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Original Article

Neural mechanisms of CALM intervention to improve CRCI in breast cancer survivors: an fMRI-based study

Chen Gan[1,2,3*], Jian Xu[1,2*], Senbang Yao[1,2*], Xinyi Zheng[3,4], Longyu Hu[3,4], Meiwen Ling[3,4], Mingjun Zhang[1,2], Huaidong Cheng[1,2,3,4]

[1]Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China; [2]Anhui Medical University, Hefei, Anhui, China; [3]Department of Oncology, Shenzhen Hospital of Southern Medical University, Shenzhen, Guangdong, China; [4]The Third Clinical Medical College of Southern Medical University, Shenzhen, Guangdong, China. [*]Equal contributors.

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Abstract: Background: Managing Cancer and Living Meaningfully (CALM) intervention's impact on chemotherapy-related cognitive impairment (CRCI) in breast cancer survivors (BCs) was investigated through resting-state functional magnetic resonance imaging (rs-fMRI) to elucidate the underlying neural mechanisms involved. Methods: 68 BCs were randomly assigned to either the CALM group (33 patients) or the care-as-usual (CAU) group (35 patients). Cognitive function was assessed before and after the intervention in both groups using the Mini Mental State Examination (MMSE) scale. Pre- and post-intervention rs-fMRI data were also collected for regional homogeneity (ReHo) and functional connectivity (FC) analyses in the CALM group. A total of 68 BCs were randomly assigned to either the CALM group (n = 33) or the care-as-usual (CAU) group (n = 35). Cognitive function was evaluated pre- and post-intervention using the Mini-Mental State Examination (MMSE). In the CALM group, rs-fMRI data were acquired before and after the intervention to assess alterations in regional homogeneity (ReHo) and functional connectivity (FC). Results: CALM intervention demonstrated a greater enhancement in cognitive function compared to CAU (P = 0.004). Following CALM, ReHo exhibited an increase in bilateral occipital and temporal regions, including the superior, middle, and inferior occipital gyri, lingual gyrus, as well as the middle and superior temporal gyri, while a decrease was observed in frontal and cingulate regions, including the bilateral middle, medial, and dorsolateral superior frontal gyri, anterior cingulate and paracingulate gyri, precuneus, posterior cingulate, and left angular gyrus. FC analysis revealed diminished connectivity between the middle frontal gyrus and occipital/calcarine regions, whereas connectivity strengthened with the left anterior cingulate/paracingulate and right orbital frontal regions. ΔMMSE exhibited a positive correlation with ReHo in the left middle frontal gyrus (r = 0.355, P = 0.042) and a reduction in middle frontal-occipital FC (left calcarine: r = 0.353, P = 0.044; right/left middle occipital: r = 0.388/0.423, P = 0.029/0.014). Conclusion: CALM intervention mitigates CRCI in BCs, with the middle frontal gyrus may play a critical.

Keywords: Breast cancer survivors, CALM, CRCI, rs-fMRI, FC, ReHo

Introduction

Breast cancer (BC) remains the most commonly diagnosed malignancy among women worldwide [1]. Advances in treatment have markedly increased the 5-year survival rate of Chinese BC patients [2], contributing to a rising population of survivors. Chemotherapy continues to be a fundamental component of BC management, enhancing prognosis while being linked to cognitive dysfunction [3]. Cancer-related cognitive impairment (CRCI) post-chemotherapy manifests through deficits in memory, processing speed, and attention [4], affecting up to 75% of BC survivors (BCs) during and/or after treatment [5]. CRCI substantially disrupts daily activities, intensifies occupational and personal stress, and severely diminishes overall quality of life [6]. Addressing CRCI through effective interventions has thus emerged as a pressing concern for both oncologists and BC survivors.

Interventions for CRCI include both pharmacologic and nonpharmacologic approaches. Given

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the limited efficacy of pharmacologic treatments for CRCI [7], increasing emphasis has been placed on nonpharmacologic strategies. Among these, cognitive rehabilitation has demonstrated efficacy in improving both subjective and objective cognitive functions in cancer survivors [8, 9], including processing speed, memory [10], and executive function [11]. Within this context, the Managing Cancer and Living Meaningfully (CALM) program, a brief, tailored supportive-expressive psychotherapy developed by the Princess Margaret Cancer Centre in Toronto, Canada, targets four core domains: symptom management, communication with healthcare providers, shifts in self-identity and interpersonal relationships, psychological well-being, existential meaning, and concerns related to mortality and future planning [12]. CALM interventions have yielded favorable outcomes in mitigating anxiety and depression [13], enhancing cognitive function [14], and improving overall quality of life [15] in patients with BC. However, the mechanisms underlying CALM's impact on CRCI remain poorly understood, posing challenges to its broader integration into clinical practice.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive technique employed to examine brain activity in the absence of explicit tasks or stimuli, allowing for the assessment of intrinsic brain function during rest [16, 17]. Recent advancements in rs-fMRI have significantly contributed to cognitive neuroscience by elucidating the neural mechanisms associated with the onset, progression, and resolution of CRCI. Regional homogeneity (ReHo), an index of local neural synchronization, quantifies functional coherence by analyzing frequency fluctuations across spatially adjacent voxels, thereby providing insights into brain connectivity patterns [18]. Functional connectivity (FC), which captures the spatial organization of temporal correlations between spontaneous low-frequency oscillations across different brain regions, serves as a critical marker of network integrity. Altered neural activity and disrupted connectivity in BC patients following chemotherapy may underlie cognitive impairment. Structural and functional alterations induced by chemotherapy predominantly affect the frontal lobes, with the middle frontal gyrus (MFG) emerging as a core component of the executive control network. The MFG is integral to cognitive processes such as executive function, working memory, and prospective memory [19]. Empirical findings indicate that BC patients exhibit increased frontal lobe activation to sustain working memory performance [20], while subsequent studies suggest that heightened parietal lobe activation following systemic chemotherapy may reflect compensatory neural adaptation [21]. As a result, fMRI remains a powerful tool for investigating network-level mechanisms implicated in CRCI and its potential recovery.

The neural pathways mediating the effects of CALM intervention on CRCI in BC survivors remain unclear. Understanding these mechanisms is crucial to enhancing the effectiveness and clinical application of CALM. Accordingly, the present study posits that CALM intervention enhances cognitive function in BCs, with the potential underlying neural mechanisms involving altered ReHo values and/or FC in specific brain regions, as observed through fMRI analysis.

Methods

Participants

The BCs cohort for this study was sourced from the Second Affiliated Hospital of Anhui Medical University, with eligible patients identified via the hospital's electronic case system based on predefined criteria. Inclusion parameters included: (1) age ≥ 18 years at BC diagnosis; (2) histopathologically confirmed BC, completion of 4-6 cycles of paclitaxel- and anthracycline-based chemotherapy, with the final cycle administered 4-8 weeks prior and without intolerable adverse effects; (3) a Karnofsky Performance Status (KPS) score ≥ 80; and (4) self-reported cognitive complaints. Exclusion criteria comprised: (1) presence of severe comorbidities or malignancies other than BC; (2) prior diagnosis of depression, schizophrenia, dementia, Alzheimer's disease, or other psychiatric or neurodegenerative disorders; and (3) cachexia.

Sample size

The study utilized a single-blind, randomized controlled trial design, assigning participants to either the CALM intervention group or the Care as Usual (CAU) control group. An indepen-

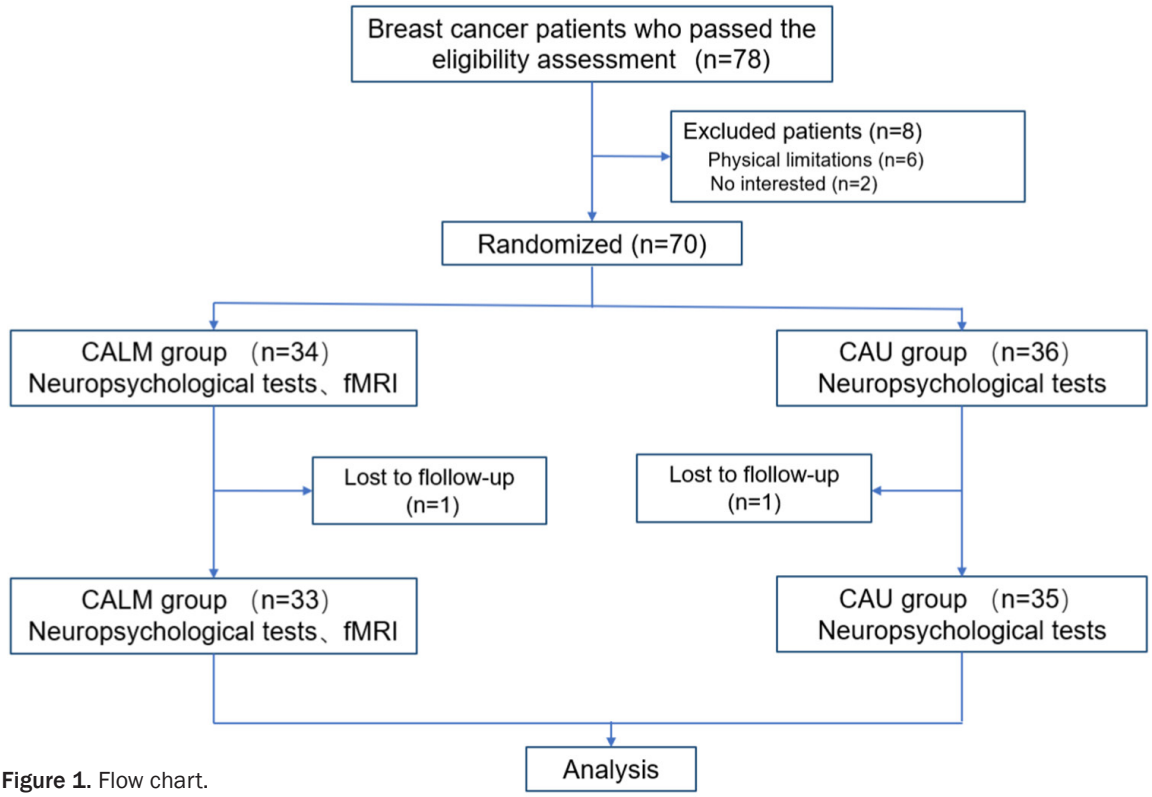

Figure 1. Flow chart.

dent statistician performed the statistical analysis and generated the random allocation sequences via computer software. These sequences, secured in sealed envelopes, remained inaccessible to the research team throughout the trial. Sample size estimation was based on prior research assessing the impact of CALM/CAU intervention on MMSE (26.30 ± 3.27 vs. 21.49 ± 3.27) [22], applying a two-sided $\alpha = 0.05$ and 90% power. The calculation followed the formula $n = 2(Z_\alpha + Z_\beta)^2 \times \sigma^2/\delta^2$, determining that each group required 15 participants [23]. With a 1:1 randomization ratio, 15 participants per group were deemed necessary. To accommodate a 15% attrition rate from missed visits or withdrawals, the final minimum sample size was adjusted to 18 per group, leading to a total of at least 36 participants. Ultimately, 68 BCs were enrolled, with 33 assigned to the CALM group and 35 to the CAU group. Ethical approval was obtained from the Anhui Medical University Ethics Committee, and all patients provided written informed consent. **Figure 1** presented the study flowchart.

Intervention program

BCs in the CALM group participated in a structured 12-week intervention administered biweekly. Sessions took place in a tranquil environment with soothing background music, each lasting approximately 30 to 60 minutes. In contrast, the CAU group did not receive additional psychotherapy or counseling. A comprehensive account of the CALM intervention's implementation was available in the Supplementary Table 1.

Neuropsychological tests

The Mini-Mental State Examination (MMSE) was employed to evaluate general cognitive function, including multiple domains such as memory, temporal and spatial orientation, working memory, visuospatial processing, object recognition, literacy skills, and complex motor coordination. With a total score of 30, higher values denote superior cognitive performance [24].

MRI data acquisition

MRI data were obtained using a Siemens 3.0 T scanner (Germany) equipped with a 16-channel head coil at the Second Affiliated Hospital of Anhui Medical University. The scanning session lasted approximately 30 minutes. rs-fMRI was conducted with a gradient-recalled echo-planar

imaging (GRE-EPI) pulse sequence under the following parameters: TE = 25 ms, TR = 2000 ms, acquisition matrix = 64 × 64, FA = 90°, FOV = 240 × 240 mm, slice thickness = 4.0 mm, slice gap = 0 mm, NEX = 1.0, 36 slices, and 240 time points. T1-weighted 3D SPGR images were acquired with TR = 1900 ms, TE = 2.48 ms, FA = 9°, acquisition matrix = 256 × 256, FOV = 240 × 240 mm, slice thickness = 1.0 mm, slice gap = 0 mm, 176 slices, and NEX = 1.0. Throughout the procedure, participants remained with eyes closed, minimizing external distractions.

Data preprocessing

All rs-fMRI data underwent processing on the MATLAB 2022 platform, utilizing the Data Processing Assistant for Resting-State fMRI (DPARSF) software package (http://fmri.org/DPARSF) for BOLD data preprocessing. The workflow comprised the following steps: (1) file format conversion from DICOM to NIfTI; (2) removal of the initial 10 time points to minimize instability associated with subject adaptation and machine startup; (3) temporal correction to align acquisition timing across sequences; (4) head motion correction to reduce artifacts induced by minor movements, including those from respiration and blood flow pulsation; (5) spatial normalization to the Montreal Neurological Institute template with voxel resampling at 3 mm; (6) spatial smoothing using a Gaussian kernel (6 mm full-width at half-maximum) to optimize signal quality, while ReHo data remained unsmoothed to prevent analytical distortions; (7) correction of baseline signal drift to eliminate systemic biases; (8) regression of covariates, including white matter signals, cerebrospinal fluid, and 24 cephalometric parameters, to remove linear drift in time series variables; (9) band-pass filtering to suppress high-frequency physiological noise, preserving signals within the 0.001-0.01 Hz range.

Brain regions exhibiting differences were identified through ReHo analysis identified brain regions with differential activity, which were then designated as seed points. FC was computed between these seed points and all brain voxels, with Pearson correlation coefficients quantifying the relationship between their respective time series. To ensure data normalization, Fisher's r-to-z transformation was applied, yielding z-transformed FC maps for further statistical evaluation.

Statistical analysis

Clinical and scale data were processed using SPSS 27.0. Pearson's chi-square test evaluated associations across education level, KPS scores, tumor stage, and molecular pathology types (n/%). Independent samples t-tests assessed differences in neuropsychological scale scores between patient groups concerning age and baseline characteristics. Post-intervention differences in neuropsychological scale scores were analyzed using analysis of covariance (ANCOVA). Results were presented as mean ± standard deviation, with statistical significance defined as $P < 0.05$. Functional data were processed with SPM12 in MATLAB (2022a) and xjView software, employing a general linear model for ReHo ($P < 0.05$, FDR corrected at the peak level) and FC ($P < 0.005$, no FDR correction, cluster size ≥ 20). Spearman's correlation analysis examined associations between scale scores and fMRI alterations, with $P < 0.05$ considered statistically significant. fMRI visualizations were generated using xjView (http://www.alivelearn.net/xjview8/) and BrainNet (https://helab.bnu.edu.cn/brainnet-viewer/), while correlation plots were produced in GraphPad Prism 9.3.

Results

Demographic and baseline characteristics of the two patient groups

The demographic and clinical characteristics of both groups were summarized in **Table 1**. No statistically significant differences were identified between the groups in terms of age, education level, KPS score, molecular classification, pathological type, or clinical stage.

Comparative analysis of MMSE score improvements following intervention

Figure 2 illustrated that baseline MMSE scores did not differ significantly between the two groups. However, post-intervention assessment revealed significantly higher MMSE scores in the CALM group compared to the CAU group (27.09 ± 1.28 vs. 25.91 ± 1.56; $F = 9.182$; $P = 0.004$), indicating a greater cogni-

Table 1. Comparison of demographic characteristics and clinical information of BCs between the two groups

Variables	CALM (n = 33)	CAU (n = 35)	t/χ^2	*p*
Age (years)	52.97 ± 7.66	51.23 ± 6.19	1.034	0.305
Educational level, n (%)			0.003	0.999
Primary school and below	18 (54.55)	19 (54.29)		
Junior high school	14 (42.42)	15 (42.86)		
University and above	1 (3.03)	1 (2.86)		
KPS scores n (%)			0.185	0.667
80	12 (36.36)	11 (31.43)		
90	21 (63.64)	24 (68.57)		
Molecular typing n (%)			0.819	0.845
Luminal A	4 (12.12)	6 (17.14)		
Luminal B	19 (57.58)	18 (51.43)		
Her-2 overexpression	7 (21.21)	9 (25.71)		
Triple-negative	3 (9.09)	2 (5.71)		
Pathological type n (%)			0.608	0.435
Non-invasive carcinoma	2 (6.06)	4 (11.43)		
Invasive carcinoma no special type	31 (93.94)	31 (88.57)		
Invasive carcinoma special type	0 (0)	0 (0)		
Tumor stage n (%)			1.247	0.742
I	4 (12.12)	7 (20.00)		
II	15 (45.45)	17 (48.57)		
III	9 (27.27)	7 (20.00)		
IV	5 (15.15)	4 (11.43)		

Abbreviations: CALM, Managing Cancer and Living Meaningfully; CAU, Care as Usual.

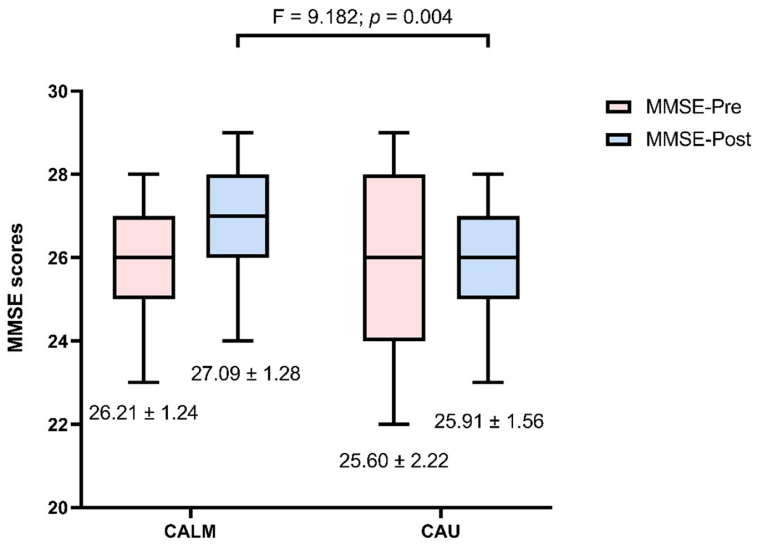

Figure 2. MMSE scores before and after intervention in both groups of BCs. Analysis of covariance results showed that the CALM intervention improved MMSE significantly more than CAU (F = 9.182; *P* = 0.004). Numerical results are mean ± standard deviation.

tive benefit associated with the CALM intervention.

Widespread ReHo changes in the brain following CALM intervention

As detailed in **Table 2** and **Figure 3**, the CALM intervention led to significant ReHo increases in the bilateral occipital lobes (including the superior, middle, and inferior occipital gyri), bilateral lingual gyrus, bilateral middle temporal gyrus, and right superior temporal gyrus. Conversely, significant ReHo reductions were detected in the bilateral MFGs, bilateral medial superior frontal gyrus, bilateral dorsolateral superior frontal gyrus, bilateral anterior cingulate and paracingulate gyrus, bilateral inferior frontal gyrus triangular regions, left MFG orbital region, bilateral medial and paracingulate gyrus, bilateral precuneus, and posterior

Table 2. Region details with group difference in ReHo value

Brain regions (Anatomical Automatic Labeling)	L/R	Voxels	MNI coordinate			*T* value	P_{FDR}
			X	Y	Z		
CALM-post > CALM-pre							
Cluster 10			-45	-81	6	11.275	< 0.001
Occipital_Mid	L	276					
Occipital_Mid	R	198					
Occipital_Inf	R	124					
Calcarin	L	93					
Temporal_Mid	R	81					
Occipital_Sup	L	73					
Cuneus	L	71					
Temporal_Inf	R	60					
Occipital_Inf	L	51					
Cuneus	R	50					
Calcarine	R	49					
Temporal_Mid	L	35					
Occipital_Sup	R	32					
Cluster 13			9	-57	0	5.6698	0.001
Lingual	R	35					
Lingual	L	26					
Cerebelum_4_5	L	25					
Cluster 23			66	-39	12	5.4358	0.002
Temporal_Sup	R	30					
CALM-post < CALM-pre							
Cluster 11			-3	42	27	-7.7955	< 0.001
Frontal_Mid	L	286					
Frontal_Sup_Medial	L	283					
Frontal_Mid	R	236					
Frontal_Sup_Medial	R	193					
Frontal_Sup	R	178					
Cingulum_Ant	L	153					
Frontal_Sup	L	122					
Frontal_Inf_Tri	L	104					
Cingulum_Ant	R	93					
Frontal_Med_Orb	L	56					
Cingulum_Mid	R	53					
Cingulum_Mid	L	49					
Rectus	L	46					
Supp_Motor_Area	L	44					
Supp_Motor_Area	R	33					
Precentral	L	30					
Frontal_Inf_Tri	R	25					
Cluster 24			-36	6	6	-5.6722	0.001
Insula	L	34					
Cluster 25			-9	-57	24	-6.0693	< 0.001
Precuneus	L	96					
Cingulum_Post	L	69					
Precuneus	R	48					

Cingulum_Mid	L	45					
Cingulum_Post	R	30					
Cluster 26			-30	-66	33	-4.9055	0.002
Angular	L	23					
Cluster 31			24	15	51	-4.7484	0.002
Frontal_Sup	R	24					

Abbreviation: CALM, Managing Cancer and Living Meaningfully.

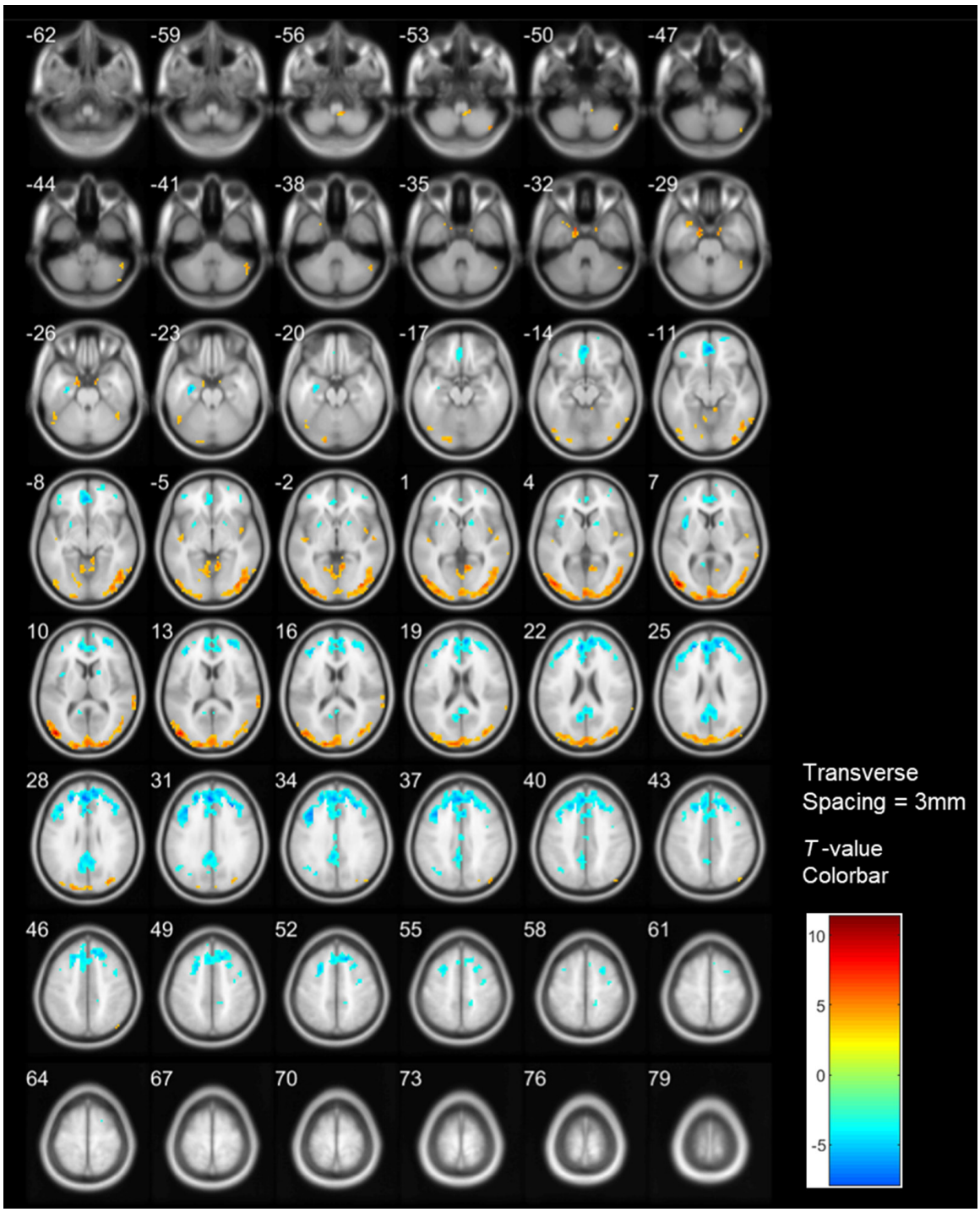

Figure 3. Brain regions with increased and decreased ReHo values after CALM intervention. The bottom right corner contains a T-value color bar: regions with increased T values (elevated ReHo) are depicted in red, while those with decreased T values (reduced ReHo) appear in blue; greater color intensity corresponds to higher absolute T values. As shown in the figure, post-CALM ReHo increases were observed in the bilateral occipital and temporal regions, including the superior, middle, and inferior occipital gyri, lingual gyrus, and middle and superior temporal gyri. In contrast, ReHo reductions were noted in the frontal and cingulate regions, including the bilateral middle, medial, and dorsolateral superior frontal gyri, anterior cingulate and paracingulate gyri, precuneus, posterior cingulate, and left angular gyrus.

Table 3. Region details with group difference in FC value

Brain regions (Anatomical Automatic Labeling)	L/R	Voxels	MNI coordinate			*T* value	*P*
			X'	Y	Z		
CALM-post < CALM-pre							
Cluster 1			33	-81	-18	-4.6577	< 0.001
Lingual	R	14					
Cluster 3			-18	-75	-15	-4.5913	< 0.001
Calcarine	L	34					
Lingual	L	23					
Calcarine	R	12					
Cluster 4			42	-78	-9	-4.8614	< 0.001
Occipital_Mid	R	14					
Temporal_Inf	R	13					
Cluster 5			-36	-93	-3	-5.3029	< 0.001
Occipital_Mid	L	21					
CALM-post > CALM-pre							
Cluster 2			9	42	-12	4.1366	< 0.001
Cingulum_Ant	L	7					
Frontal_Med_Orb	R	6					

Abbreviation: CALM, Managing Cancer and Living Meaningfully.

cingulate gyrus following the CALM intervention.

Altered brain FC patterns after CALM intervention

Based on the ReHo analysis results, the bilateral MFGs were selected as the region of interest (ROI) for FC analysis. As detailed in **Table 3** and **Figure 4**, post-intervention comparisons indicated a significant reduction in FC between the ROI and the bilateral lingual gyrus, bilateral calcarine sulci, bilateral middle occipital gyrus, and right inferior temporal gyrus. In contrast, a notable increase in FC was observed between the ROI and the left anterior cingulate and paracingulate gyrus, as well as the right MFG orbital region, following CALM intervention.

Correlation between cognitive function changes and fMRI alterations after CALM intervention

As illustrated in **Figure 5**, the change in MMSE (ΔMMSE) exhibited a positive correlation with ΔReHo in the left MFG (P = 0.042, r = 0.355). Additionally, FC analyses revealed significant associations between ΔMMSE and the left calcarine (P = 0.044, r = 0.353), right middle occipital gyrus (P = 0.029, r = 0.388), and left middle occipital gyrus (P = 0.014, r = 0.423).

Discussion

This study demonstrated that CALM intervention yielded a marked improvement in cognitive function among BCs compared to CAU. Post-intervention ReHo analysis indicated significant increases in the bilateral superior, middle, and

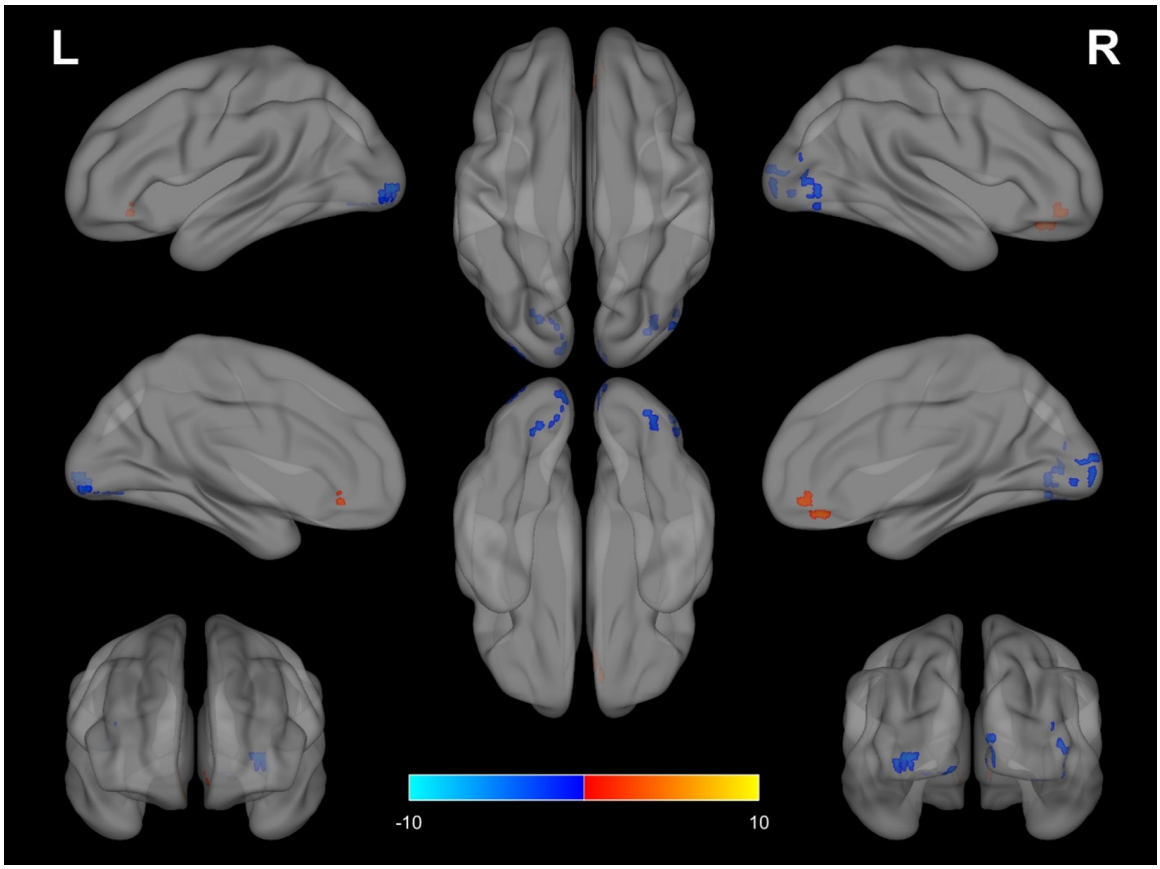

Figure 4. Brain regions with enhanced and reduced functional connectivity after CALM intervention. The accompanying color bar represents T values, with red indicating regions of increased FC and blue denoting areas with reduced FC. Greater absolute T values correspond to more intense coloration. As illustrated in the figure, FC analysis revealed diminished connectivity between the middle frontal gyrus and occipital/calcarine regions, while enhanced connectivity was observed with the left anterior cingulate/paracingulate and right orbitofrontal regions.

inferior occipital gyri, lingual gyrus, middle temporal gyrus, and right superior temporal gyrus. Conversely, ReHo values exhibited significant reductions in the bilateral MFGs, medial and dorsolateral superior frontal gyri, anterior cingulate and paracingulate gyri, inferior frontal gyrus triangles, left orbital MFG, medial and paracingulate gyri, bilateral precuneus, posterior cingulate gyrus bilaterally, and left angular gyrus. FC analysis, with the bilateral MFGs as the ROI, revealed decreased FC between the ROI and regions including the bilateral lingual gyrus, calcarine, middle occipital gyrus, and right inferotemporal gyrus. In contrast, FC between the bilateral MFGs and the left anterior cingulate and paracingulate gyrus, along with the right orbital MFG, demonstrated a notable increase. Cognitive function enhancement may be linked to decreased ReHo values in the left MFG and reduced FC between the ROI and regions such as the left calcarine, right middle occipital gyrus, and left middle occipital gyrus.

The posterior-anterior shift in aging (PASA), first identified by Grady et al. in 1994 through a positron emission tomography (PET) study on face and position perception [25], describes the age-related decline in occipitotemporal activity accompanied by increased frontal activation. Subsequent research has associated PASA with alterations in cognitive domains such as attention [26], visual cognition [25], and working memory [27]. Evidence suggests that heightened frontal lobe activity serves as a compensatory mechanism when diminished occipital lobe function fails to support cognitive demands in older adults [28]. A comparable pattern has been observed in BC patients experiencing CRCI, where frontal hyperactivation relative to healthy controls is particularly evi-

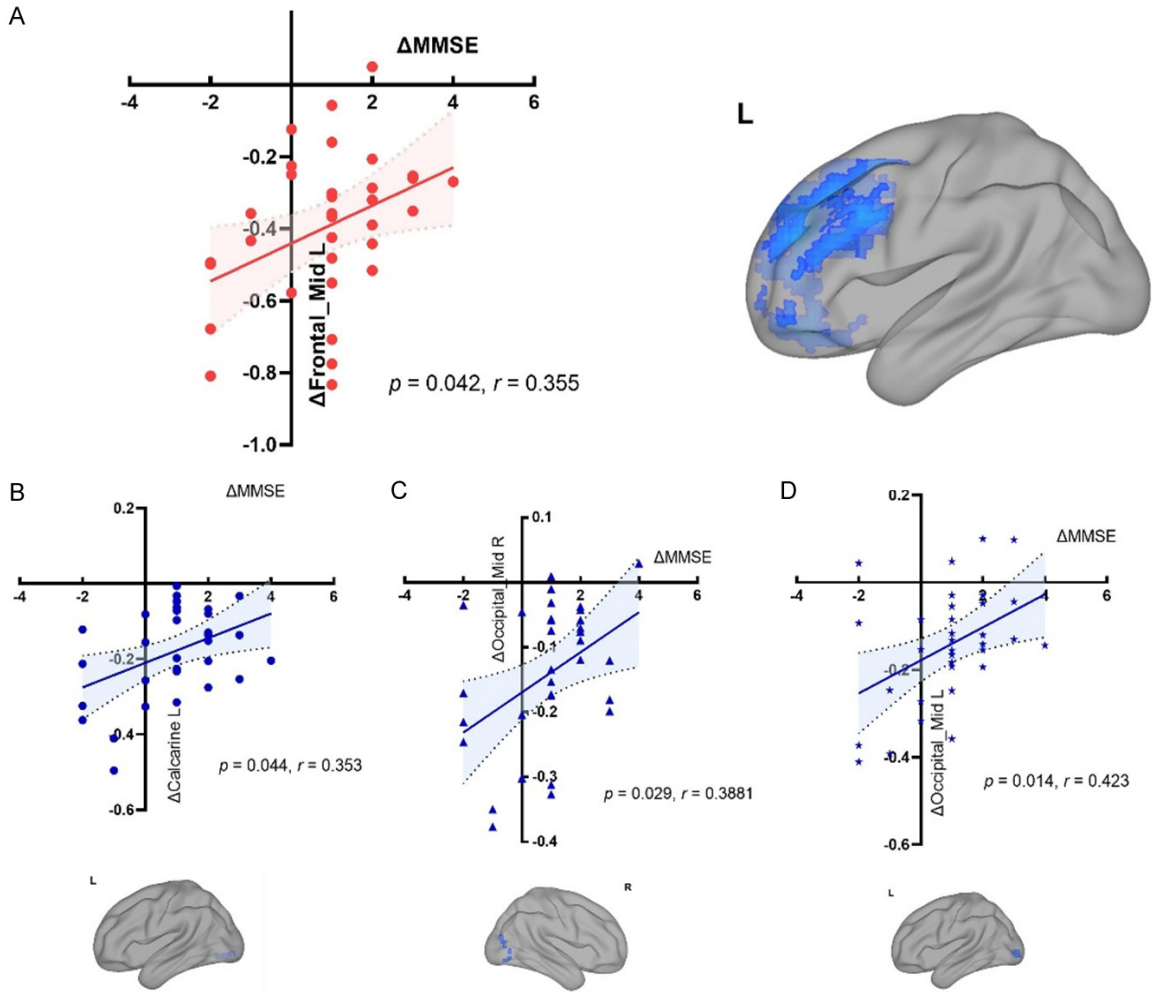

Figure 5. Correlation between ΔReHo/FC and ΔMMSE after CALM intervention. Red boxes represent the correlation analysis between ΔReHo and ΔMMSE, while blue boxes depict the correlation analysis between ΔFC and ΔMMSE. Specific brain regions are visualized using BrainNet. After the CALM intervention, ΔMMSE exhibited a positive correlation with the ΔReHo value in the left MFG (A, *P* = 0.042, r = 0.355). FC analysis revealed significant associations between the MFG and the left calcarine (B, *P* = 0.044, r = 0.353), right middle occipital gyrus (C, *P* = 0.029, r = 0.388), and left middle occipital gyrus (D, *P* = 0.014, r = 0.423) with ΔMMSE.

dent post-chemotherapy [29]. This shift in neural processing reflects an adaptive redistribution of cognitive resources to frontal regions to counteract posterior deficits, notably in the posterior parietal lobe and pontine cortex [30]. Increased ReHo values in the right orbitofrontal region and left dorsolateral prefrontal cortex have been reported in BC patients following chemotherapy, though some studies have found no significant correlation between these changes and cognitive performance [31]. Additionally, DTI-based analyses have revealed substantial reductions in fractional anisotropy (FA) within occipital white matter tracts, which correlate with impairments in attention and verbal memory [32]. In the present study, reduced ReHo values following CALM intervention were primarily observed in the frontoparietal lobe, whereas increased ReHo values were predominantly localized to the occipital lobe. Notably, lower ReHo values in the frontal region were associated with enhanced cognitive performance. These results suggest that CALM intervention may promote compensatory neural mechanisms, reallocating cognitive resources to regions essential for cognitive processing. However, as only post-intervention data are analyzed, longitudinal studies are required to

validate these observations and elucidate the sustained effects of CALM intervention on cognitive function in patients with BC.

The default mode network (DMN), including the posterior cingulate cortex (PCC), precuneus, anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC), exhibits heightened susceptibility to chemotherapy-induced disruptions [33, 34]. Changes in DMN connectivity have been identified as key neuroimaging markers of aging and disease-related cognitive decline [35]. Retrospective analyses indicate that chemotherapy in patients with BC predominantly affects the precuneus and medial frontal gyrus within the DMN [36]. The precuneus, a medial parietal region essential for spatial function, navigation, and memory [37], serves a central function in DMN activity and cognitive processing [38]. Low-frequency amplitude (ALFF)-based studies have reported increased neural activity in DMN regions post-chemotherapy in patients with BC [39]. In contrast, the present study identified reduced ReHo in the bilateral precuneus following CALM intervention, with no observed correlation to cognitive changes. This raises the possibility that such alterations may reflect functional brain recovery, warranting further investigation. Future research should clarify the dynamic changes in precuneus activity post-chemotherapy and its broader role within the DMN in patients with BC.

The MFG, a key region within the ventral medial prefrontal cortex, is involved in higher-order cognition, prospective memory [40], emotional regulation [41], and cognitive impairment [42]. A significant reduction in ReHo within bilateral MFGs was observed following CALM intervention, with decreased synchronized neuronal activity in the left MFG showing a significant correlation with cognitive improvement. However, the lack of data from BC patients who do not receive chemotherapy raises uncertainty regarding whether the extensive ReHo reduction in the frontal lobe post-CALM represents a novel alteration or the resolution of prior compensatory mechanisms. While ReHo analysis primarily quantifies localized neural activity, FC evaluates functional communication across spatially distinct brain regions. A previous study on post-chemotherapy BC patients reported diminished FC between the PCC and MFG compared to healthy controls, with this decline associated with attention performance. That study, which designated the PCC as the ROI, did not identify any regions with increased FC to the PCC [43]. In contrast, no alterations in FC between the MFG and PCC were detected in this study, potentially due to differences in ROI selection and reference standards. Chemotherapy-induced modifications in functional connectivity are not unidirectional, likely reflecting compensatory neural mechanisms. When connectivity in a specific brain region is disrupted by injury, increased activity in other regions may emerge to counteract cognitive deficits [44, 45]. In such cases, as neural efficiency declines, the brain becomes less selective in recruiting specific regions for task execution but compensates by reorganizing and forming new connections. Hosseini et al. reported both hypo- and hyper-connectivity in BC patients post-chemotherapy compared to non-chemotherapy patients and healthy controls [46]. Notably, heightened connectivity between the MFG and subparietal lobule correlated with cognitive alterations, suggesting an adaptive response that may help preserve cognitive function following chemotherapy. Similarly, in the present study, CALM intervention resulted in both hypo- and hyper-connectivity in MFG-based FC analyses, with only hypo-connectivity changes associated with cognitive improvement. These findings highlight the need for future interventional studies on CRCI to incorporate multiple time points, allowing for a more comprehensive investigation into the mechanisms governing functional brain connectivity restoration.

The MFG functions as a central interface between top-down and bottom-up attentional control mechanisms [47, 48], with the right MFG serving as a key hub connecting the dorsal attention network (DAN) and ventral attention network (VAN). Beyond regulating these networks, it modulates both endogenous and exogenous attention [49-51]. A study on major depressive disorder (MDD) identified reduced ReHo in the left mid-frontal cortex among untreated patients, with FC analysis indicating a weakened connection between the left MFG and supra-frontal gyrus before treatment. This connectivity was strengthened following transcranial magnetic stimulation, though no correlation with depression scores was observed

[52]. In contrast, the present study detected a significant reduction in ReHo values in the bilateral MFG after CALM intervention. While FC analysis using this ROI does not reveal significant associations with the VAN and DAN, the functional relevance of the MFG in attentional processes warrants further exploration, particularly in longitudinal studies on CRCI in patients with BC.

Despite offering valuable insights, several limitations must be considered. First, although the CALM intervention proves more effective than the CAU intervention in enhancing cognitive function in patients with BC, fMRI data are only collected pre- and post-intervention for the CALM group. A more comprehensive study design incorporating pre- and post-intervention data for both groups would strengthen the reliability of conclusions. Second, with longitudinal data limited to two time points, the study does not capture the dynamic trajectory of CRCI in patients with BC or its specific effects on cognitive function. Expanding future research to include multiple follow-up assessments - such as pre-chemotherapy, post-chemotherapy, and post-intervention - would provide a more detailed characterization of cognitive impairment and recovery. Third, while the MMSE is widely used in CRCI studies for its reliability and validity, its limited sensitivity reduces its effectiveness in detecting subtle cognitive shifts. A more extensive battery of neuropsychological assessments should be incorporated in future studies to refine cognitive evaluations. Lastly, the relatively small sample size constrains the generalizability of the findings. Larger-scale studies with increased participant numbers are essential to enhance the validity and reliability of the results.

Conclusion

CALM intervention contributes to cognitive function improvement in patients with BC exhibiting CRCI, with the MFG potentially serving as a key factor in this process. Further investigation into the underlying neural mechanisms of CALM intervention is necessary to facilitate its broader application.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

Address correspondence to: Mingjun Zhang and Huaidong Cheng, Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China. E-mail: 1386595-2007@163.com (MJZ); chd1975ay@126.com (HDC)

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Supplementary Table 1. The details of each session in CALM intervention

Session	Topic	Content
Session 1	Managing sysptoms of patients and talking with their healthcare providers	This section requires the therapist to pay close attention to the patient's symptoms, physical condition. In order to change their misunderstandings about breast cancer, therapist will popularizing breast cancer-related knowledge, such as the occurrence and prevention of hair loss, cognitive impairment, fatigue, sleep disorders and other symptoms. Patients will learn that these symptoms will alleviated over time. Since the unknown is the source of fear, the therapist will introduce the mechanism of different treatment methods in an easy to understand way, thus will make patients more confident in their treatment plans. The therapist will communicate with their healthcare providers to understand the emotional state of the patient at home and make plans for the next session of intervention.
Session 2	Changes in themselves and relationships with close others	In this session, patients can discuss with the therapist about their changes after illness. The therapist will pay close attention to patient's relationships with their healthcare providers amd analyze the patient's relationship with family and friends from various perspectives. The patients will get some guidance to return to the normal life circle from the therapist.
Session 3	Review and summary	After two sessions, patients will be guided to establish positive patterns of thinking. In this session, patients will be directed to talking about their harvest in the process of the first two interventions and their recent changes in mentality. And the therapist will provide some methods such as mindfulness meditation to help patients relieving nervousness, which will help patients to relax physically and mentally.
Session 4	Spirtual wellbeing and a sense of meaning and purpose	In this session, therapists will help patients recall happy times during treatment and perceive spiritual wellbeing. Patients will learn that cancer is only a part of life setbacks, and many people's experiences are more painful. Learn to face these setbacks and span it to find sense of meaning and purpose.
Session 5	Concerns about mortality and future	Mortality and future are the greatest concerns of every patient, the therapist will communicate with patients about attitudes toward future and their fears about dying from cancer. The therapist may encourage patients to face up fears and anxieties, then facilitate attention to advanced care planning and death preparation.
Session 6	Review and summary	The patients will be guided to review their feelings of participating in CALM intervention, and summarize their feelings on the current state and their plans for future life to the therapist. The therapist will record the patient's feelings and help the patient summarize the coping measures for the unhealthy mentality.