Focused Emotion Regulation Interventions Embedded in a Mobile Healthcare App on Resting-State Brain Functional Connectivity in Individuals with High Level of Anxiety and Depression

Background: Disorder related to anxiety and depression are prevalent, particularly in individuals with high anxiety. Traditional treatment methods often face barriers, so mobile healthcare interventions, especially those incorporating emotion regulation strategies that focused on the one of the anxious individual's traits 'self-focused attention' might show potential in addressing these challenges. This study aimed to assess the effectiveness of such an intervention in reducing anxiety and depression changing brain functional connectivity.

Method: A 12-week mobile healthcare app intervention was implemented, focusing on three emotion regulation strategies: acceptance and commitment therapy, self-affirmation and heart-smile training. Participants underwent functional MRI to measure changes in brain connectivity, along with clinical assessments of anxiety and depression.

Results: The intervention led to significant reductions in anxiety and depression, with the experimental group showing greater improvements. Neuroimaging results revealed increased functional connectivity in key brain networks, such as the default mode network and salience network, which are involved in attention control and emotion regulation.

Conclusion: The study highlights the potential of mobile interventions to enhance emotional well-being by modulating brain connectivity. Further research is needed to explore these effects in diverse populations while accounting for external factors.

Key words: anxiety, mobile healthcare, self-focused attention, emotion regulation, functional connectivity, default mode network, salience network, executive control network, functional MRI

I. INTRODUCTION

1. Anxiety, Depression and Self-focused Attention

Anxiety is a natural emotional response to stress or perceived danger, characterized by feelings of worry, tension, and nervousness[1]. While occasional anxiety is normal, anxiety disorders involve excessive, persistent fear that interferes with daily life. From a neurological perspective, anxiety and related disorders are linked to altered brain connectivity, particularly hypo-connectivity between the affective network and both the executive control (ECN) and default mode networks (DMN). Additionally, reduced anti-correlation between the ECN and DMN, and weakened connectivity within the salience (SN) and sensorimotor networks, are observed in individuals with anxiety[2].

Another study investigated that generalized anxiety disorder (GAD) patients show increased connectivity in the ECN and decreased connectivity in the insula-cingulate network (salience network)[3]. In social anxiety disorder (SAD), connectivity decreases in the right precuneus (PCUN) and increases in the dorsomedial prefrontal cortex (dmPFC), regions tied to anxiety processing and social cognition[4]. Similarly, highly anxious individuals exhibit reduced functional connectivity in the key DMN regions, such as the posterior cingulate cortex (PCC), affecting self-reflection and social cognition[5].

Depression is defined as the emotional expression of a state characterized by persistent feelings of sadness, hopelessness, and a lack of interest or pleasure in activities once enjoyed[7]. This condition is associated with disrupted neural processes, particularly in areas of emotional regulation and reward processing. Individuals with major depressive disorder (MDD) often show increased activity in the anterior cingulate cortex (ACC) and amygdala, which are associated with heightened emotional reactivity. Concurrently, there is reduced activation in the striatum and dorsolateral prefrontal cortex (dlPFC), regions linked to reward processing and cognitive control[7,8,9]. These neural patterns highlight a bias in emotional processing and impaired regulatory mechanisms, contributing to the chronic emotional and motivational challenges observed in depression.

One of the cognitive issues associated with high anxiety and depression is maladaptive self-focused attention[10], where individuals excessively focus on internal thoughts and feelings rather than external stimuli[11]. Those with anxiety often dwell on negative emotions and events, leading to behaviors like extensive self-talk about negative experiences[12]. This imbalance in self-focus prevents anxious individuals from benefiting fully from positive events, amplifying the impact of negative experiences, and leading to maladaptive behaviors that harm self-esteem, work performance, and mental health[10]. Neurologically, high social anxiety and maladaptive self-focused attention are linked to reduced functional connectivity between the PCC and the bilateral superior parietal lobule (SPL). Abnormal PCC-SPL connectivity may reflect difficulties in shifting focus from internal to external attention[13]. Moreover, increased brain activity in regions such as the medial prefrontal cortex (mPFC) and temporo-parietal junction (TPJ) is seen when individuals with social anxiety are inwardly focused. This self-focused attention further heightens activity in areas like the mPFC, right anterior insula (aINS), and PCC[14].

Similarly, MDD patients showed reduced negative blood oxygen level-dependent response in anterior medical cortical regiones (related to the DMN) urging self-referential emotional judgments[15]. In addition, people with a history of depression showed positive correlation with the negative self-focused thought and increased resting state functional connectivity between the dmPFC and pregenual ACC seed and dlPFC[16]. Additionally, these individuals displayed greater overall neural network activation and increased directed connectivity from the DMN to SN when engaging in the negative word Stroop test. These findings suggest that enhanced functional connectivity between the DMN and SN may amplify negativity bias in previously depressed individuals, contributing to persistent maladaptive thought patterns[17].

Early studies suggested redirecting the attention of individuals with high anxiety and depression away from themselves and toward unrelated external stimuli to mitigate their self-focused attention [18]. However, making this shift can be difficult for those with high anxiety as it requires considerable effort[19]. Moreover, this strategy may increase repression and self-avoidance, potentially leading to a resurgence of mental health problems[20,21]. Additionally, this method has limitations in effectively addressing long-term and persistent anxiety[22]. Consequently, there is a growing demand for cognitive treatments that encourage individuals to focus inward in a healthy, constructive way. Recently, mindfulness-based cognitive therapies such as Acceptance and Commitment Therapy (ACT), Mindfulness-based Cognitive Therapy (MBCT), and Mindfulness-based Stress Reduction (MBSR) have emerged as promising alternatives[23].

2. Self-affirmation and Positive Self-talk

Several emotion regulation strategies have been developed to promote mental well-being, and they have been linked to numerous cortical and subcortical brain activations[24,25]. One such strategy is self-talk, which refers to the continuous internal dialogue hat continuously occurs in a person's mind. Self-talk can be functionally described as verbal expressions directed toward oneself, encompassing different dimensions such as overt or covert, instructional or motivational and positive or negative. These expressions also involve interpretations that are shaped by the context in which they are used[26]. Positive self-talk, especially when used for self-affirmation, is particularly important as it can influence decision-making[27], support emotion regulation[28], and overcoming challenges[29]. As a result, it has been utilized in various activities, such as improving sports performance[30,31], increasing academic engagement[32], and managing anxiety in public speaking[33].

Self-affirmation involves recognizing and focusing on one's positive traits, strengths and values. According to self-affirmation theory, when individuals affirm their core values in the face of perceived threats to their self-integrity, they are less likely to exaggerate or misinterpret the threat. This allows them to handle the situation more openly and objectively[34]. This ability to affirm unrelated values helps in managing emotions, such as reducing the negative emotions associated with experiences of helplessness[35] or discomfort from cognitive dissonance[36]. Additionally, self-affirmation may enhance stress resilience by moderating physiological stress responses, such as lowering cortisol levels in stressful conditions[37] and reducing epinephrine during exams[38]. Research has shown that self-affirmation activates brain areas involved in self-referential thinking, like the mPFC and PCC[39,40], as well as regions associated with reward processing, including the ventral striatum[39,41].

3. ACT and Cognitive Defusion

Mindfulness and acceptance focus on developing awareness of the present moment and observing one's thoughts, emotions, and physical sensations without judgment[42]. This approach emphasizes allowing emotions and thoughts to exist as they are, without trying to alter or suppress them, regardless of whether they are positive or negative. ACT incorporates mindfulness and acceptance techniques alongside behavior change strategies, aiming to increase psychological flexibility—this is the ability to adapt to life's experiences while making decisions that align with one's core values[43]. Like self-affirming self-talk, mindfulness and acceptance help reduce stress[44], enhance attention and concentration[45], improve emotional regulation[46], and build resilience[47]. These techniques have found application in areas such as sports performance[48], meditation[49], and clinical treatments[50].

Neuroimaging studies on mindfulness and ACT have demonstrated significant brain connectivity changes. Mindfulness practice is associated with increased connectivity between the PCC (brain region belongs to the DMN) and the dlPFC (brain region belongs to the ECN), as well as between the dorsal ACC and aINS (brain region belongs to the SN). Additionally, mindfulness shows decreased connectivity between the cuneus and rostral ACC and between the rostral ACC and amygdala, enhancing attention control, self-awareness, and emotion regulation[51]. Similarly, ACT interventions in neural mechanisms of acceptance-commitment therapy for obsessive-compulsive disorder patients have been linked to increased brain activity in regions involved in salience, multisensory integration, language processing, and self-referential processes, suggesting therapeutic benefits in these areas[52].

ACT uses six core processes, collectively referred to as the "hexaflex," to promote psychological flexibility. One key process is cognitive defusion, which involves stepping back from thoughts and recognizing them as mere mental events. This approach seeks to alter one's relationship with cognitive and verbal processes, allowing individuals to engage in behaviors despite experiencing challenging thoughts and emotions[53]. It helps people choose which experiences to hold onto and which to release. Research has shown that applying cognitive defusion techniques, such as repeating a single word to address negatively evaluated self-referential content, significantly reduced the believability and discomfort associated with negative self-relevant thoughts, compared to thought-control methods like positive self-talk[54]. Another intervention using this approach led to decreased discomfort and increased openness toward negative thoughts[55].

When individuals are "fused" with their thoughts, they tend to believe their thoughts are accurate reflections of reality. Cognitive defusion techniques in ACT aim to create distance between the individual and their thoughts, helping them view their thoughts from a more objective perspective[53]. Another cognitive defusion technique encourages individuals to observe their thoughts metaphorically[53,56], such as imagining thoughts as leaves floating on a stream or soldiers carrying posters in a parade. Neuroimaging studies have shown that cognitive defusion reduces neural activity in subcortical areas like the brainstem, thalamus, hippocampus, and amygdala[57]. This suggests that approaching negative thoughts with emotional detachment can reduce emotional intensity and lower physiological stress responses.

4. The Compassion Meditation: Heart-Smile Training

Heart-Smile Training (HST) is a loving-kindness meditation rooted in the teachings of Mahayana and Zen Buddhism. The practice emphasizes the idea that we are all inherently endowed with boundless wisdom and compassion, aiming to help individuals realize their deep interconnectedness with the universe. HST encourages the cultivation of loving-kindness—defined as a warm, compassionate, and peaceful state of being—and helps us see that we are not isolated beings but part of a universal oneness[58].

HST is structured around a main meditation practice and four auxiliary practices: Heart-Smile Gratitude and Acceptance, Heart-Smile Movement 33, Heart-Smile Body Scan, and Sound Meditation. The primary goal of these auxiliary practices is to relax the body and mind, allowing practitioners to engage more fully with the main meditation. Gratitude and Acceptance, for example, encourages self-compassion and mental ease. Unlike traditional loving-kindness meditations, particularly those in Theravada Buddhism which often rely on the repetition of phrases, HST focuses on directly awakening loving-kindness through the body. The practice involves both bodily sensations and movement, with the goal of making loving-kindness a felt experience, not just a mental exercise[59].

HST aims to not only cultivate compassion for others but also promote self-acceptance. The auxiliary practice of Gratitude and Acceptance helps participants embrace themselves as they are, alleviating self-hatred and negative self-concepts. It lays the groundwork for the broader loving-kindness meditation by restoring gentleness and kindness toward oneself[58,59,60].

The effects of Heart-Smile Training have been studied in controlled settings, with both quantitative and qualitative research showing positive outcomes. Participants report increased self-compassion, self-esteem, and emotional regulation, along with reductions in shame, self-judgment, anger, and hostility. The practice has also been shown to foster empathy, forgiveness, and a deeper sense of connection with others. On a spiritual level, many participants report enhanced feelings of inner confidence, a stronger sense of connection to the world, and an improved sense of meaning in life[59]. Moreover, the first investigation into the feasibility and neurocardiac mechanisms (electroencephalography) of HST in depressed patients is currently underway[60].

5. The Relationship between the DMN, SN and ECN: Triple Network

The Triple Network Model of the brain encompasses three core neural networks that underpin cognition, emotion, and behavior: the DMN, SN, and ECN[61]. Dysregulation among these networks is implicated in various mental health conditions, such as depression, bipolar, anxiety, and schizophrenia[61]. So, understanding these interactions provides a foundation for developing targeted interventions, including mindfulness and cognitive therapies, to restore network balance and improve mental health outcomes.

The DMN includes regions such as the mPFC, PCC, and posterior parietal cortex. The DMN is predominantly active during states of rest, introspection, mind-wandering, and self-referential thinking. It plays a role in processes like autobiographical memory, daydreaming, planning for future events, and considering the perspectives of others[62].

The SN is with regions like the ventrolateral prefrontal cortex (vlPFC), aINS, and PCC. The SN is involved in detecting stimuli that are subjectively significant, whether cognitive, homeostatic, or emotional. It acts as a switch between the DMN and ECN, identifying important stimuli and determining which network to engage, depending on what requires attention at the moment[63,64]. Previous studies have demonstrated that activation of the SN is accompanied by the activation of the ECN and deactivation of the DMN.

The ECN encompasses the dlPFC and posterior parietal cortex and is activated during tasks that demand cognitive effort and attention. The ECN is essential for high-level cognitive processes, including working memory, decision-making, and attention regulation. It becomes active when we focus on goal-oriented, problem-solving tasks[65,66].

Due to the close relationship between the DMN, SN, and ECN, research has shown that consistent mindfulness meditation practice over a month significantly enhances the interconnectivity between these networks[67].

6. Mobile Intervention for Controlling Anxiety and Depression

Depression and anxiety are prevalent and debilitating disorders that often occur together[68]. Approximately 25% of individuals with depression or anxiety report experiencing symptoms before the age of 20[69]. Despite the increasing prevalence of anxiety and depression, the rate of help-seeking remains low[70], which may be attributed to various personal, social, and structural barriers, such as limited mental health literacy, fear of stigma, financial constraints, and difficulties in accessing transportation[71]. One potential solution to overcome these obstacles is mobile health (m-health), a range of electronic applications designed to enhance physical or mental well-being[72].

Several studies have examined the effectiveness of mobile health interventions. For instance, one study assessed the impact of a self-guided mobile app (the Feel Stress Free app) on anxiety and depression in university students. After six weeks of use, the app led to a significant reduction in depression symptoms[73]. Another study evaluated an anxiety-reducing app (MindShift™) aimed at helping college students manage anxiety. Over three weeks, the app significantly alleviated somatic anxiety, general anxiety, and depression symptoms in students[74]. Lastly, a meta-analytic review of randomized controlled trials on internet- and mobile-based interventions (IMIs) confirmed their effectiveness. The review found that guided interventions yielded better outcomes in reducing anxiety and depression symptoms and improving adherence compared to unguided interventions[75].

7. Overview of Studies and Current Study Goals

This study aimed to evaluate the effectiveness of a mobile-based self-focused emotion regulation healthcare application designed for long-term use in reducing anxiety and depression. It leveraged self-regulation strategies tailored to participants' emotional states, promoting sustained mental well-being through consistent, structured intervention. This application drew its foundation from ACT and incorporates insights from the self-affirmation theory and compassion meditation (HST) to address the challenges associated with excessive self-focused attention. ACT places a strong emphasis on encouraging individuals to experience and embrace their thoughts, emotions, and sensations without judgment. This is achieved through various processes, including cognitive deconvergence, mindfulness, and acceptance. More specifically, this intervention sought to guide users toward engaging in activities that revolve around understanding themselves better, fostering positive emotions, and connecting with related experiences. Simultaneously, it promoted "self-distancing" activities, preventing users from becoming overly immersed in events and experiences linked to negative emotions. Additionally, it offered a combination of self-talk techniques to facilitate a well-balanced transition towards effective self-focus. Previous research has suggested that self-talk can be understood through the lens of self-regulation theory[76]. It allows individuals to process information about themselves and can either maintain or shift their focus depending on the language and content of their self-talk [77,78,79]. Additionally, self-talk can simultaneously induce self-focused attention[80]. This process of self-talk has been found to be effective in shifting attention and providing relief from stress[81] and depression[77]. When combining self-talk with training based on self-affirmation theory ACT and HST, it appeared to have a synergistic effect in relieving anxiety and depression. However, it's worth noting that while inner communication through self-talk is closely tied to "self-awareness," it remains unclear whether individuals with high level of anxiety and depression can effectively and flexibly balance self-focused attention for various emotional experiences. To sum up, this study investigated the effects of a long-term training program aimed at helping individuals with high anxiety and depression develop better emotional self-management skills by using techniques that involved self-distancing, self-referencing and compassion meditation with their own voices. The study aimed to assess how this self-focused emotion regulation intervention impacts psychological flexibility, decreased anxiety and depression levels, influenced neuronal activation and plasticity when dealing with negative emotions, and promoted the generation of positive emotions through self-regulation of attention and emotions.

The primary goal of this study was to investigate the effectiveness of self-focused emotional regulation intervention in a novel mobile healthcare app in alleviating anxiety, and depression and promoting neuronal adaptability. While ACT, self-affirmation theory, and HST have been used as constructive cognitive approaches, there was a limited body of research on how these therapies impact neuronal adaptability, anxiety levels, depression level when combined with self-talk over extended periods. Consequently, this study intended to compare anxiety and depression levels between participants in the control group and those in the experiment group before and after they received the self-focused emotion regulation intervention. Additionally, changes in resting-state functional connectivity were assessed by analyzing functional magnetic resonance imaging (fMRI) data collected alongside psychometric assessments.

The fMRI analysis was conducted in two parts. Part 1 (analysis 1) focused on comparing resting-state functional connectivity before and after the intervention between the control and experiment groups, as previously mentioned. Part 2 (analysis 2) examined differences in resting-state functional connectivity in response to self-respect (positive emotion) and self-criticism (negative emotion) before and after the intervention, based on the participants' group assignment (control vs experiment).

This study hypothesized two key outcomes from the self-focused emotion regulation intervention. Since the intervention primarily employed three emotion regulation strategies—self-affirmation, ACT, and HST—based on participants' self-perceived emotions and supported by previous studies, it was expected that the fMRI experiment would reveal effects on brain networks, specifically the DMN, SN, and ECN, influenced by the mobile intervention. In Analysis 1, hypothesized that after the intervention, seed-based functional connectivity in resting-state brain networks (the DMN, SN, and ECN) would increase in the experimental group compared to the control group. Second, in Analysis 2, expected that the experimental group would show different seed-based functional connectivity after engaging in self-respect and self-criticism tasks post-intervention compared to the control group.

II. MATERIALS AND METHODS

1. Participants

A total of fifty-one participants aged between 20 and 39 recruited through online advertising. To identify individuals with high level of anxiety and depression, we initially screened them using the Hospital Anxiety and Depression Scale (HADS) questionnaire[82]. This questionnaire consists of 14 items, with each item scored on a scale from zero to three. HADS includes two subscales: anxiety (7 items, total score range: 0-21) and depression (7 items, total score range: 0-21). Based on the HADS severity criteria, a score above 8 on each subscale indicates a high level of anxiety or depression. In this experiment, participants with a subscale score exceeding 8 out of 21 were considered to exhibit significant symptoms of anxiety or depression. Exclusion criteria included pregnancy, current use of medication for neurological or any medical illness, severe cognitive impairment, and psychotic symptoms. Additionally, volunteers were screened for handedness to eliminate left-dominant individuals. Consequently, we recruited individuals who scored above 8 on both the anxiety and depression subscales as participants with high levels of anxiety and depression. From this pool, we randomly assigned 29 individuals to the Experiment group and 22 individuals to the control group accounting for potential dropouts. All participants gave informed written consent prior to partaking in the study and the study was approved by the Yonsei University Severance Hospital Institutional Review Board.

2. Self-Focused Emotion Intervention

Both of experiment and control group were consisted of participants with high level of anxiety and depression. The experiment group was required to use a mobile healthcare app with self-focused emotion regulation intervention for 12 weeks. In the control group, no treatment was administered during the 12-week intervention period and they were placed on a waiting list. Experiment group participants were instructed to download a mobile healthcare application from either the Google Play Store or the Apple App Store.

Participants in the experimental group were instructed to use the mobile application twice a day, once in the morning and once in the evening. A minimum of one session per day was required for the training session to be considered valid.

Following the principles of self-focused emotion regulation, the intervention tailored its approach accordingly. When entering the app, participants can choose one of three emotions (positive/neutral/negative) to reflect their current mood and proceed with the training. Participants chose their mood by clicking on one of three emojis displayed on the screen: a smiling face for a positive mood, a blank face for a neutral mood, or an angry face for a negative mood. When participants selected a positive mood, the intervention aimed to reinforce and amplify their strengths and emotions through self-affirmation talk (SAT) scripts. For those who chose a negative mood, the training session focused on helping participants view their negative thoughts and emotions as transient events, employing techniques from ACT[88] such as cognitive defusion and self-distancing. Lastly, when a neutral mood was selected, the intervention guided participants through compassion meditation, specifically using HST[51]. These differentiated approaches were designed to align with the participants' emotional states and promote effective emotion regulation.

The app provided a total of 44 ACT, 32 SAT, 30 HST reading scripts. These scripts were preloaded in a sequence within the app and were presented in order. Once all scripts were exhausted, the sequence restarted from the beginning. All scripts were standardized in length, ranging from 350 to 450 words. Although individual reading speeds varied, it generally took participants 2–3 minutes to read the provided scripts. During the training session, participants pressed the record button displayed at the center of the screen and read the script aloud. Once they finished reading, they clicked the stop button to end the recording. They then pressed the play button to listen to the playback. As a result, a session that involved both reading and listening to a script usually lasted an average of 4–6 minutes.

After completing one session, participants could either end their session or proceed with additional training. If participants wanted additional training, they were prompted to reassess their mood, selecting whether they felt better, the same, or worse compared to their pre-session mood. Based on this selection, the app dynamically adjusted the training content for the next session. When participants selected "better" those who had read the ACT (negative mood) script in the previous training session would proceed to the HST (neutral mood) script, participants who had read the HST script would advance to the SAT (positive mood) script, and those who had read the SAT script would repeat the SAT script. If the mood was reported as "the same" the app maintained consistency, assigning the same mood-based content as the previous session (e.g., ACT - ACT, HST - HST, SAT - SAT). Conversely, when participants selected "worse" those who had read the ACT script would read it again, participants who had read the HST script would move to the ACT script, and participants who had read the SAT script would transition to the HST script. There was no limit on the number of training sessions participants could complete in a single day.

3. Clinical Assessments

All participants were evaluated a battery of questionnaires for clinical factors including Beck Anxiety Inventory (BAI)[83] and Beck Depression Inventory (BDI)[84], both consisting of 21-item 4-point Likert scales ranging from 0 (not at all) to 3 (severely), to measure anxiety and depression levels, respectively. Clinical assessments were conducted twice: once before the intervention and after the intervention to measure changes in these psychological factors.

4. fMRI Design

A. Stimuli

Before the fMRI scanning, two 5-minutes audiovisual stimuli with participants' own voices were prepared. These stimuli were designed to encourage self-respect and self-criticism condition to assess the impact of using the mobile healthcare application over 12 weeks. For the reading scripts, 38 sentences focusing on self-respect and 40 sentences addressing self-criticism were created. Participants recorded their voices while reading these scripted texts prior to the fMRI session. Our recorded voice sounds different compared to our real voice because of the lack of bone conduction (vibrations through the skull)[85]. Therefore, a tone control step was performed for each dataset to reduce the heterogeneity of the recorded voice and to substitute for the bone conduction effect. Specifically, for a base voice frequency of 1,000 Hz, the high-frequency components were reduced by 2 dB, while the low-frequency components were amplified by 2 dB[86,87]. Lastly, these recordings were then combined with animated text to form the task stimulus. These materials were intended to help participants focus on their feelings of self-respect or self-criticism by guiding them to verbally express these sentiments internally.

B. Task

On the scanning, participants underwent five 5-min runs of the fMRI scanning in the following order: baseline resting-state, first audio-visual stimuli, second resting-state, second audio-visual stimuli, and third resting-state. First and second audio-visual stimuli were consisted of self-respect and self-criticism and the order of the self-respect and self-criticism stimuli was counterbalanced among participants. Participants fixed their gaze on the crosshair in the middle of the screen during the resting states. During the scanning, participants were immersed in the psychological stimuli according to the guidance of the audiovisual stimuli. Participants spent the 5 min focusing on a mental image of their strengths in the self-respect stimuli and their weaknesses in the self-criticism stimuli and no separate behavioral responses were collected. Throughout the tasks, participants were instructed to follow along with the script by listening to the narrated voice once, then recite it silently in their head during the resting state after the stimuli whereas their eyes were fixed on the crosshair in the middle of the screen **(figure 1)**.

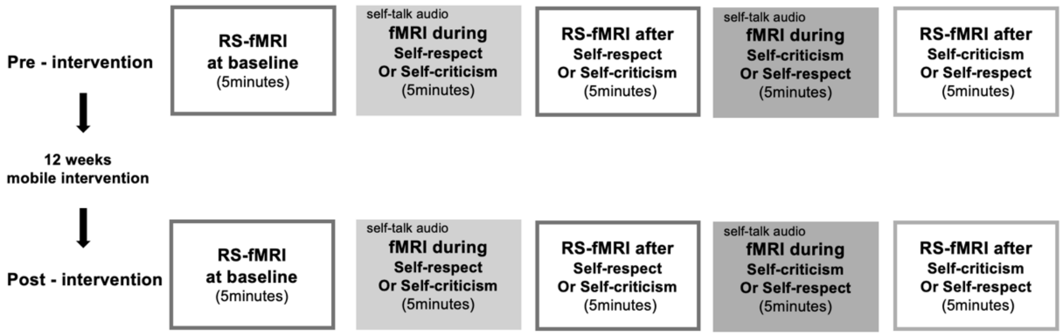

figure 1. fMRI task design.

5. fMRI Acquisition and Preprocessing

Images were to be acquired with a 3.0 Tesla MRI scanner (Ingena 3.0T CX, Philips Healthcare) with a 32-channel head coil. The fMRI imaging parameters were as follow: Gradient echo sequence by EPI (echoplanar imaging), echo time = 22 ms, TR = 2,000 ms, TE = 22 ms, field of view = 100 mm, flip angle = 90-degree, Number of acquisitions = 160, Number of slices = 31, slice thickness = 3 mm with four gaps, image matrix = 80 x 80.

T1-weighted images were also collected using a 3D spoiled gradient- recall sequence (echo time = 4.59 ms; repetition time = 9.85 ms; field of view = 100 mm; flip angle = 8; slice thickness = 1 mm with one gap; number of slices = 176; and matrix size = 224 × 224). Preprocessing steps were based on Statistical Parametric Mapping 12 (SPM12). The first 10 scans were discarded for magnetic field stabilization. The remaining 150 scans for each run were realigned to the first image and corrected for acquisition time differences among the slices. Then, individual anatomical images were co-registered to the mean fMRI image. Subsequently, the fMRI data were spatially normalized to the Montreal Neurological Institute (MNI) template space and smoothed with a 6-mm full-width at the half-maximum Gaussian kernel. The time series at each voxel was further processed to remove the effects from nuisance parameters.

6. Demographic and Clinical Data Analysis

To compare the difference in the means of the demographic and clinical variables between the groups and 12 weeks interventions, analysis of variance (ANOVA) and post hoc pair t-test was conducted. The statistical analyses were carried out on Jamovi.

7. Self-Focused Emotion Intervention Usage Analysis

To compare the differences in the means of the three self-focused emotion regulation strategies provided by the mobile application within the experimental group over the 12-week intervention, a one-way ANOVA followed by a post hoc t-test was conducted. Statistical analyses were performed using Jamovi.

8. Imaging Data Analysis -Seed-based Functional Connectivity

Based on the several previous studies about anxiety and the treatment for anxiety such as mindfulness, ACT and cognitive behavior therapy, three network; the DMN[67,89-96], SN[60,93-96] and ECN,[67,94-96] were selected in this experiment.

Seed-to-voxel analyses were conducted using 15 seeds for the DMN, SN, and ECN: 4 seeds for the DMN, 5 seeds for the SN, and 6 seeds for the ECN. Specifically, the ROIs selected for assessing functional connectivity modulation within the DMN included the left lateral parietal region (LP) (MNI coordinates: -39/-77/33), the right LP (MNI coordinates: 47/-67/23), and the bilateral PCC (MNI coordinates: 1/-61/38) from the CONN independent component analysis (ICA) network[97], as well as the bilateral PCUN (MNI coordinates: 5/19/24) based on the Harvard-Oxford Atlas sub-Cortical Structural Atlas[98].

For the SN, the selected ROIs included the bilateral ACC (MNI coordinates: 0/22/35), the left aINS (MNI coordinates: -44/13/1), the right aINS (MNI coordinates: 47/14/0), the left supramarginal gyrus (SMG) (MNI coordinates: -60/-39/31), and the right SMG (MNI coordinates: 62/-35/32), sourced from the CONN ICA network[97].

Lastly, for the ECN, the chosen ROIs included the left PFC (MNI coordinates: -43/33/28) and the right PFC (MNI coordinates: 41/38/30) from the CONN ICA network

(Whitfield-Gabrieli and Nieto-Castanon, 2012), as well as the left Thalamus (MNI coordinates: -10/-18/6), the right Thalamus (MNI coordinates: 10/-18/6), the left Caudate (MNI coordinates: -13/-9/10), and the right Caudate (MNI coordinates: 13/-9/10), based on the Harvard-Oxford Atlas sub-Cortical Structural Atlas[98].

In the first level analysis, the functional connectivity strengths between the time series of each ROI and the entire brain region were computed using Pearson's correlation analysis, and the values were converted to *z*-scores using the Fisher's *r*-to-*z* transformation. In the second level analysis, repeated-measures ANOVA were conducted to explore any significant differences in functional connectivity among groups, conditions, and interventions. Specifically in analysis 1, to focus on intervention-specific modulation of baseline resting state functional connectivity with respect to group, 2 (Group: Control and Experiment) x 2 (Time: pre and post intervention) ANOVA model was created to identify the interaction effect. In Analysis 2, the modulation of functional connectivity with respect to stimuli conditions and group differences was investigated to determine the effects of the mobile intervention. So first, among the target ROIs as mentioned above, paired t-test was conducted for self-respect and self-criticism stimuli condition in pre-intervention to find any significant difference between two conditions. Then, figured significant regional neural activity was extracted and considered to be the new ROIs for further analysis. In analysis 2-1, to focus intervention-specific modulation of functional connectivity with respect to group during the listening stimuli task, 2 (Group: Control and Experiment) x 2 (Time: pre and post intervention) ANOVA models was created to identify the interaction effect and the ROIs were set as the regions that showed significant neural activity in paired t-test for self-respect and self-criticism condition in pre-intervention. In analysis 2-2, to focus intervention-specific modulation of functional connectivity with respect to group after the listening stimuli task, 2 (Group: Control and Experiment) x 2 (Time: pre and post intervention) ANOVA models was created to identify the interaction effect, and the ROIs was same as analysis 2-1 **(figure 2)**. Significant functional connectivity was identified based on false discovery rate (FDR) $P_{FDR} < 0.05$ from clusters identified at a clusterforming threshold of $P < 0.001$. Then, for the main and interaction effects of interest, post-hoc analysis was conducted to determine the direction of differences between conditions.

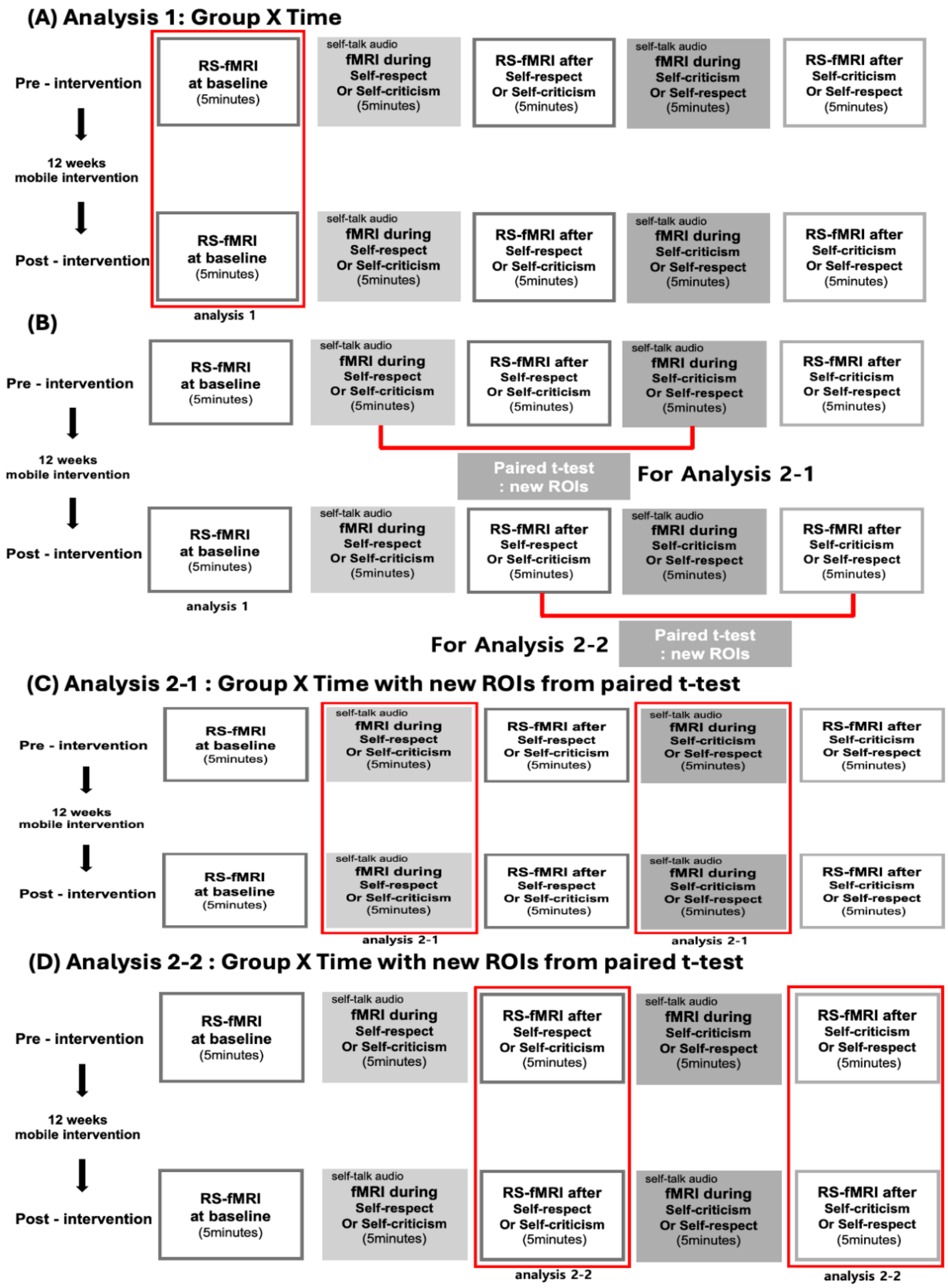
(A) Analysis 1: Group X Time
Pre - intervention
12 weeks mobile intervention
Post - intervention
RS-fMRI at baseline (5minutes)
self-talk audio
fMRI during Self-respect Or Self-criticism (5minutes)
RS-fMRI after Self-respect Or Self-criticism (5minutes)
fMRI during Self-criticism Or Self-respect (5minutes)
RS-fMRI after Self-criticism Or Self-respect (5minutes)
analysis 1
(B)
Paired t-test : new ROIs
For Analysis 2-1
For Analysis 2-2
(C) Analysis 2-1 : Group X Time with new ROIs from paired t-test
analysis 2-1
(D) Analysis 2-2 : Group X Time with new ROIs from paired t-test
analysis 2-2

figure 2. Illustration of MRI Task Design for analysis 1 and analysis 2. (A) illustrates Analysis 1, which aims to investigate the intervention-specific modulation of baseline resting-state functional connectivity. The analysis uses a 2x2 ANOVA model with factors Group (Control vs. Experimental) and Time (pre- and post-intervention). (B) explains the design for setting new targeted regions of interest (ROIs). for Analysis 2-1 and Analysis 2-2, which focused on the mobile intervention's modulation of functional connectivity in response to different stimuli conditions and groups. Paired t-tests were used to compare self-respect and self-criticism stimuli conditions from the pre-intervention phase to identify significant differences between the two conditions in the ROIs. (C) outlines Analysis 2-1, which examines the intervention-specific modulation of functional connectivity during the listening task. The analysis employs a 2x2 ANOVA model with factors Group (Control vs. Experimental) and Time (pre- and post-intervention), with the ROIs set as defined in (B). (D) illustrates Analysis 2-2, which focuses on the intervention-specific modulation of functional connectivity after the listening task. Like Analysis 2-1, it uses a 2x2 ANOVA model with factors Group (Control vs. Experimental) and Time (pre- and post-intervention), with ROIs defined in (B).

9. Correlation Analyses using Neuroimaging Data

To assess the relationship between changes in brain functional connectivity and improvements in clinical assessment scores for the experimental group, several analyses were conducted. In analysis 1, beta values for the pre- to post-mobile intervention resting-state functional connectivity were extracted. In analysis 2-1, beta values of brain functional connectivity during the listening of self-respect versus self-criticism stimuli were compared between pre- and post-intervention phases. ROIs were selected using paired t-tests for the self-respect and self-criticism conditions from the pre-intervention phase. Similarly, in analysis 2-2, beta values of functional connectivity following the exposure to self-respect versus self-criticism stimuli were analyzed, comparing pre- and post-intervention phases, with ROIs determined through paired t-tests for the respective conditions in the pre-intervention phase. The change in clinical assessments was calculated as [pre-intervention score - post-intervention score]. Subsequently, correlation analyses were conducted to assess the relationship between these connectivity changes and clinical assessment scores, including HADS-anxiety, HADS-depression, BAI, and BDI. The significance level was adjusted to $p = 0.0125$ (0.05/4) to account for the four scores used in correlation analyses.

III.RESULTS

1. Demographic and Baseline Clinical Information

Independent samples t-test were conducted to compare the demographic profile of the experiment and control group. Of the initial 51 participants, 6 were excluded from the analysis: 3 from the experimental group who did not meet the app usage criteria (defined as failing to use the app for more than 30 days or one-third of the 12-week period), and 3 from the control group who did not attend the second fMRI experiment. As a result, 45 participants were included in the final analysis, comprising 26 in the experimental group (mean age = 23.4 ± 2.7, male: 8, female: 18) and 19 in the control group (mean age = 24.5 ± 4.9, male: 5, female: 14) There was no significant difference between the mean age of the two groups (t_{44} = 0.7, p = 0.8). Moreover, independent sample t-test was conducted to compare the initial clinical measure of the experiment and control group. There was no significant difference in HADS-anxiety (t_{49} = 0.1, p = 0.9), HADS-depression (t_{49} = 0.2, p = 0.9), BDI (t_{49} = 0.6, p = 0.6) and BAI (t_{49} = 1.3, p = 0.2) between groups (**Table 1**).

Table 1. Demographic and clinical characteristics by groups

Variables	Experiment group (N = 26) Mean (SD)	Control group (N = 19) Mean (SD)	*t*	*p*
Demographics				
AGE	23.4 (2.7)	24.5 (4.9)	0.7	0.8
Clinical information				
HADS				
Anxiety	12.2 (3.4)	12.4 (3.6)	0.1	0.9
Depression	11.9 (3.0)	12 (3.7)	0.2	0.9
BAI	20.1 (8.6)	18.5 (10.5)	0.6	0.6
BDI	13.6 (7.2)	16.8 (10.3)	1.3	0.2

* Note. SD, Standard Deviation; HADS, Hospital Anxiety and Depression Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

2. Clinical Assessment

After the self-focused emotion intervention, both the experimental and control groups showed significant reductions in anxiety and depression scores. Specifically, the HADS-anxiety scores dropped to 5.4 ± 3.4 for the experimental group and 8.3 ± 2.8 for the control group. Similarly, BAI scores decreased to 10.8 ± 8.9 for the experimental group and 17.2 ± 6.9 for the control group. For depression, the HADS-depression scores fell to 5.1 ± 3.5 for the experimental group and 8.0 ± 4.0 for the control group, while BDI scores reduced to 6.9 ± 7.1 and 11.1 ± 6.5, respectively. To compare any significant difference of clinical variables between the groups and 12 weeks interventions, ANOVA and post hoc paired t-test were conducted. For anxiety, the HADS-anxiety scores presented main effect of group ($F_{1,43}$ = 4.59, p = 0.035), main effect of intervention ($F_{1,43}$ = 62.36, p < 0.001) but no interaction effect ($F_{1,43}$ = 3.86, p = 0.052) and the BAI scores presented main effect of intervention ($F_{1,43}$ = 8.41, p = 0.005), interaction effect ($F_{1,43}$ = 4.71, p = 0.033) but no main effect of group ($F_{1,42}$ = 1.70, p = 0.196). The post-hoc test revealed that the HADS-anxiety scores for both the experimental and control groups were significantly reduced after the intervention compared to their scores before the intervention (t_{43} = 7.68, p < 0.001 and t_{43} = 3.92, p = 0.001, respectively). Additionally, the post-hoc test revealed that BAI scores of experiment group was significantly reduced after the intervention compared to their scores before the intervention (t_{43} = 3.88, p = 0.001). For depression, the HADS-depression scores presented main effect of group ($F_{1,43}$ = 4.41, p = 0.039), main effect of intervention ($F_{1,43}$ = 54.52, p < 0.001) but no interaction effect ($F_{1,43}$ = 3.42, p = 0.068) and the BDI scores presented main effect of group ($F_{1,43}$ = 5.19, p = 0.025), main effect of intervention ($F_{1,43}$ = 14.46, p < 0.001) but no interaction effect ($F_{1,43}$ = 0.08, p = 0.771). The post-hoc test revealed that HADS-depression scores for both the experimental and control groups were significantly reduced after the intervention compared to their scores before the intervention (t_{43} = 7.07, p < 0.001 and t_{43} = 3.66, p = 0.003, respectively). In addition, like BAI, BDI scores of experiment group was significantly reduced after the intervention compared to their scores before the intervention (t_{43} = 3.13, p = 0.014) **(Figure 3)**.

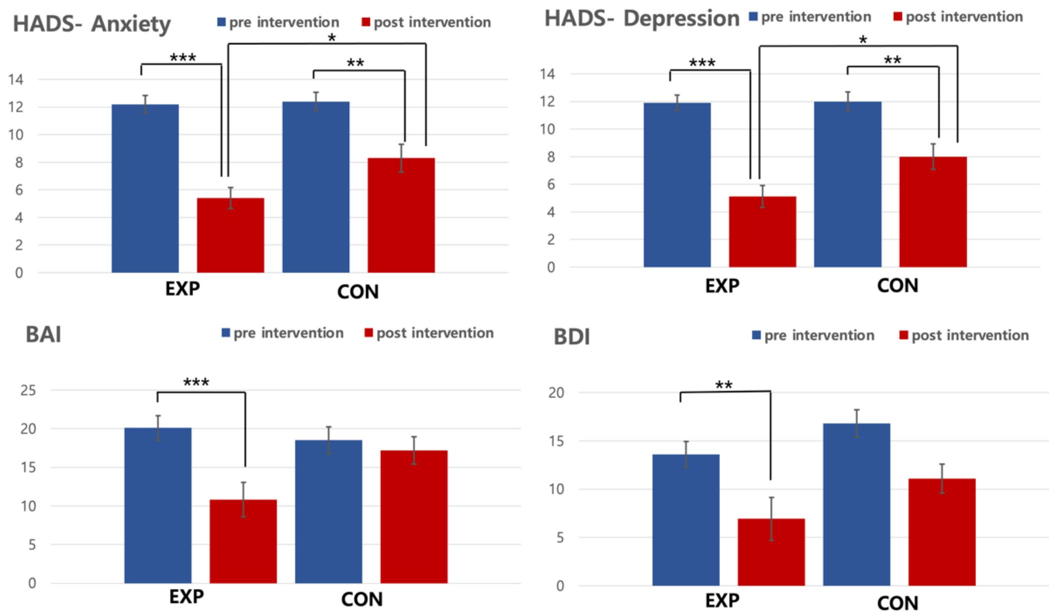

Figure 3. The summary of clinical assessment results. * Note. EXP, Experiment; CON, Control; HADS, Hospital Anxiety and Depression Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory. p < 0.05, **p < 0.01, ***p < 0.001.

3. Self-Focused Emotion Intervention Usage

On average, 29 participants in the experimental group used 124 ± 51 app interventions over 12 weeks. Of these, 65.2 ± 42.7 times they used the self-affirmation treatment with a positive mood choice, 37.84 ± 24.6 times they used the HST treatment with a neutral mood choice, and 20.8 ± 22.5 times they used the ACT treatment with a negative mood choice. To compare any significant difference among three intervention strategies, one-way ANOVA was conducted. The result presented that there was significant mean difference among the usage of self-focused motion regulation strategies ($F_{2,52.3} = 11.9$, $p < 0.001$). The post-hoc t-test revealed that the mean usage of self-affirmation talk was significantly higher than ACT ($t_{83} = 5.20$, $p < 0.001$) and HST ($t_{83} = 3.14$, $p = 0.007$). However, there was no significant usage difference between ACT and HST ($t_{83} = -2.08$, $p = 0.101$) **(Figure 4)**.

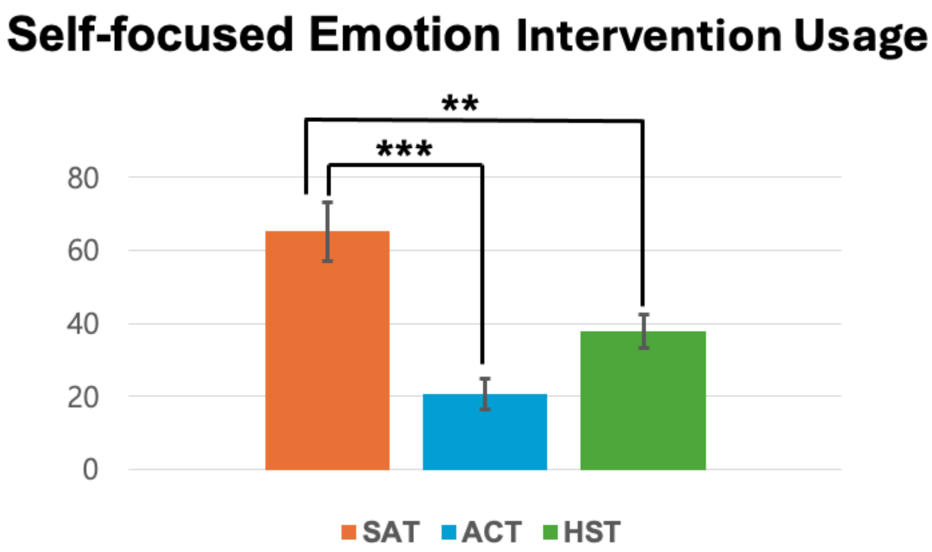

Figure 4. The summary self-focused emotion intervention usage results. * Note. SAT, Self-affirmation talk; ACT, Acceptance and commitment therapy; HST, Hear-smile trainig. p < 0.05, **p < 0.01, ***p < 0.001.

4. Neuroimaging Results

A. Analysis 1

(A) Main Effect (group/ time)

As shown in **Table 2** and **Table 3**, significant main effect of group and time were yielded through seed-based functional connectivity analysis. Regarding the group effect, relative to the control group, bilateral ACC seed-based functional connectivity in the experiment group was significantly increased with the INS. On the other hand, left PFC seed-based functional connectivity with the right paracingulate cortex (Pacig) of control group was significantly increased compared to experiment group (**Table 2**). Main effect of time was found in bilateral ACC seed-based functional connectivity with the right lateral occipital cortex (LOC), left Pacig and left putamen; left thalamus seed-based functional connectivity with the left caudate; right thalamus seed-based functional connectivity with the right intracalcarine cortex (ICC) and left caudate seed-based functional connectivity with the left thalamus. Post-hoc tests confirmed that most of this connectivity were significantly increased in the post-intervention compared to pre-intervention except bilateral ACC seed-based functional connectivity with the left Pacig (**Table 3**).

Table 2. Brain regions showing main effect of group (analysis 1)

Network	Seed	Target	MNI Coordinate (x y z)			Nvox	t	Direction
Main effect of group								
DMN	L.LP	No sig. reg.						
	R.LP	No sig. reg.						
	B.PCC	L.INS	-36	20	4	38	6.40	EXP> CON
	B.PCUN	No sig. reg.						
SN	B.ACC	No sig. reg.						
	L.aINS	No sig. reg.						
	R.aINS	No sig. reg.						
	L.SMG	No sig. reg.						
	R.SMG	No sig. reg.						
ECN	L.PFC	R.Pacig	2	48	10	23	-4.96	EXP<CON
	R.PFC	No sig. reg.						
	L.Thalamus	No sig. reg.						
	R.Thalamus	No sig. reg.						
	L.Caudate	No sig. reg.						
	R.Caudate	No sig. reg.						

Abbreviation: MNI, Montreal Neurological Institute; Nvox, number of voxels; t, post-hoc t score of the peak voxel; DMN, Default mode network; SN, salience network; ECN, executive control network; L., left; R., right; B., bilateral; LP, lateral parietal region; PCC, posterior cingulate cortex; PCUN, precuneus; ACC, anterior cingulate cortex; aINS, anterior insula; SMG, supramarginal gyrus; PFC, prefrontal cortex; Pacig, paracingulare gyrus.

Table 3. Brain regions showing main effect of time (analysis 1)

Network	Seed	Target	MNI Coordinate (x y z)			Nvox	t	Direction
Main effect of time								
DMN	L.LP	No sig. reg.						
	R.LP	No sig. reg.						
	B.PCC	No sig. reg.						
	B.PCUN	No sig. reg.						
SN	B.ACC	R.LOC	40	-74	16	27	5.06	PRE>POST
		L.Pacig	-8	36	-4	25	-5.86	PRE<POST
		L.Putamen	-16	14	2	20	-5.15	PRE<POST
	L.aINS	No sig. reg.						
	R.aINS	No sig. reg.						
	L.SMG	No sig. reg.						
	R.SMG	No sig. reg.						
ECN	L.PFC	R.midFG	30	12	64	19	-4.86	PRE<POST
	R.PFC	No sig. reg.						
	L.Thalamus	L.Caudate	-16	18	0	21	-5.69	PRE<POST
	R.Thalamus	R.ICC	12	-68	10	25	-4.85	PRE<POST
	L.Caudate	L.Thalamus	-6	-10	6	30	-6.04	PRE<POST
	R.Caudate	No sig. reg.						

Abbreviation: MNI, Montreal Neurological Institute; Nvox, number of voxels; t, post-hoc t score of the peak voxel; DMN, Default mode network; SN, salience network; ECN, executive control network; L., left; R., right; B., bilateral; LP, lateral parietal region; PCC, posterior cingulate cortex; PCUN, precuneus; ACC, anterior cingulate cortex; aINS, anterior insula; SMG, supramarginal gyrus; PFC, prefrontal cortex; LOC, lateral occipital cortex; Pacig, paracingulate gyrus midFG, middle frontal gyrus.; ICC, intracalcarine cortex.

(B) Interaction effect

The significant group × intervention interaction effect was seen in bilateral PCC seed–based functional connectivity with the right superior frontal gyrus (SFG), bilateral PCUN seed–based functional connectivity with the right SFG, bilateral ACC seed–based functional connectivity with the right supracalcarine cortex (SCC), bilateral ACC seed–based functional connectivity with the bilateral PCUN, bilateral ACC seed–based functional connectivity with the right midFG, right aINS seed–based functional connectivity with the bilateral PCC and left SMG seed–based functional connectivity with the bilateral PCC (**Table 4**). The results from a post-hoc analysis on this functional connectivity values to characterize the interactions were shown in **Figure 5.**

Table 4. Brain regions showing the interaction effects of group x time (analysis 1)

Network	Seed	Target	MNI Coordinate (x y z)			Nvox	F
Group x Time Interaction							
DMN	L.LP	No sig. reg.					
	R.LP	No sig. reg.					
	B.PCC	R.SFG	22	-8	70	26	33.23
	B.PCUN	R.SFG	22	-8	70	24	29.70
SN	B.ACC	R.SCC	0	-76	14	42	26.89
		L.PCUN	-4	-74	40	17	17.88
		R.PCUN	6	-76	36	18	22.48
		R.midFG	40	14	58	26	18.77
	L.aINS	No sig. reg.					
	R.aINS	B.PCC	0	-30	46	18	17.36
	L.SMG	R.PCC	4	-42	44	20	12.05
	R.SMG	No sig. reg.					
ECN	L.PFC	No sig. reg.					
	R.PFC	No sig. reg.					
	L.Thalamus	No sig. reg.					
	R.Thalamus	No sig. reg.					
	L.Caudate	No sig. reg.					
	R.Caudate	No sig. reg.					

Abbreviation: MNI, Montreal Neurological Institute; Nvox, number of voxels; F, F score of the peak voxel; DMN, Default mode network; SN, salience network; ECN, executive control network; L., left; R., right; B., bilateral; LP, lateral parietal region; PCC, posterior cingulate cortex; PCUN, precuneus; ACC, anterior cingulate cortex; aINS, anterior insula; SMG, supramarginal gyrus; PFC, prefrontal cortex; SFG, superior frontal gyrus; SCC, supracarcaline cortex midFG, middle frontal gyrus.

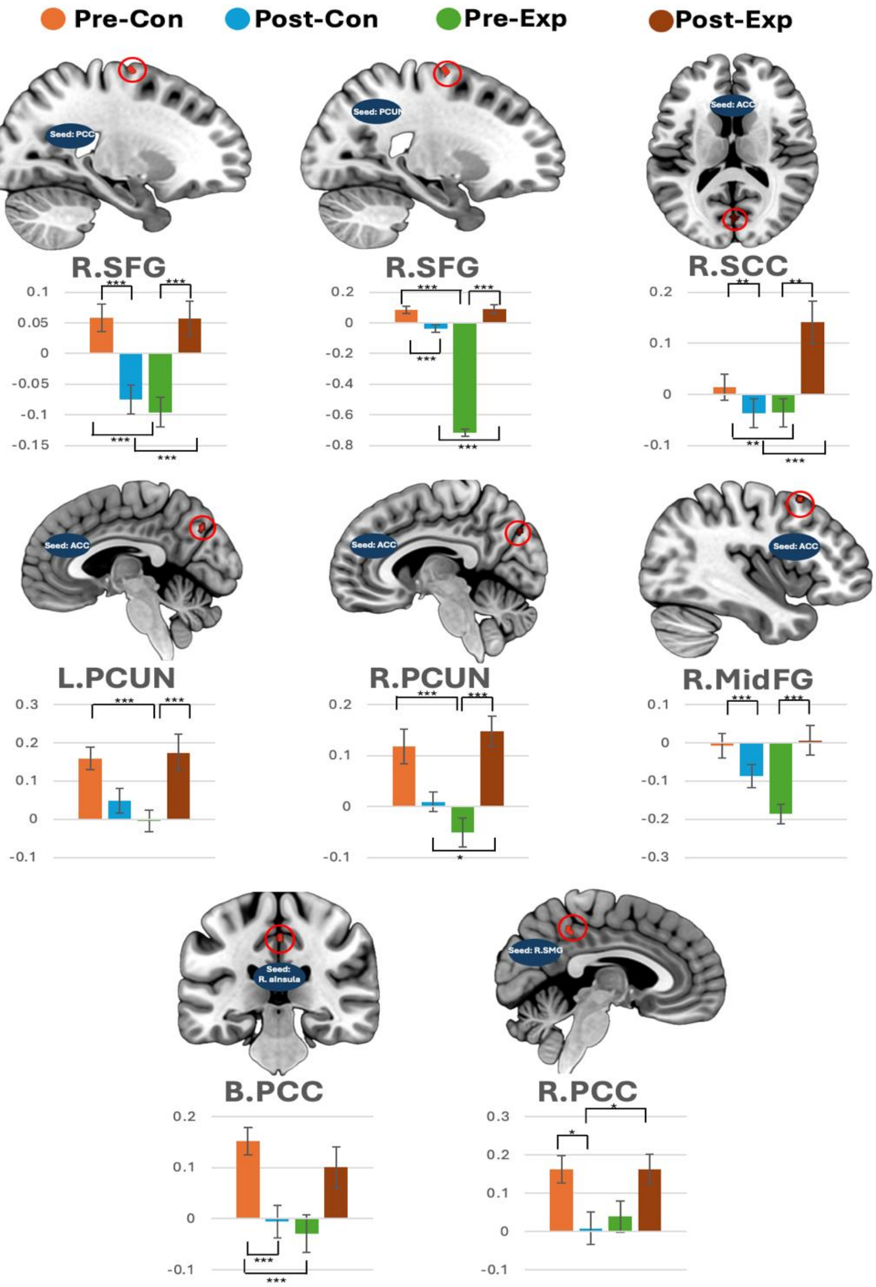

Figure 5. post-hoc results of group × time interaction effect (analysis 1). Abbreviation. Pre-Con, pre- intervention and control group; Post-Con, post- intervention and control group; Pre-Exp, pre-intervention and experiment group; Post-Exp, post- intervention and experiment group. L., left; R., right; B., bilateral; SFG, superior frontal gyrus; SCC, supracarcaline cortex; PCUN, precuneus; midFG, middle frontal gyrus; PCC, posterior cingulate cortex. $p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

(C) Correlations between Neural Activity and Clinical Assessments

Among the seven functional connectivity changes showing a significant group × time interaction effect, only the change in connectivity strength between the ACC seed and the right SCC was significantly correlated with changes in HADS-depression scores in the experimental group. Specifically, the beta value for pre- and post-resting state functional connectivity of the ACC seed-based the right SCC was positively correlated with the HADS-depression score change (r = 0.54, p = 0.004). However, this correlation was not observed in the control group (r = 0.02, p = 0.948) (**Figure 6**).

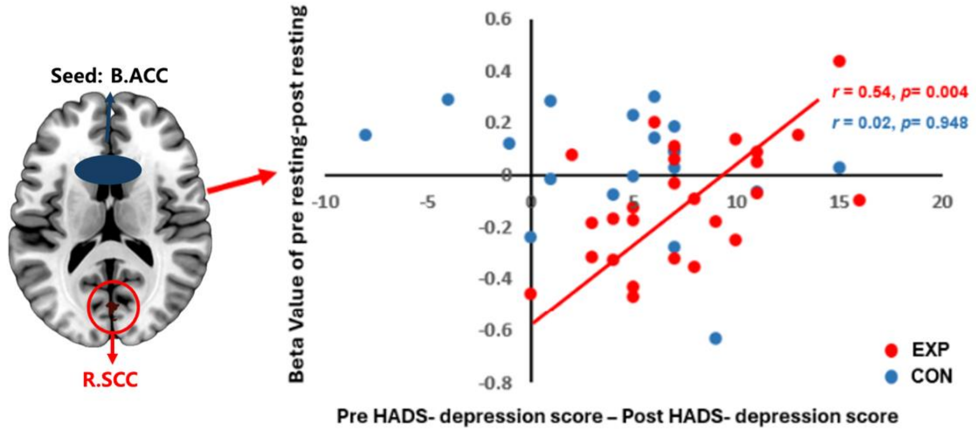

Figure 6. Significant correlations between brain regions and clinical assessment (analysis 1) * Note. B.,bilateral; R.,right; EXP, experiment; CON, control; HADS, Hospital Anxiety and Depression Scale. ACC,anterior cingulate cortex; SCC, supracalcarine cortex.

B. Analysis 2-1

(A) Interaction effect

The result of paired t-test on self-respect and self-criticism conditions at pre-intervention during listening task was as below (**Table 5**). In the SN, right aINS seed-based functional connectivity with the right lateral occipital cortex and cerebellum showed significantly increased activity during listening self-criticism, otherwise right aINS seed-based functional connectivity with the bilateral mPFC showed significantly increased activity during listening self-respect. In the ECN, right thalamus seed-based functional connectivity with the cerebellum connectivity and right caudate seed-based functional connectivity with the right occipital pole showed significantly increased activity during listening self-criticism but right thalamus seed-based functional connectivity with the right inferior frontal gyrus (IFG) showed significantly increased activity during listening self-respect. This seed was used as the new target ROIs to identify any significant group × time interaction effects in these ROIs, but no significant interaction effects were found (**Table 6**).

Table 5. Brain regions showing the result of paired t-test on self-respect and self-criticism conditions at pre-intervention during listening task

Network	Seed	Target	MNI Coordinate (x y z)			Nvox	t	Direction
Main effect of condition (paired- t test)								
DMN	L.LP	No sig. reg.						
	R.LP	No sig. reg.						
	B.PCC	No sig. reg.						
	B.PCUN	No sig. reg.						
SN	B.ACC	No sig. reg.						
	L.aINS	No sig. reg.						
	R.aINS	R.LOC	26	-72	30	336	-5.5	Respect < Criticism
		R.LOC	14	-80	46	127	4.5	Respect < Criticism
		R.mPFC	10	42	-20	273	-5.6	Respect > Criticism
		R.Cerebellum	42	-48	-46	149	-4.7	Respect < Criticism
	L.SMG	No sig. reg.						
	R.SMG	No sig. reg.						
ECN	L.PFC	No sig. reg.						
	R.PFC	No sig. reg.						
	L.Thalamus	No sig. reg.						
	R.Thalamus	L.Cerebellum	-42	-56	-40	284	-5.3	Respect < Criticism
		R.IFG	54	20	20	173	5	Respect > Criticism
	L.Caudate	No sig. reg.						
	R.Caudate	R.Occipital pole	18	-78	2	415	-5.4	Respect < Criticism

Abbreviation: MNI, Montreal Neurological Institute; Nvox, number of voxels; t, t score of the peak voxel; DMN, Default mode network; SN, salience network; ECN, executive control network; L., left; R., right; B., bilateral; LP, lateral parietal region; PCC, posterior cingulate cortex; PCUN, precuneus; ACC, anterior cingulate cortex; aINS, anterior insula; SMG, supramarginal gyrus; PFC, prefrontal cortex; LOC, lateral occipital cortex; mPFC, medial prefrontal cortex; IFG, inferior frontal gyrus.

Table 6. Brain regions showing the result of group × time interaction effect in the new targeted ROIs

Network	Seed	Target	MNI Coordinate (x y z)	Nvox	F	p
group × time interaction effect						
DMN	L.LP	No sig. reg.				
	R.LP	No sig. reg.				
	B.PCC	No sig. reg.				
	B.PCUN	No sig. reg.				
SN	B.ACC	No sig. reg.				
	L.aINS	No sig. reg.				
	R.aINS	R.LOC	26 -72 30	336	0.56	0.45
		R.LOC	14 -80 46	127	1.48	0.23
		R.mPFC	10 42 -20	273	0.48	0.49
		R.Cerebellum	42 -48 -46	149	0.02	0.90
	L.SMG	No sig. reg.				
	R.SMG	No sig. reg.				
ECN	L.PFC	No sig. reg.				
	R.PFC	No sig. reg.				
	L.Thalamus	No sig. reg.				
	R.Thalamus	L.Cerebellum	-42 -56 -40	284	1.32	0.25
		R.IFG	54 20 20	173	0.54	0.47
	L.Caudate	No sig. reg.				
	R.Caudate	R.Occipital pole	18 -78 2	415	0.51	0.48

Abbreviation: MNI, Montreal Neurological Institute; Nvox, number of voxels; t, t score of the peak voxel; DMN, Default mode network; SN, salience network; ECN, executive control network; L., left; R., right; B., bilateral; LP, lateral parietal region; PCC, posterior cingulate cortex; PCUN, precuneus; ACC, anterior cingulate cortex; aINS, anterior insula; SMG, supramarginal gyrus; PFC, prefrontal cortex; LOC, lateral occipital cortex; mPFC, Medial prefrontal cortex; IFG, Inferior frontal gyrus.

C. Analysis 2-2

(A) Interaction effect

The result of paired samples t-test on self-respect and self-criticism conditions at pre-intervention after listening task was as below (**Table 7**). In the SN, left SMG seed-based functional connectivity with the right superior temporal gyrus (STG) and right posterior superior temporal gyrus (pSTG) showed significantly increased activity during listening self-criticism, otherwise SMG seed-based functional connectivity with the bilateral mPFC showed significantly increased activity during listening self-respect. In the ECN, left caudate seed-based functional connectivity with the left frontal pole (FP) showed significantly increased activity during listening self-criticism. The seed was used as the new target ROIs, as in Analysis 2-1, and an attempt was made to identify any significant group × time interaction effects in these ROIs. The significant group × intervention interaction effect was seen in left SMG seed-based functional connectivity with the right pSTG (**Table 8**). The results from a post-hoc analysis on this functional connectivity values to characterize the interactions were shown in **Figure 7**.

Table 7. Brain regions showing the result of paired t-test on self-respect and self-criticism conditions at pre-intervention after listening task

Network	Seed	Target	MNI Coordinate (x y z)			Nvox	t	Direction
Main effect of condition (paired- t test)								
DMN	L.LP	No sig. reg.						
	R.LP	No sig. reg.						
	B.PCC	No sig. reg.						
	B.PCUN	No sig. reg.						
SN	B.ACC	No sig. reg.						
	L.aINS	No sig. reg.						
	R.aINS	No sig. reg.						
	L.SMG	R.STG	26	42	4	17	-5.7	Respect < Criticism
		R.pSTG	50	-30	2	15	-5.3	Respect < Criticism
		L.FP	-32	40	-10	15	4.8	Respect > Criticism
	R.SMG	No sig. reg.						
ECN	L.PFC	No sig. reg.						
	R.PFC	No sig. reg.						
	L.Thalamus	No sig. reg.						
	R.Thalamus	No sig. reg.						
	L.Caudate	L.FP	-32	-40	-2	22	4.3	Respect > Criticism
	R.Caudate	No sig. reg.						

Abbreviation: MNI, Montreal Neurological Institute; Nvox, number of voxels; t, t score of the peak voxel; DMN, Default mode network; SN, salience network; ECN, executive control network; L., left; R., right; B., bilateral; LP, lateral parietal region; PCC, posterior cingulate cortex; PCUN, precuneus; ACC, anterior cingulate cortex; aINS, anterior insula; SMG, supramarginal gyrus; PFC, prefrontal cortex; STG, superior temporal gyrus; pSTG, posterior superior temporal gyrus; FP, frontal pole.

Table 8. Brain regions showing the result of group × time interaction effect in the new targeted ROIs

Network	Seed	Target	MNI Coordinate (x y z)			Nvox	F	p
group × time interaction effect								
DMN	L.LP	No sig. reg.						
	R.LP	No sig. reg.						
	B.PCC	No sig. reg.						
	B.PCUN	No sig. reg.						
SN	B.ACC	No sig. reg.						
	L.aINS	No sig. reg.						
	R.aINS	No sig. reg.						
		R.STG	26	42	4	17	0.51	0.47
	L.SMG	R.pSTG	50	-30	2	15	9.73	0.002
		L.FP	-32	40	-10	15	0.62	0.43
	R.SMG	No sig. reg.						
ECN	L.PFC	No sig. reg.						
	R.PFC	No sig. reg.						
	L.Thalamus	No sig. reg.						
	R.Thalamus	No sig. reg.						
	L.Caudate	L.FP	-32	-40	-2	22	0.38	0.54
	R.Caudate	No sig. reg.						

Abbreviation: MNI, Montreal Neurological Institute; Nvox, number of voxels; t, t score of the peak voxel; DMN, Default mode network; SN, salience network; ECN, executive control network; L., left; R., right; B., bilateral; LP, lateral parietal region; PCC, posterior cingulate cortex; PCUN, precuneus; ACC, anterior cingulate cortex; aINS, anterior insula; SMG, supramarginal gyrus; PFC, prefrontal cortex; STG, superior temporal gyrus; pSTG, posterior superior temporal gyrus; FP, frontal pole.

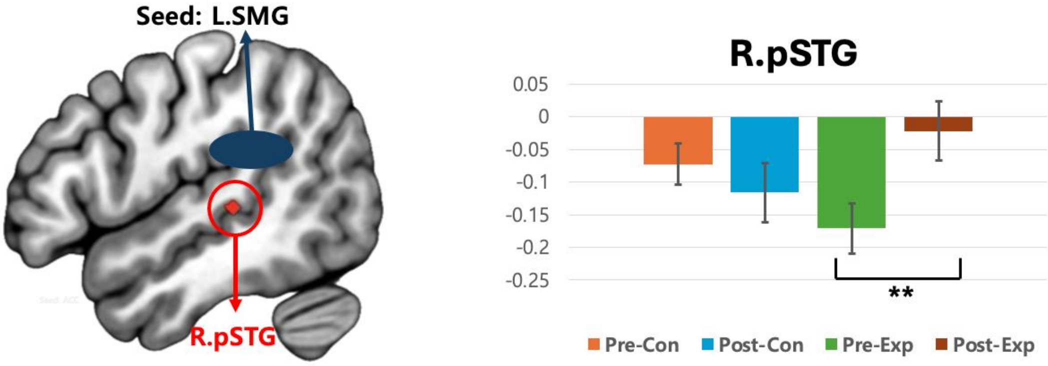

Figure 7. post-hoc results of group × time interaction effect (analysis 2-2)**.** Abbreviation. Pre-Con, pre- intervention and control group; Post-Con, post- intervention and control group; Pre-Exp, pre-intervention and experiment group; Post-Exp, post- intervention and experiment group; L., left; R., right; SMG, supramarginal gyrus; pSTG, posterior superior temporal gyrus. p < 0.05, **p < 0.01, ***p < 0.001.

(B) Correlations Between Neural Activity and Clinical Assessments

Since significant group × intervention interaction effect for left SMG seed-based functional connectivity with the right pSTG was found, correlation analysis with four clinical assessments were conducted. After applying a significance threshold of $p = 0.0125$ (0.05/4), no significant correlations with clinical variables were identified. However, in the experimental group, a negative correlation trend with the change in BDI scores ($r = -0.4$, $p = 0.032$) were found, in the difference in beta values of stimuli conditions pre- and post-intervention for left SMG seed-based functional connectivity with the right pSTG. This trend was not observed in the control group ($r = -0.004$, $p = 0.869$) (see figure 7).

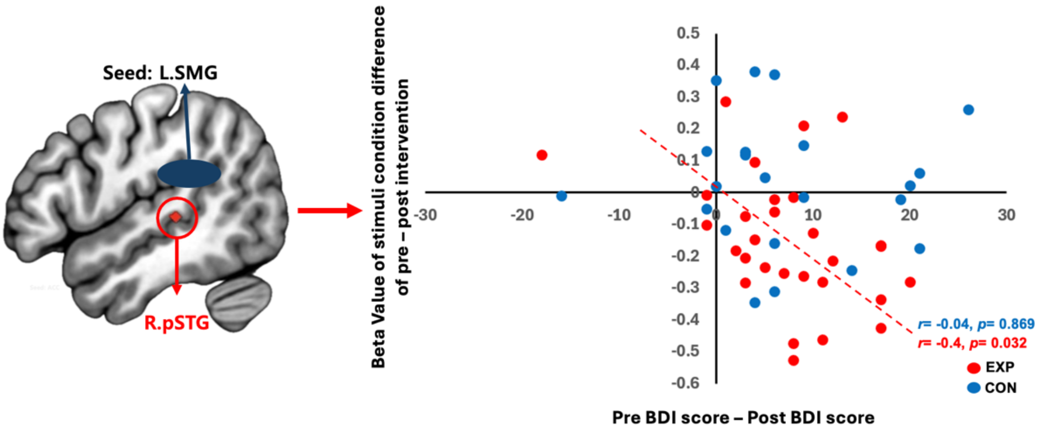

Figure 8. the result of correlations between brain regions and clinical assessment (analysis 2-2) * Note. L.,left; R.,right; EXP, experiment; CON, control; BDI, Beck Depression Inventory; SMG,supramarginal gyrus; pSTG, posterior superior temporal gyrus.

IV.DISCUSSION

The main objective of this study was to investigate how a self-focused emotion regulation intervention using self-distancing (ACT), self-referencing (SAT) and compassion meditation techniques (HST) in a novel mobile healthcare application helped individuals with high level of anxiety and depression improve their emotional self-management. Specifically, the study assessed how this intervention reduced anxiety and depression levels, influenced brain activation and plasticity when processing negative emotions, and enhanced the generation of positive emotions through better control of attention and emotions. In Analysis 1, changes in neuronal functional connectivity in the resting-state brain were specifically examined after the intervention. In Analysis 2, it was examined whether significant differences existed in how the experimental group processed emotional stimuli by analyzing changes in brain connectivity after the intervention.

1. Clinical Assessment

When considering the HADS-Depression and BDI scores, which measure participants' levels of depression, there was no significant interaction effect between group and time. This indicated that there was no significant reduction in depression levels in the experimental group compared to the control group. However, both the experimental and control groups exhibited significant reductions in depression levels after the intervention. Interestingly, the experimental group showed a somewhat larger decrease in depression, though this difference was not statistically significant. When examining BAI scores, a significant interaction effect between group and time was found, indicating that the experimental group experienced a significantly greater reduction in anxiety levels compared to the control group after the mobile healthcare intervention. This suggests that the app played a pivotal role in improving emotional well-being, particularly by helping participants reduce their anxiety, through its structured approach to emotion management. However, as no significant interaction effects were observed for the HADS-Depression, HADS-Anxiety, and BDI scores, it is important to consider external factors and participant characteristics. Most of participants were in their 20s and college students. During the period before and after the intervention, several external factors, such as college vacation and the easing of out-of-home restrictions due to COVID-19, may have created a generally less stressful environment, contributing to the reductions in both groups. Additionally, since participants were not individuals diagnosed with anxiety and depression disorders but healthy individuals with high levels of anxiety and depression, it could not be confirmed that these results would be the same for actual patients. In fact, a follow-up study with individuals diagnosed with anxiety disorders found a significant difference in anxiety and depression levels between the experimental and control groups after using the app. These findings underscored the need for future studies to control for environmental variables to better isolate the true impact of the intervention. Further research is necessary to investigate the differential effects of the intervention on these emotional states.

2. Interaction Effect of Group × Intervention (analysis 1)

This study employed self-focused emotion regulation strategies, such as ACT, SAT and HST utilizing participants' own voices to enhance self-awareness and emotional regulation. A significant group × intervention interaction effect revealed changes in brain networks, including the DMN and SN, though no effects were found in the ECN. Specifically, in the DMN, bilateral PCC seed-based functional connectivity with the right SFG was increased, as well as bilateral PCUN seed-based functional connectivity with the right SFG in the experimental group after the intervention.

Post-hoc analysis showed a significant increase in connectivity between these regions, which play crucial roles in self-referential processing[99,100] and internally directed cognition[101,102]. The PCC is known for its involvement in the DMN[84], particularly in autobiographical memory retrieval [103,104] and attention regulation[105], while the PCUN is linked to episodic memory and self-referential thought[106]. Additionally, the SFG is implicated in cognition and attention[107], with its medial section being a key component of the DMN[94,95]. Taken together, the study's findings suggested that after the mobile intervention, the experimental group showed enhanced the DMN activation during rest compared to the control group, indicating improvements in attention control and self-referential processing.

Increased functional connectivity was observed between the bilateral ACC of the SN and several regions, including the right SCC, bilateral PCC, and right midFG, solely in the experimental group. The SN is not only recognized for its crucial role in detecting the relevance of stimuli from both internal (emotions) and external (sensory information) sources[108] and guiding behavior[109] but also for its role in switching between other brain networks, such as the DMN for introspective tasks and the ECN for goal-directed activities[92]. The SN consists primarily of two regions: the aINS and ACC. The aINS is involved in interoception[110], while the ACC is understood to be a critical part of an attentional circuit that modulates both emotional and cognitive responses[111]. Additionally, higher levels of emotional awareness are correlated with the greater ACC involvement during emotional arousal[112]. Moreover, the midFG, known as the medial frontal cortex, which consist of ECN also plays a pivotal role in emotion regulation[113,114] and theory of mind[115,116] contributing significantly to emotional and social functioning. The MFG is involved in modulating emotional responses by facilitating cognitive strategies, such as reappraisal[117,118], which allows individuals to reinterpret emotional situations to reduce their impact. Regarding theory of mind, the MFG helps individuals navigate complex social interactions by interpreting social cues and predicting others' behaviors[115,116]. Through these functions, the MFG not only supports self-regulation of emotions but also fosters empathy and enhances social understanding. Based on this information, the results can be interpreted as showing that the self-focused emotion intervention effectively enhanced participants' self-awareness, attention control, and emotional regulation and social functioning by modulating key brain networks involved in these processes. This aligns with prior research, which linked improved self-awareness to increased connectivity between the DMN and SN[44].

However, there were no significant functional connectivity changes observed in the

ECN, specifically in the limbic system (e.g., thalamus and caudate) with any ROI. This could be attributed to the fMRI protocol used in Analysis 1. The limbic system plays a critical role in emotional responses such as emotion dysregulation and hypersensitivity[119,120]. For instance, the thalamus is integral to emotion processing by integrating sensory information[121] and relaying it to the amygdala and prefrontal cortex[122], which are crucial for evaluating emotional stimuli and generating appropriate responses. Additionally, the head of the caudate nucleus contains several neuronal clusters functionally connected to cortical areas involved in both cognitive and emotional processing[123,124]. Thus, the limbic system in the ECN is involved in emotion regulation and cognitive functions by integrating external events that trigger emotional responses and sending them to the prefrontal cortex. However, the fMRI protocol used did not provide sensory input to elicit emotional responses during the resting state, as participants only focused on the crosshair in the middle of the screen for five minutes. As a result, this protocol may have made it difficult to observe any significant changes in functional connectivity. It is possible that functional changes in the limbic system could be observed in Analysis 2.

3. Correlation with clinical factors (analysis 1)

There was a significant positive correlation between the beta value for pre- and post-resting state functional connectivity of ACC seed-based the SCC and the change in HADS-depression scores in the experiment group. This indicates that, in the experiment group, individuals who showed increased SN activity after the self-focused emotion intervention also experienced a greater reduction in their HADS-depression scores. This finding makes sense because the ACC is known to be involved in emotional arousal. Moreover, higher levels of emotional awareness are associated with the greater ACC involvement during emotional arousal, suggesting that this brain region plays a role in the conscious processing of emotions, attention to emotional signals, and response selection[112]. Therefore, as expected, after the intervention—which helps people regulate their emotions—participants who reported a decrease in their depression levels also showed increased activity in ACC seed-based functional connectivity with the SCC. In summary, our self-focused emotion intervention effectively facilitated emotional regulation by reducing participants' depression levels.

4. Interaction Effect of Group × Intervention (analysis 2)

One of the main goals of this study is to determine the differences in seed-based brain functional connectivity between groups after engaging in self-respect and self-criticism tasks post-intervention. To address this, a significant group × intervention interaction effect was found using new target ROIs extracted from the paired t-test conducted for self-respect and self-criticism stimuli conditions at pre-intervention. This revealed changes in brain networks within the SN, specifically involving left SMG seed-based the right posterior STG connectivity. Post-hoc analysis showed that, before the mobile intervention, this connectivity was significantly higher during the self-criticism condition compared to the self-respect condition. However, after the intervention, this difference was significantly reduced only in the experimental group. Given that the supramarginal gyrus is involved in empathy and understanding others' emotions[125], it helps regulate appropriate emotional responses by distinguishing between one's own emotions and those of others. Additionally, the STG plays a key role in theory of mind—the ability to understand and infer the emotions and thoughts of others, which is crucial for empathy, social interactions, and emotional intelligence[126].Taken together, the study's findings suggest that the self-focused emotion intervention effectively helped the experimental group by reducing emotional sensitivity when dealing with negative statements.

Moreover, as mentioned earlier, in Analysis 2, significant functional connectivity differences in the limbic system were observed between self-respect and self-criticism stimuli in the paired t-test (see Tables 5 and 7). However, these significant differences were not sustained when conducting the group × intervention interaction analysis. There are two possible explanations for this outcome. First, the group × intervention interaction analysis applied to these ROIs is complex and may not have effectively captured significant effects. Second, although participants used the intervention for 12 weeks, the daily training time was relatively short (on average 5 minutes) and entirely self-directed. This combination of factors may have contributed to difficulties in maintaining significant functional connectivity differences in the limbic system. Further research is needed to address these issues.

Additionally, in Analysis 2, no significant functional connectivity differences in the DMN were found in either the paired t-test or the group × intervention interaction analysis. This result was expected, as the DMN is typically active during resting states. However, the fMRI protocol for Analysis 2 involved continuous exposure to two voice-recorded listening stimuli during the scanning, which likely suppressed DMN activation.

5. Correlation with Clinical Factors (analysis 2)

There was a significant negative correlation trend between the beta values for the difference in pre- and post-intervention functional connectivity of left SMG seed-based the right posterior STG and the changes in BDI scores in the experimental group. This suggests that, within the experimental group, individuals with smaller differences in SN activity after the intervention tended to show larger reductions in BDI scores. In other words, after the intervention, participants who experienced a reduction in BDI scores exhibited decreased sensitivity in functional connectivity differences between self-respect and self-criticism stimuli. Since the SMG and pSTG are associated with emotional intelligence, empathy, and social cognition, this result can be interpreted as evidence that the self-focused emotion intervention strengthened functional connectivity in brain regions related to emotional intelligence. This improvement likely made individuals less sensitive to self-critical stimuli, contributing to better emotional regulation.

V. LIMITATION

There are limitations to this study that should be acknowledged. First, the clinical assessment data revealed significant self-reported reductions in anxiety and depression levels in the control group as well. As discussed earlier, these results might be influenced by participants' characteristics and external factors. Therefore, this outcome should be interpreted with caution, and future research should aim to control these variables more rigorously.

Second, as the mobile healthcare application is designed for practical use by patients with anxiety and depression disorders, it included three different emotion regulation interventions based on distinct cognitive therapy strategies. Moreover, there was a significant difference in the mean usage of these interventions, making it difficult to determine which specific strategies contributed to the observed changes in functional connectivity. Nevertheless, as outlined in the introduction, these strategies are known to influence similar brain networks, such as the DMN and SN. Additionally, a follow-up study with individuals diagnosed with anxiety disorders demonstrated a significant difference in anxiety and depression levels between the experimental and control groups after using the app. These findings suggest that the three strategies likely interacted and collectively influenced brain network activity. Future research should aim to isolate and differentiate these strategies to better understand their individual contributions to changes in brain functional connectivity. This would provide a clearer picture of how each approach uniquely impacts brain function and emotional regulation.

VI.CONCLUSION

This study aimed to evaluate the efficacy of a self-focused emotion regulation intervention in a noble mobile healthcare app in reducing anxiety and depression levels by promoting neuronal adaptability. To achieve this, changes in brain functional connectivity were assessed using fMRI data collected alongside psychometric assessments.

The clinical assessment data revealed a significant interaction effect between group and time in BAI scores, indicating that the experimental group experienced a significantly greater reduction in anxiety levels compared to the control group after using the mobile healthcare intervention.

In Analysis 1, the results demonstrated that the self-focused emotion intervention notably enhanced functional connectivity within the DMN and SN, as well as between the SN and the medial frontal cortex, which are associated with attention control and emotion regulation. This finding supports the first hypothesis that after the intervention, seed-based functional connectivity in resting-state brain networks (DMN, SN, and ECN) would increase in the experimental group compared to the control group. In Analysis 2, the results revealed significant functional connectivity differences within the SN, specifically involving left SMG seed-based the right posterior STG connectivity. Furthermore, this change was correlated with the clinical factor of BDI scores in the experimental group. These findings suggest that the mobile intervention enhanced the function of social brain networks, improving the experimental group's empathy skills and resilience to negative emotions. This result supports the second hypothesis that the experimental group would exhibit distinct seed-based functional connectivity patterns after engaging in self-respect and self-criticism tasks post-intervention compared to the control group.

This study highlights the potential of noble mobile healthcare interventions rooted in three self-focused, emotion-based strategies—ACT, self-affirmation theory, and HST techniques—to facilitate improvements in emotional well-being by modulating key brain networks and decreasing anxiety and depression levels.

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모바일 헬스케어 앱에 내장된 자기 집중적 정서제어 중재들이 불안도와 우울도가 높은 사람들의 안정 상태 뇌 기능 연결성에 미치는 영향

배경: 불안과 우울증은 특히 불안이 심한 개인에게 널리 퍼져 있다. 전통적인 치료 방법은 한계점이 있기에, 모바일 헬스케어 중재, 특히 불안한 개인의 특성 중 하나인 '자기 집중 주의'에 초점을 맞춘 감정 조절 전략을 통합한 모바일 헬스케어 중재는 이러한 문제를 해결하는 데 잠재력을 보여줄 수 있다고 추론했다. 이 연구는 이러한 개입이 불안과 우울증을 감소시켜 뇌 기능적 연결성을 변화시키는 효과를 평가하는 것을 목표로 했다.

방법: 수용 및 헌신 요법, 자기 긍정, 마음 미소 훈련이라는 세 가지 감정 조절 전략에 초점을 맞춘 12주간의 모바일 헬스케어 앱 처치를 시행했다. 피험자들은 불안과 우울증에 대한 임상 평가와 함께 뇌 연결의 변화를 측정하기 위해 기능적 MRI(fMRI)를 시행했다.
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결과: 모바일 헬스케어 처치 후 불안과 우울증이 크게 감소했으며, 실험 그룹은 더 큰 개선 효과를 보였다. 신경 영상 검사 결과 주의력 조절과 감정 조절에 관여하는 디폴트 모드 네트워크(DMN)와 돌출성 네트워크(SN)와 같은 주요 뇌 네트워크의 기능적 연결성이 증가한 것으로 나타났다.

결론: 이 연구는 뇌 연결성을 조절하여 정서적 웰빙을 향상시킬 수 있는 모바일 치료의 잠재력을 확인했다. 외부 요인을 고려하면서 다양한 집단에서 이러한 효과를 살펴보기 위한 추가 연구가 필요하다.

핵심되는 말 : 불안, 모바일 헬스케어, 자기 집중 주의,정서 제어, 기능적 연결성, 디폴트 모드 네트워크, 돌출성 네트워크, 집행 제어 네트워크, 기능적 자기 공명 영상