The Effects of a Serious Game on Depressive Symptoms and Anxiety in Breast Cancer Patients with Depression: A Pilot Study Using Functional Magnetic Resonance Imaging

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Abstract

Objective: Depression is common in cancer patients. We investigated the effects of playing a serious game in breast cancer patients with mild to moderate depression using functional neuroimaging.

Materials and Methods: Thirty-five participants were randomly assigned to the Game group and the Nongame group, and fifteen participants in each group completed the study protocol. Participants in the Game group were asked to play a serious game, ''Hit the Cancer'' (RAW HAND, Seoul, Korea), for at least 30 minutes/day, 5 days/week, for 3 weeks. Participants in the Nongame group received usual care. At baseline and follow-up, all participants were assessed with the Beck Depression Inventory (BDI), Beck Anxiety Inventory, Stress Response Inventory (SRI), and 3-Tesla resting-state functional magnetic resonance imaging. Changes in functional connectivity (FC) between the brain regions in the default mode network (DMN) and salience network (SN) were analyzed.

Results: After the intervention, BDI and SRI scores in the Game group greatly decreased compared with those in the Nongame group. In addition, compared with the Nongame group, the Game group showed decreased post-intervention FC between the right posterior cingulate cortex (PCC) of the DMN and right insula of the SN. The improvement in BDI and SRI scores correlated with the decrease in FC between the right PCC and right insula.

Conclusion: Selective attention training and repetitive stimulation of the insula by serious game play might cause normalization of the FC between the SN and DMN, thus improving depressive mood.

Keywords: Breast cancer, Depression, Default mode network, Insula, Salience network, Serious game

Introduction

DEPRESSION IS one of the most common mental disorders in cancer patients.[1,2] Approximately 25%–30% of cancer patients suffer from major depressive disorder (MDD) and other depressive disorders.[3] The risk for depression in breast cancer patients is twofold that of the general female population.[4,5] In addition, 10%–30% of breast cancer patients experience depression within 5 years after cancer diagnosis.[6]

The psychosocial factors that affect breast cancer patients include fear of death and cancer recurrence; negative insights about body image; and changes in femininity, attractiveness, and sexual functions.[7] However, these conditions are often disregarded in clinical practice in spite of the negative consequences of depression among cancer patients, such as reduced self-efficacy and treatment compliance, decreased

physical activity, increased somatic complaints and suicidality, and poor prognosis.[8,9] Therefore, routine assessment and adequate management of depressive disorders must be part of a comprehensive care strategy for cancer patients, including breast cancer patients.

Recently, serious games related to physical health have been intensively developed and studied. Various advantageous effects of these games have been identified, including the provision of health-related knowledge and skills to patients or doctors, promotion of self-management of disease, pain relief through distraction, encouragement of physical activity, and improvement of treatment adherence.[10] Since the release of ''Re-Mission'' (HopeLab, Palo Alto, CA), serious games for patients with various forms of cancer have been an important subcategory in the field of cancer treatment. While playing ''Re-Mission,'' players manipulate a

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virtual nanorobot to achieve tasks inside virtual bodies related to destroying malignant cells using weapons such as chemotherapy, antibiotics, and radiation.[11]

In a randomized controlled trial (RCT), game intervention with ''Re-Mission'' significantly enhanced medication adherence, self-efficacy, and knowledge regarding cancer in adolescent and young adult cancer patients.[12] In a serious game for patients with localized prostate cancer, ''Time After Time'' (Archimage, Inc., Houston, TX), evidence-based therapeutic outcome data were translated into a game format.[13] In a survey on acceptability of the game, patients with localized prostate cancer responded that the game was helpful for making treatment-related decisions.[13] Two serious video games, ''Escape from Diab'' and ''Nanoswarm: Invasion from Inner Space'' (both from Archimage, Inc.), were designed to encourage a healthy diet and physical activity in healthy children. According to study results, the games were also suitable for pediatric cancer patients and survivors.[14]

There have been numerous studies on serious games for mental health, including depression.[15] In their review and meta-analysis, Li et al.[15] divided gamified interventions for depression into four categories. First, in the psychoeducation and training category, there were two RCTs targeting adolescent depression, both using a game based on self-help computerized cognitive-behavioral therapy.[16,17] According to the study results, playing the serious game decreased depressive symptoms in adolescents.[16,17]

Regarding the second category, the virtual reality (VR) therapy category, studies indicated that the games were effective in combating post-traumatic stress disorder and specific phobias; significant decreases in depressive symptoms were also reported.[18,19] Additionally, VR computer games were more effective at decreasing depressive symptoms in children hospitalized with cancer compared with typical care.[20] The third category comprised exergames, video games that combine game play with exercise. In a study on adults with subclinical depression, playing an exergame was effective for improvement of symptoms of depression.[21] Last, the fourth category consisted of entertainment games, for which one RCT found that playing an entertainment game improved mood and decreased stress.[22]

Resting-state networks (RSNs) refer to spontaneous low-frequency neural activities that form networks of associated brain regional activities when a person is awake and alert, but not actively performing any activity that needs attention or a goal-directed action. Many previous studies on RSNs in mental disorders have focused on the default mode network (DMN) and salience network (SN).

The DMN includes the medial prefrontal cortex (mPFC), ventral portion of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC)/precuneus, and medial, lateral, and inferior parietal cortex.[23] The DMN is associated with self-referential processing, including rumination.[24] The SN plays a role in identifying the most relevant among several internal and external sensory inputs to support choice and modulation of behavior.[25] It is structurally correlated with the ACC and the bilateral insula. The majority of previous research on MDD has reported increased connectivity between the SN and anterior regions of the DMN, such as the mPFC, PCC, and bilateral parietal cortex.[26]

In this study, we aimed to investigate the effects of a serious game on depressive symptoms in breast cancer patients with depression using clinical scale measures and analyzing RSNs.

The first hypothesis addressed in this study was that playing a serious game would improve depressive symptoms, anxiety, and stress levels in breast cancer patients with depression. The second hypothesis was that playing a serious game would produce a change in functional connectivity (FC) in RSNs, including the DMN and SN, as well as the connectivity between them. The third hypothesis was that there is an association between improvement in depressive symptoms and anxiety and any changes in the FC of RSNs.

Methods

Participants

Thirty-eight pathologically proven, clinical stage I-IV breast cancer patients with depressive mood were recruited through an advertisement in hospital bulletins from the Chung-Ang University Hospital from March 2015 to May 2016. For screening, all participants were interviewed regarding mood and anxiety. MDD was diagnosed independently by two psychiatrists (S.M.K. and D.H.H.) based on the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV).[27]

Inclusion criteria were (1) female adult patients with breast cancer, (2) diagnosis of mild to moderate MDD with a Beck Depression Inventory (BDI)[28] score range from 10 to 29, and (3) being right-handed because dominant handedness would lead to differences in the brain activity between right and left hemispheres. Exclusion criteria were (1) past or current episodes of any psychiatric diagnosis other than MDD or severe medical illness other than cancer, (2) previous diagnosis of primary brain tumor or brain metastasis, (3) past or current substance abuse or dependence, (4) current psychotropic medication use other than benzodiazepine and Z-drugs, (5) intelligence quotient (IQ) <80, (6) history of head trauma, and (7) claustrophobia.

Two participants were excluded because one did not satisfy the diagnostic criteria of MDD and one reported taking selective serotonin reuptake inhibitors during the last month. The Institutional Review Board of Chung-Ang University Hospital approved the protocol of this study (C2016066). Clinical trial registration was approved by the Clinical Research Information Service (KCT0002501). All participants provided written informed consent.

Thirty-five participants were randomly classified into the Game group ($N=18$) and the Nongame group ($N=17$). During the study period, all participants briefly met psychiatrists once a week to screen for aggravation of depression. Among the 35 participants, 15 in the Game group and 15 in the Nongame group completed the study protocol. One participant dropped out because brain metastasis was detected at the baseline functional magnetic resonance imaging (fMRI) assessment. One participant dropped out because she started taking antidepressants. One participant dropped out because she did not satisfy the game playing time in our study protocol. Two participants were excluded because they did not undergo follow-up assessment.

Mobile game "Hit the Cancer"

The mobile game, ''Hit the Cancer'' (RAW HAND, Seoul, Korea), was created to produce psychological outcomes associated with successful cancer treatment. ''Hit the

Cancer'' is a third-person shooter game in the serious games genre. In the current study, it was played as an Android Package Kit (APK). The game's key pedagogical features are (1) reduction of stress, (2) mood encouragement, and (3) breaking a negative paradigm by stimulating selective attention in cancer patients with depressed mood.

At the start of game play, the background is generated based on the patient's own metastatic lesions, including blood vessels, gut, liver, and lungs (Fig. 1). Normal body cells express happy faces, while ugly cancer cells show depressed faces. Game players are asked to selectively remove the cancer cells, with a higher score achieved for removal of a large number of cancer cells. At the easy level of game play, one, two, or three cancer cells with five, six, or seven normal cells with happy faces are presented every 5 seconds.
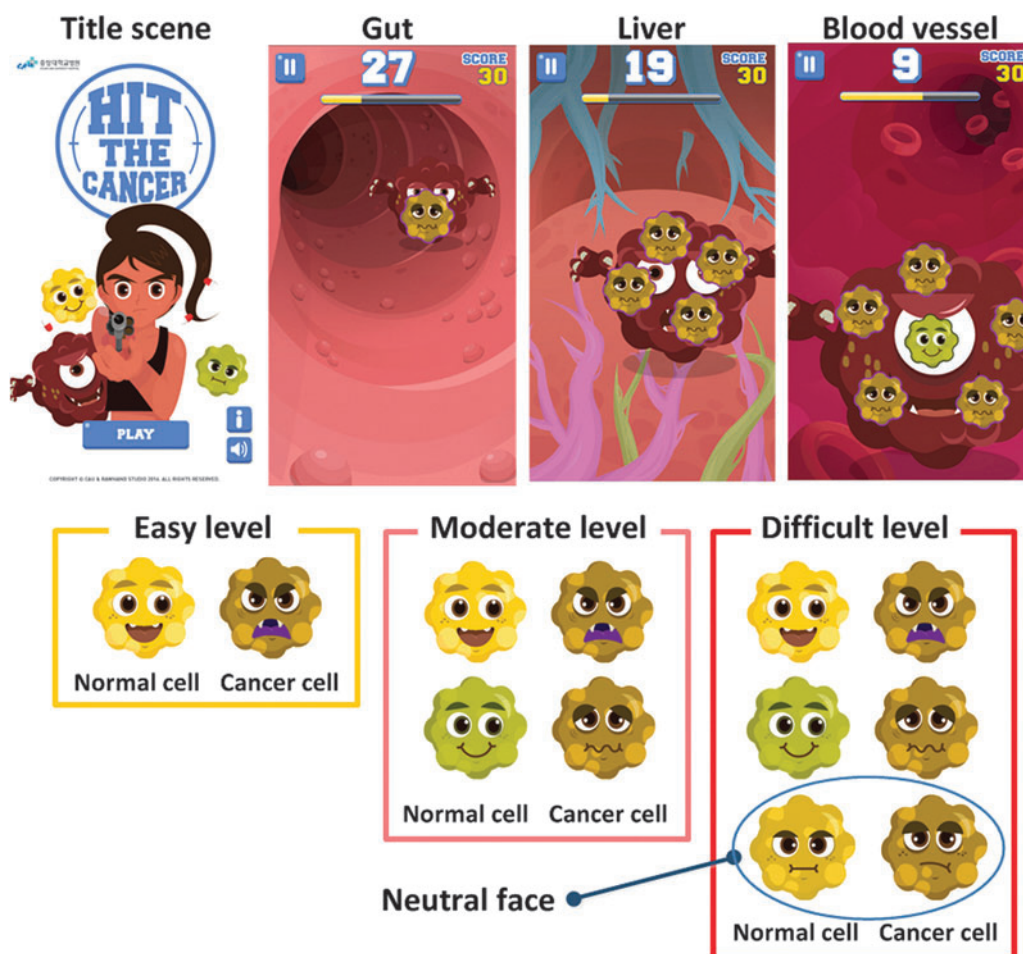
Cancer cells had a dark color with angry faces, while normal cells had a bright color with smiling faces. At the moderate level of game play, differentiation between normal cells and cancer cells can be more difficult due to decreasing contrast between healthy and cancer cell color and expression between cells. In addition, the time limit decreases to 3 and 4 seconds. At the difficult level of game play, neutral faces are added to the cells used in the moderate level.

Assessments and processing

After enrollment screening, all participants were assessed with the BDI,[28] Beck Anxiety Inventory (BAI),[29] a modified form of the Stress Response Inventory (SRI),[30,31] and fMRI. The BDI and BAI are self-report measures of the severity of depression and anxiety, respectively. The SRI is another self-rating scale regarding participant stress responses. For the next 3 weeks, participants in the Game group were asked to play the serious game ''Hit the Cancer'' for at least 30 minutes/day and 5 days/week for 3 weeks. The game platform automatically recorded participant game playing time. Participants in the Nongame group received typical care for 3 weeks. At the end of 3 weeks, we repeated BDI, BAI, and SRI assessments and fMRI.

Brain imaging data analysis

All imaging data of resting-state brain activity were collected using 3T blood oxygen level-dependent (BOLD) fMRI (Philips Achieva 3.0 Tesla TX MRI scanner, Eindhoven, The Netherlands, TR = 3 s, 12-minute scan, 240 volumes, 128×128 matrix, 40 slices at 4.0-mm slice thickness). Preprocessing included despiking, motion correction, coregistration to the

FIG. 1. Mobile game ''Hit the cancer.'' The background of the game is chosen based on the patient's own metastatic lesions, including blood vessels, gut, liver, and lungs. Cancer cells have a dark color with angry faces, while normal cells have a bright color with a smiling face. When the level of game play goes up, the differentiation between normal cells and cancer cells becomes more difficult due to less contrast in cell color and expression between cells.

MPRAGE image, normalization to MNI space, temporal detrending, bandpass filtering, and voxel-wise regression of an identical bandpass-filtered time series of six head motion parameters, degraded cerebrospinal fluid, degraded white matter, and facial soft tissue.[32,33] To correct for head movement, censoring of time points with head motion >0.2 mm was used.[34,35]

No regression of the global signal was performed.[36,37] Ten regions from the automated anatomical labeling in PickAtlas software[38,39] were predefined to identify differential FC between hubs of major functional brain networks. The DMN comprised six regions: the left/right mPFC, left/right PCC, and left/right precuneus (Fig. 2). The SN consisted of four regions: the left/right dorsal ACC (dACC) and left/right insula. Correlation coefficients were measured for each pair of ROIs in each subject.[40–42]

Statistical analysis

Demographic and clinical characteristics were analyzed using the chi-square test and Mann–Whitney U test, with significance set at $P < 0.05$. Repeated measures analysis of variance (ANOVA) and a two-tailed t-test were used to evaluate cancer patients with depressed mood in the Game group compared with cancer patients in the Nongame group, and multiple comparison correction over 78 pairs of 12 regions was performed using an acceptable false discovery rate of $q < 0.05$. Correlation analyses between changes in clinical scale scores and changes in FC were conducted to assess the specific impact of each clinical symptom on FC of brain regions with a threshold of $P < 0.05$, as determined using commercially available software (SPSS, version 20; IBM).

Results

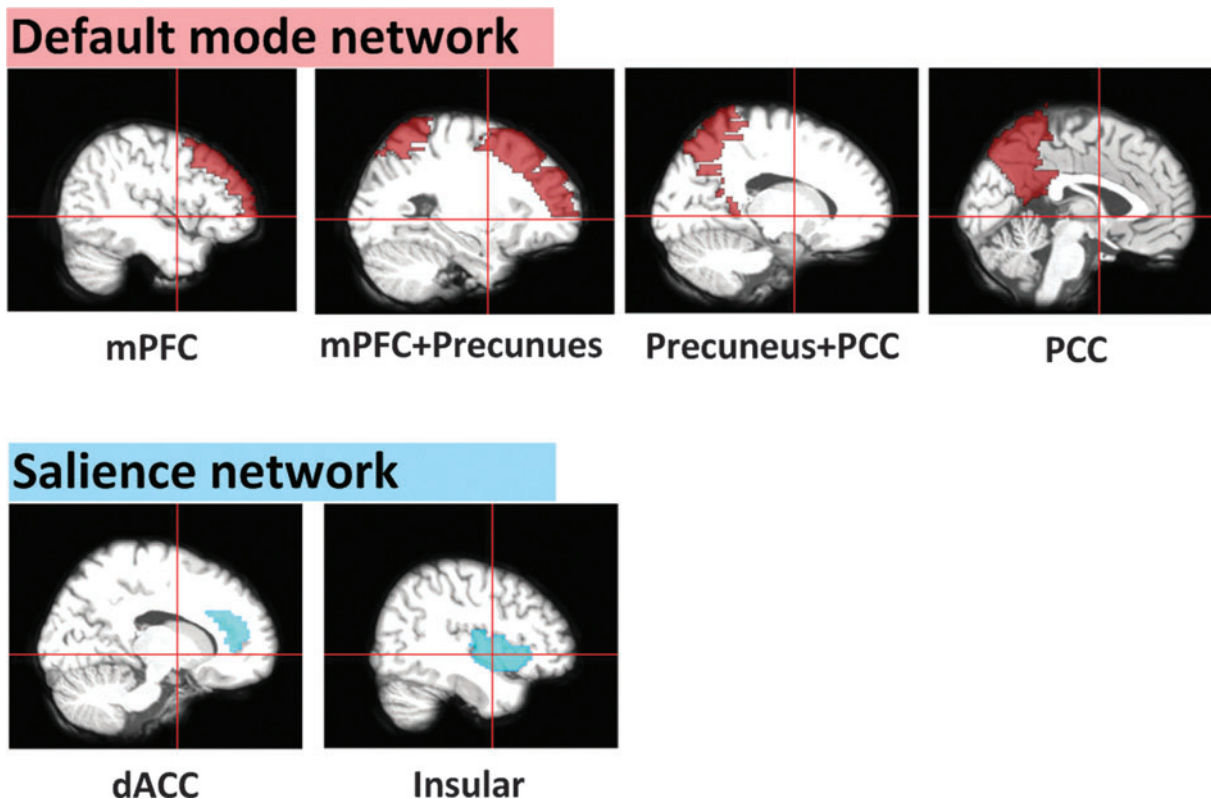#### Demographic and clinical characteristics of the patients

Finally, 15 breast cancer patients with depressive mood in the Game group (mean age 48.4 ± 10.8 years) and 15 patients in the Nongame group (47.9 ± 10.3 years) were included in the final analyses. The characteristics of the study population are summarized in Table 1. Systemic chemotherapy was performed on the basis of the decision of attending physicians. Patients had received a median of two chemotherapeutic regimens with palliative systemic chemotherapy at the time of enrollment. There were no significant differences in demographic, medical, or psychological variables at baseline between the Game and Nongame groups.

Changes in clinical symptoms

After 3 weeks of game play, the BDI scores [$F(1, 28) = 4.26$, $P < 0.05$] and SRI scores [$F(1, 28) = 4.36, P < 0.05$] in the Game group greatly decreased compared with those in the Nongame group (Table 2) (Fig. 3).

Changes in FC

At baseline, there were no significant differences in FC between the Nongame group and the Game group. After 3

FIG. 2. Default mode network and salience network. The default mode network comprises six regions: left/right mPFC, left/right PCC, and left/right precuneus. The salience network comprises four regions: left/right dACC and left/right insula. dACC, dorsal anterior cingulate cortex; mPFC, middle prefrontal cortex; PCC, posterior cingulate cortex.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT BASELINE

Variables	Game group Mean (SD), number	Nongame group Mean (SD), number	Statistics z/χ^2, P
Demographic variables			
Age, years	48.4 (10.8)	47.9 (10.3)	0.46, 0.65
Years of education	13.3 (2.4)	12.2 (1.2)	0.46, 0.65
Socioeconomic status (High/middle/low)	3/8/4	2/10/2	1.06, 0.59
Medical variables			
Duration from breast cancer diagnosis (months)	32.4 (5.5)	35.5 (6.5)	−0.37, 0.71
PS (ECOG) (0-1/2)	10/5	12/3	0.68, 0.41
Histology (Invasive ductal carcinoma/invasive lobular carcinoma)	13/2	14/1	0.37, 0.54
Menopausal status (Premenopausal/postmenopausal)	3/12	5/10	0.68, 0.41
ER (Negative/positive)	6/9	9/6	1.20, 0.27
HER2 (Negative/positive)	5/10	7/8	0.56, 0.46
Triple negative (Nontriple negative/triple negative)	12/3	13/2	0.24, 0.62
Initial stage[a] (Stage I-IIIA/stage IIIB-IIIC/stage IV)	4/5/6	3/8/4	1.24, 0.54
Metastatic location (Nonvisceral lesion/visceral lesion)	6/9	4/11	0.60, 0.44
Chemotherapy line (1-2nd line/≥3rd line)	12/3	9/6	1.43, 0.23
Psychological variables			
Duration of depressive mood	16.0 (4.2)	13.1 (3.2)	0.15, 0.88
Beck Depression Inventory	25.1 (9.1)	23.0 (8.4)	0.51, 0.60
Beck Anxiety Inventory	21.0 (10.7)	20.3 (9.2)	0.18, 0.85
Stress Response Inventory	14.4 (12.9)	13.5 (11.3)	0.25, 0.80

Demographic and clinical characteristics were analyzed using the chi-square test and Mann–Whitney U test, with significance set at $P < 0.05$.

[a]According to the TNM classification of 2010 AJCC staging.

PS, performance status; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2.

weeks of game play, compared with the Nongame group, the Game group showed decreased FC between four pairs of regions, satisfying uncorrected $P < 0.05$: the right mPFC and right insula (F = 3.74, $P < 0.05$), the right PCC and right insula (F = 4.92, $P < 0.01$), the left parietal cortex and right insula (F = 3.91, $P < 0.05$), and the right dACC and left insula (F = 4.11, $P < 0.05$; Fig. 4). Of the four pairs, the right PCC and right insula satisfied the $q < 0.05$ false discovery rate.

Correlations between changes in clinical scale scores and FC

Improvement of BDI score was significantly correlated with FC decrease between the right PCC and the right insula in all cancer patients (r = 0.48, $P < 0.05$; Fig. 5). In addition, improvement of SRI score in the Game group was negatively correlated with FC from the right PCC to the right insula (r = 0.62, $P < 0.05$).

Discussion

The current results suggest that 3 weeks of serious game play improved depressive symptoms and stress levels in breast cancer patients with depression. Playing a serious game produced a change in FC between the right insula of the SN and the right PCC of the DMN. In addition, there was an association between improvement in depressive symptoms and stress levels and change in FC between the right insula of the SN and right PCC of the DMN.

The key pedagogical features of the serious game ''Hit the Cancer'' were reduction of stress level, mood encouragement, and disruption of the negative paradigm by stimulating selective attention in cancer patients with depressed mood. The most important mechanism of the game seemed to be the training of selective attention. In this game, players were asked to selectively remove ugly cancer cells with a depressed facial expression. As the difficulty increased, the players had
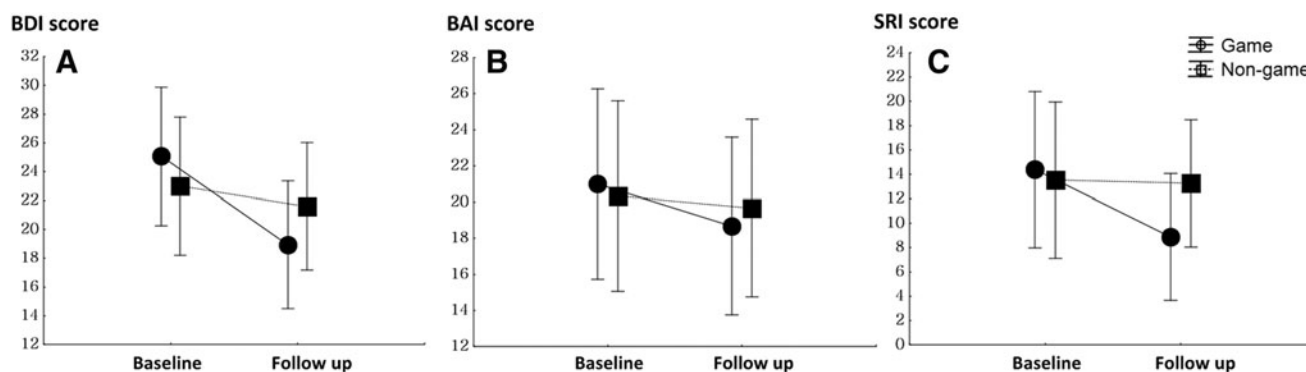
TABLE 2. CHANGES IN MEAN SCORES OF PSYCHOLOGICAL VARIABLES FROM BASELINE TO FOLLOW-UP

	Game group		Nongame group		Repeated measures ANOVA
	Baseline Mean (SD)	Follow-up Mean (SD)	Baseline Mean (SD)	Follow-up Mean (SD)	Treatment × Visit effect F, P
BDI	25.1 (9.1)	18.9 (10.2)	23.0 (8.4)	21.6 (6.0)	4.26, <0.05
BAI	21.0 (10.7)	18.7 (10.7)	20.3 (9.2)	19.7 (7.7)	0.39, 0.53
SRI	14.4 (12.9)	8.8 (8.0)	13.5 (11.3)	13.2 (11.4)	4.36, <0.05

A repeated measures analysis of variance (ANOVA) was used to evaluate cancer patients with depressed mood in the Game group compared with cancer patients in the Nongame group.

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; SRI, Stress Response Inventory.
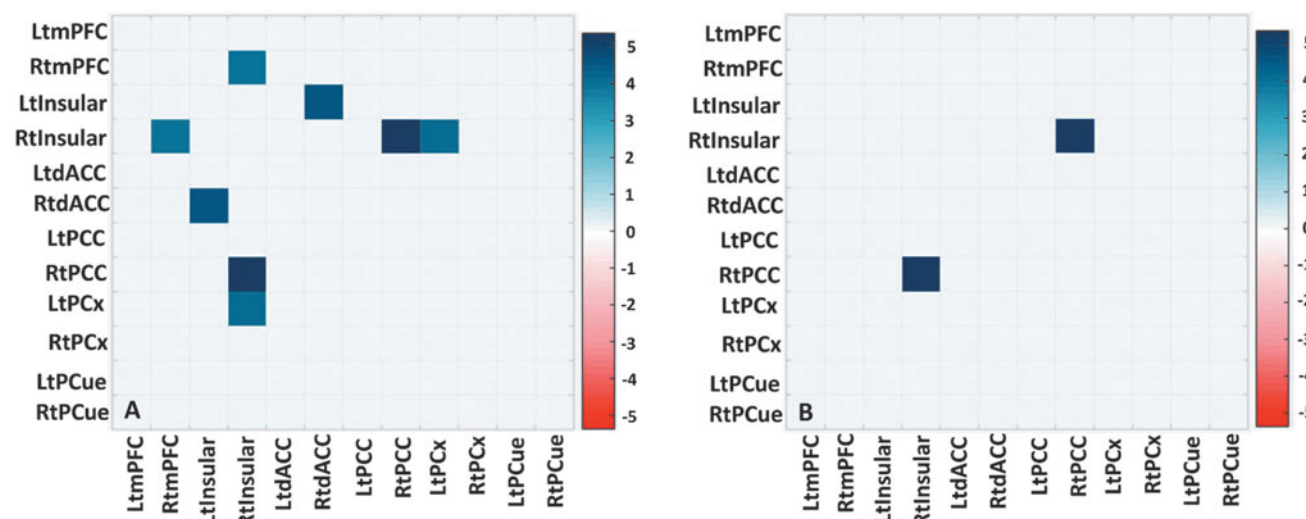
FIG. 3. The comparison of changes in clinical symptoms between the Game and Nongame groups. A repeated-measures ANOVA was used to evaluate cancer patients with depressed mood in the Game group compared with cancer patients in the Nongame group. **(A)** BDI scores: $F(1,28) = 4.26$, $P < 0.05$, **(B)** BAI scores: $F(1, 28) = 0.39$, $P = 0.53$, **(C)** SRI scores: $F(1, 28) = 4.36$, $P < 0.05$. ANOVA, analysis of variance; BAI, Beck Anxiety Inventory; BDI, Beck Depressive Inventory; SRI, Stress Response Inventory.

to engage greater selective attention as the time limit decreased and a third cell expression (neutral) was added to the happy and depressed cells. In this study, playing a serious game produced a change in FC between the right PCC of the DMN and right insula of the SN. PCC is associated with monitoring of internal and extrapersonal circumstances.[23]
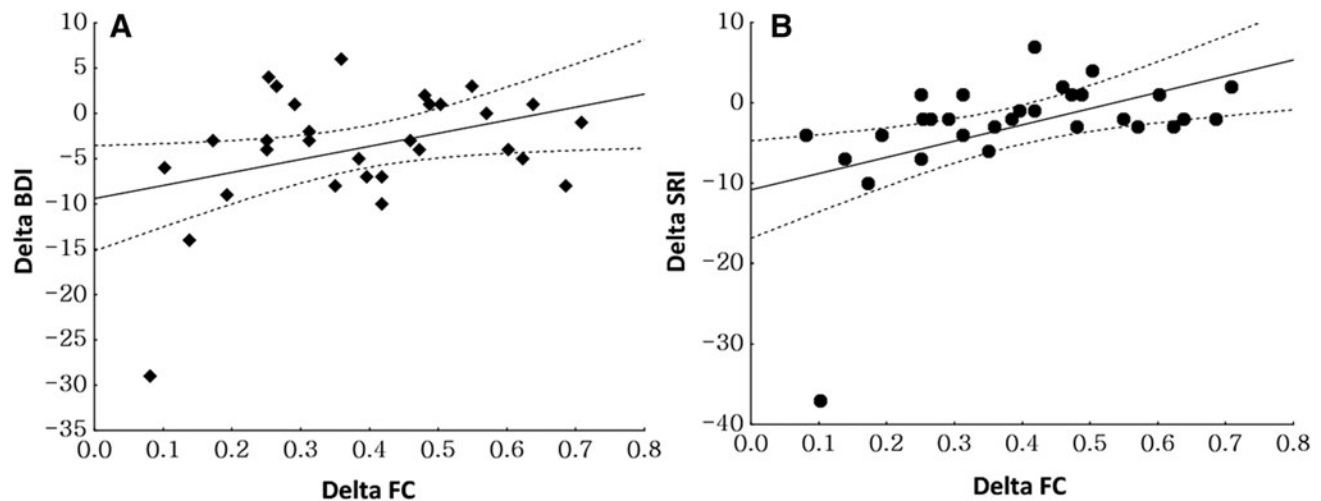
The insula has been reported to play an important role in the initial assessment of implications of sensory and emotional stimuli.[25] Once a salient stimulus is detected, the insula is activated to switch between other RSNs to enable access to attention and working memory functions.[43] The insula functions as a link between brain areas related to monitoring the internal environment and stimulus-driven activity.[44] Increased connectivity between the SN and DMN has been reported in patients with MDD.[26] Dysfunction in switching between self-focused thinking and goal-directed cognitive processes seems to contribute to MDD.[45] Because

of this, patients with MDD have difficulty disengaging from self-referential thought and negative rumination.[45]

The right anterior insula in the SN modulates the switch between self-referential and goal-directed cognitive processes.[46] Regarding changes during therapeutic intervention, increases in FC of the DMN, such as the precuneus, PCC, and right lateral parietal cortex, normalized following treatment with antidepressants.[47,48] However, there have been few studies regarding the effects of antidepressants on FC of the SN as well as the connectivity between the SN and DMN. The results of the present study indicate that selective attention training and repetitive stimulation of the insula in the SN by serious game play caused normalization of FC between the SN and DMN; as a result, depressive mood was improved. Increased function in modulating the switch between self-focused thinking and goal-directed cognitive processes might help breast cancer patients with

FIG. 4. Comparison of changes in functional connectivity between the Game group and Nongame group. A two-tailed *t*-test was used to evaluate cancer patients with depressed mood in the Game group compared with cancer patients in the Nongame group, and multiple comparison correction over 78 pairs of 12 regions was performed using an acceptable false discovery rate of $q < 0.05$. **(A)** Uncorrected $P < 0.05$: right mPFC to right insula ($F = 3.74$, $P < 0.05$), right PCC to right insula ($F = 4.92$, $P < 0.01$), left parietal cortex to right insula ($F = 3.91$, $P < 0.05$), and right dorsal anterior cingulate cortex to left insula ($F = 4.11$, $P < 0.05$), **(B)** right PCC to right insula, false discovery rate $q < 0.05$.

FIG. 5. Correlations between changes in clinical scale scores and changes in FC between the right PCC and right insula. Correlation analyses between changes in clinical scale scores and changes in FC were conducted to assess the specific impact of each clinical symptom on FC of brain regions with a threshold of $P < 0.05$. **(A)** Changes in scores of Beck Depression Inventory (Delta BDI) versus changes in FC between the right PCC and right insula: $r = 0.48$, $P < 0.05$. **(B)** Changes in scores of Stress Response Inventory (Delta SRI) versus changes in FC between the right PCC and right insula: $r = 0.62$, $P < 0.05$. FC, functional connectivity.

MDD disengage from self-referential thought and negative rumination.

In addition, reductions in depressive symptoms and stress levels in the Game group might be due, in part, to brain stimulation and obtaining a sense of accomplishment. In this game, game players could assess their performance using their score during play. In a cross-sectional survey on cancer survivors who play recreational games, such games seem to be supportive of the emotional health of survivors, especially with regard to obtaining stimulation and a sense of achievement as well as in connecting with others.[49] Like the effects of a casual game on mood and stress level,[22] the entertaining features of "Hit the Cancer" might be helpful in improving mood and decreasing stress.

Although "Hit the Cancer" does not target any relevant health beliefs or health-related behaviors like previous serious games developed for cancer patients (such as "Re-Mission" and "Time After Time"), inclusion of cancer content is still important as this specific topic may increase interest and immersion in the game in a group of cancer patients who might otherwise be difficult to engage. When we designed "Hit the Cancer," we decided to use game scenes related to breast cancer, such as cancer cells and the patient's own metastatic lesions, because these scenes are one of the most salient features of stimulation to cancer patients,[50] for selective attention training and to disrupt the negative paradigm. Both the increased immersion and salience attributed to cancer content are likely to maximize the effects of the game. To confirm this strength of games with cancer content, future research should compare the current game with games without a cancer theme and that have a mechanism for enhancing selective attention.

Limitations

This study has several limitations. First, there were a small number of participants and a short research period. There-fore, the findings from this study might not be generalizable to a larger population of breast cancer patients or to other cancer patients. Second, the heterogeneity of anticancer drug regimens and inconsistent study enrollment at varying stages of cancer could be limitations of this study. In addition, although less than five percent of drugs comprising very small molecules are capable of crossing the blood–brain barrier, there could be direct neurotoxic effects and indirect mechanisms related to immune dysfunction, hormonal changes, and DNA damage due to chemotherapy, which could affect brain function.[51]

To overcome these limitations, we set a short study period of 3 weeks, with all participants prescribed the same anticancer drug at baseline and follow-up, and ensured that the medical condition of participants had not changed dramatically. Last, the current study did not assess the usability of the game in cancer patients. Future studies should consider game usability as a treatment tool in a large number of cancer patients as well as comparing the current game with games without a cancer theme and that have a mechanism for enhancing selective attention.

Conclusions

Selective attention training and repetitive stimulation of the insula in the SN by serious game play can normalize FC between the SN and DMN; as a result, depressive mood can be improved. The serious game seemed to be effective by disengaging self-referential thought and negative rumination by training for enhanced function in modulating the switch between self-focused thinking and goal-directed cognitive processes. Future studies in a large cohort over a long-term period are needed to strengthen the results of this study.

Acknowledgment

Author Disclosure Statement

No competing financial interests exist.

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