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THE CREATIVE PSYCHOSOCIAL GENOMIC HEALING EXPERIENCE (CPGHE) AND GENE EXPRESSION IN BREAST CANCER PATIENTS: A FEASIBILITY STUDY

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Abstract

Background—Biomarkers associated with inflammation and immune function are increasingly being used to examine mechanisms of the effects of mind-body therapies. Less researched are biomarkers associated with cognitive and executive functioning in the study of mind-body therapy mechanisms and effects. This study explored the feasibility of recruiting breast cancer patients (BCPs) and implementation fidelity of participation in a research project utilizing the 4-stage Creative Psychosocial Genomic Healing Experience (CPGHE), a mind-body protocol that is theorized to create epigenetic effects via targeted psychological change in emotional triggers in coping with cancer.

Methods—Eight BCPs were identified as eligible (stages I, II, III, early phases of treatment) and five consented to one of two intervention groups (allocated to a single session or two sessions of CPGHE). Blood draws were examined pre- and post- intervention for a stress/inflammation gene expression marker, Nuclear Factor kappa-B (NF-kB), and three markers associated with synaptic plasticity undergirding cognitive and executive functioning: Early Growth Response 1 (EGR1), activity-regulated cytoskeleton-associated protein (Arc), and brain-derived neurotrophic factor (BDNF).

Results—One consented BCP dropped out due to illness. The remaining four adhered to the 4-stage CPGHE protocol and found the CPGHE experience beneficial. Blood samples for the gene expression results were collected and processed according to planned protocol without incident.

Conclusion—Implementing the CPGHE and achieving good adherence among a sample of BCPs is feasible. Processing of blood samples collected from BCPs for gene expression data is also feasible.

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Keywords

Mind-body therapy; stress; NF-kB gene expression; Arc gene expression; EGR1 (zif-268) gene expression; BDNF gene expression; breast cancer

1. Introduction

Breast cancer patients often deal with symptoms that are related to the impact of initial diagnosis, disease, and treatment, including physical symptoms such as fatigue, nausea, pain, headaches, bowel irritability and insomnia, and psychological conditions such as depression, anxiety, fear, and cognitive dysfunction (Goldman, 2017; Harris et al., 2017; O'Regan and Hegarty, 2017; Perez-Fortis et al., 2017; Zdenkowski et al., 2016). A wide body of research has documented the efficacy of mind-body therapies (MBT) to support breast cancer patients coping with the symptoms associated with the stress of diagnosis and treatment sequelae, indicating these therapies provide some amelioration for many of these symptoms (Fong et al., 2017; Jeitler et al., 2017; Stefanopoulou and Grunfeld, 2016; Derry et al., 2015; Dobos et al., 2015; Larkey et al., 2015; Irwin et al., 2014; Montgomery et al., 2010).

Knowledge about the biological mechanisms mediating MBTs supportive effect is increasing mostly focused on MBT's effect on pro-inflammation factors and the effects on symptoms (Bower and Irwin, 2016; Bower et al., 2014; Black et al., 2012; Creswell et al., 2012; Dusek et al., 2008). The biological mechanisms less understood and studied are MBT's potential supportive effects for cognitive dysfunction, a common symptom complaint from BCPs (Jung et al., 2017; Meattani et al., 2017; O'Sullivan and Ruddy, 2016; Paquet et al., 2017; Janelsins et al., 2016; Rendeiro et al., 2016; Schmidt et al., 2016). The etiology for cognitive dysfunction in BCPs remains elusive, but includes potential causative factors such as fatigue, anxiety, depression, stress management, sleep quality and post-traumatic stress, (Hermelink et al., 2017; Oh, 2017; Ramalho, et al., 2017; Vardy et al., 2017; Henneghan, 2016; Jean-Pierre and McDonald, 2016, Li et al., 2016).

Most studied are common chemotherapeutic agents used for BCPs linked to cognitive dysfunction (Fardell, Vardy, Menning et al., 2017; Kesler and Blayney, 2016; Yao et al., 2016; Monds and Johnston, 2015; Kitamura et al., 2015; Salas-Ramirez et al., 2015). There is a need for more rigorous research to measure the effects of MBTs on cognitive dysfunction in BCPs (Bragard et al., 2017; Wirkner et al., 2017; Derry et al., 2015; Avisar et al., 2012; Galantino et al., 2012).

Gene expression has recently become an important arena of investigation for more specifically understanding the biological mechanisms of MBT's effects on symptoms associated with the cancer experience. Gene expression analyses have demonstrated the efficacy of MBTs to reverse inflammation-related gene expression (Bower and Irwin, 2016; Irwin et al., 2014; Bowers et al., 2014). Bowers and Irwin (2016) reviewed 26 randomized controlled trials and found MBTs had mixed effects on circulating inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6). They found more consistent effects of MBTs on decreased expression of pro-inflammation genes through reduced

signaling along pro-inflammation transcription factor Nuclear Factor kappa-B (NF-kB) pathways (Bower and Irwin, 2016).

Less understood, is the efficacy of MBTs to promote gene expression associated with cognitive and executive function (McEwen, 2017; Zheng et al., 2015; Tang, 2011). Specifically, what is not understood clearly is the potential of MBTs to affect synaptic plasticity supporting cognitive and executive function (Apple et al., 2015; Mandelblatt, et al., 2016, Lange et al., 2016). The gene expression of Early Growth Response 1 (EGR1), activity-regulated cytoskeleton-associated protein (Arc), and brain-derived neurotrophic factor (BDNF) are all linked to synaptic plasticity supporting cognitive and executive function (Lacar et al., 2016; Oikkonen et al., 2016; Ninan, 2014; Karpova, 2014; Alder et al., 2003; Bramham and Panja, 2013, Sakuragi et al., 2013).

The 4-stage Creative Psychosocial Genomic Healing Experience (CPGHE) is a mind-body intervention developed by psychologists who use therapeutic hypnosis with their clients (Rossi et al., 2011). The CPGHE protocol's objective is to facilitate problem solving and emotional healing that potentially modulates a variety of biological mechanisms connecting mind and body pathways associated with inflammation and, possibly cognitive function (Rossi et al., 2011).

The CPGHE protocol invites the participant to become aware of personal and troubling issues with the goal of identifying the issue clearly. This is followed with the identification of a resolution for this identified issue. The protocol concludes with the integration of this resolution into the life of the participant. This protocol is based on "ideodynamic" self-discovery (Ross, 2002). Ideodynamic refers to the association between an idea and the psychobiological dynamic changes it can generate through the imagination of the participant. The therapist provides guidance for the participant and uses a semi-hypnotic state for deep, meditative consideration during the process.

The CPGHE protocol seeks to reduce perceived stress and enable learning by creating a safe space for participants to engage those seemingly unresolvable issues at the root of their emotional discomfort. Breast cancer patients face a myriad of issues related to their cancer experience, both emotional and physical. The CPGHE protocol appears to offer potentially an avenue for breast cancer patients to address both emotional and physical distress related to their cancer.

This study explored the feasibility of recruiting breast cancer patients (BCPs) to participate in a research project utilizing the 4-stage Creative Psychosocial Genomic Healing Experience (CPGHE) protocol, as a resource for coping with a cancer diagnosis and treatment. This study also explored the feasibility of utilizing peripheral blood samples collected from BCPs to extract data on gene expression as a biomarker. The following genes were measured as biomarkers: Nuclear Factor kappa-B (NF-kB), Early Growth Response 1 (EGR1), activity-regulated cytoskeleton-associated protein (Arc), and brain-derived neurotrophic factor (BDNF).

2. Methods and materials

The Pomona Valley Hospital Medical Center (PVHMC) Institutional Review Board approved the protocol used in this study. All the study participants completed a signed informed consent form prior to enrollment into this study. The participants were recruited from the outpatient population receiving their care at the PVHMC Cancer Care Center.

2.1. Study Design and Patient Recruitment

This is a two-arm, varied dose, pilot study with pre- and post intervention data collection to examine the feasibility of recruitment and the implementation fidelity and potential of the CPGHE protocol as a resource for coping with cancer with associated gene expression biomarkers. As a small pilot feasibility study with high costs per gene expression analysis, the recruitment goal was five BCPs. The following were the BCP inclusion criteria: stages I, II, III of breast cancer, early stages of cancer treatment, and English speaking. The exclusion criteria were: patients who are severely cognitively impaired, patients who are too weak or ill to participate, and patients under the age of 18.

The oncology staff, from the outpatient Cancer Care Center at PVHMC identified eligible BCPs and referred them to the research project team. Referred potential participants were asked if they were interested in enrollment in the study. If yes, the research staff (the first author, the clinical trials coordinator, or the breast health nurse educator) reviewed the informed consent form with the patient, and if agreed, signature was obtained.

The consented participants were non-randomly assigned to two arms, a low and high dose option, to assure equal numbers of participants in each arm. The low dose arm (Participants 1 and 2) received one CPGHE session and the high dose arm (Participants 3 and 4) received two CPGHE sessions. Each CPGHE session was approximately 25–35 minutes in duration. The two CPGHE sessions for the high dose arm were delivered 7 days apart. This was done to preliminarily observe any differences after experiencing more than one CPGHE session. The first author guided the research participants through the four stages of the CPGHE protocol.

2.2. The Creative Psychosocial Genomic Healing Experience (CPGHE) Protocol

This study used the Creative Psychosocial Genomic Healing Experience (CPGHE) as a Mind-Body therapy. The Creative Psychosocial Genomic Healing Experience (CPGHE) is a four-stage protocol. The first author guided the study participants through four stages and utilized the script developed for the CPGHE protocol. The first stage of CPGHE is “**Focusing Consciousness**.” In the first stage, the participant is guided to becoming more self-aware of thoughts and feelings. The second stage is “**Problem Review**.” In the second stage, the participant evaluates thoughts and feelings discovered during the first stage with an emphasis on the identification of an issue or item needing resolution.

The third stage is “**Problem Solving**.” In the third stage, the participant learns how to resolve and/or deal with the issues identified during the third stage. The fourth stage is “**Self-Care**.” In the fourth stage, the participant applies the learning from the third stage in real

life. The participants had the option to share their CPGHE experiences with other study participants (Rossi et al., 2011).

Participants could experience anxiety when exploring memories during the CPGHE session. The CPGHE protocol anticipates such experiences and is designed to create a safe place to explore all emotions related to experience. The study team agreed to report unanticipated and serious adverse events to the Institutional Review Board in a timely manner on an ongoing basis. During the course of the CPGHE session, the participant could find the exploration of experiences emotionally upsetting. If the patient were to become emotionally upset and asked to be removed from the study, then this would be considered an adverse event. If the study team observed that reaction, the participant would be referred to the licensed clinical social worker at the Cancer Care Center for follow-up support.

2.3. Measures: Protocol adherence, mental engagement, stress differences, and comments

Study participant data were collected regarding protocol adherence, mental engagement, stress changes, and comments on the benefits of the CPGHE sessions. The Creative Psychosocial Genomic Healing Experience Scoring and Assessment (CSA) form was used to collect data on these measures as reported by the study participants (Rossi, 2012). The questions posed to the study participants were from the CSA form and addressed protocol adherence/fidelity and two outcome-related evaluation questions to assess mental engagement and stress.

Each stage of the four stages of the CPGHE protocol has an experiential objective for the participant. Fidelty was defined in terms of the participant's ability to experience this objective. Immediately after the CPGHE session, the first author assessed perception of intervention fidelity by asking the participants to respond "yes" or "no" questions regarding their experiences with the objectives for each stage of the protocol.

Mental engagement was defined as the participant's ability to immerse herself in the protocol, evidenced by the loss of the ability to accurately track elapsed time. Immediately after the CPGHE session, the first author asked the participants what was their "estimated time" in minutes of the CPGHE session (Rossi, 2012). This estimated time was compared to the "real time" in minutes of the CPGHE session to calculate the "mental engagement" of the participants with the CPGHE protocol. This calculated mental engagement percentage is understood to be directly proportional to the participant's ability to immerse into the protocol.

Prior to the CPGHE session, the first author asked the participants what the percentage of their perceived "initial stress" was on a scale of 0 to 100 (Rossi, 2012). Then, immediately after the CPGHE session, the participants were asked what the percentage of their "final stress" was on a scale of 0 to 100. This data was used to calculate the self-perceived stress change percentages, pre- and post-CPGHE sessions. The participants' comments about their opinion on the benefits of the CPGHE protocol were also collected after the CPGHE session.

2.4. Measures: Blood Sample Collection for Gene Expression Data

The clinical trails coordinator collected blood samples at baseline and post-CPGHE sessions to examine gene expression changes. For the high dose arm, the post-CPGHE session blood draw was done 7 days after baseline. The blood samples were transported to the genomics lab at the Children's Hospital of Los Angeles (CHLA). The genomics lab at CHLA extracted the mRNA from the blood samples and transported the mRNA to the genomics lab at the University of Nevada Las Vegas (UNLV) for microarray analysis. Blood and RNA samples sent to CHLA and UNLV were identified solely by codes assigned by the PI to the participants' samples.

The genomics lab at the UNLV conducted the microarray analysis with the GeneChip® PrimeView™, Human Gene Expression Array, manufactured by Affymetrix. Once completed, the UNLV genomics lab sent the data file results from the microarray analysis to the first author by secured email. This study used Partek® Genomics Suite statistical software manufactured by Partek® to analyze the microarray data files (Partek®, 2014).

3. Results

3.1. Study Participant Recruitment and Retention

The oncology staff from the outpatient Cancer Care Center at PVHMC referred eight eligible BCPs to the research project team. Of the eight study eligible BCPs, five consented to participate in the study. One of the five consented participants dropped out of the study due to illness. All participants were female, age mean: 53; race: one Asian and three White.

3.2. Study Participant Mental Engagement with CPGHE Protocol

The real time CPGHE session for Participant 1 was 32 minutes, and she estimated the CPGHE session at 15 minutes, resulting in a mental engagement of 213%. The real time CPGHE session for Participant 2 was 27 minutes, she estimated the CPGHE session at 30 minutes, resulting in a mental engagement of 90%. The first real time CPGHE session for Participant 3 was 27 minutes, and she estimated the first session at 18 minutes, resulting in a mental engagement of 150%.

The first real time CPGHE session for Participant 4 was 32 minutes, and she estimated the first session at 30 minutes, resulting in a mental engagement of 106%. The second real time CPGHE session for Participant 3 was 27 minutes, and she estimated the second session at 30 minutes, resulting in a mental engagement of 90%. The second real time CPGHE session for Participant 4 was 27 minutes, and she estimated the second session at 23 minutes, resulting in a mental engagement of 117%.

3.3. Study Participant Stress Differences

Participant 1 reported a 25% reduction in stress after the CPGHE session. Participant 2 reported a 10% reduction in stress after the CPGHE session. Participant 3 reported a 27% *increase* in stress after the first CPGHE session and after the second CPGHE session she reported a 0% in stress reduction. Participant 4 reported a 38% decrease in stress after the

first CPGHE session and after the second CPGHE session she reported a 25% in stress reduction.

3.4. Study Participant Comments

The study participants reported they experienced the CPGHE protocol as beneficial. Participant 1 described: “the CPGHE session was a calming experience.” Participant 2 reported, “the CPGHE session was helpful relief from stress”. Participant 3 explained, “the CPGHE session was helpful” and Participant 4 shared, “the CPGHE session was similar to self-hypnosis”. The four participants also reported high levels of adherence and various levels of fidelity with the CPGHE protocol.

3.5. Gene Expression Data

Group 1 (n=2)	NF-kB GE Down-Regulated	EGR 1 GE Up-Regulated	Arc GE Up-Regulated	BDNF GE Up-Regulated
Participant 1	Yes	Yes	No	Yes
Participant 2	No	Yes	No	Yes
Group 2 (n=2)				
Participant 3	No	No	No	No
Participant 4	No	Yes	No	No

Participant 1 evidenced down-regulation in the NF-kB signaling pathway and participants 2, 3, and 4 did not evidence down-regulation in the NF-kB signaling pathway. Participants 1, 2, and 4 evidenced up-regulation in EGR1 gene expression and participant 3 did not evidence up-regulation of EGR1 gene expression. Participants 1, 2, 3, and 4 all did not evidence up-regulation in Arc gene expression. Participants 1 and 2 evidenced up-regulation in BDNF gene expression. Participants 3 and 4 did not evidence up-regulation in BDNF gene expression.

4. Discussion

This feasibility study is the first attempt to utilize the 4-stage CPGHE protocol with breast cancer patients. The study participants engaged in the CPGHE protocol through the 4 stages of the protocol with high levels of adherence to each step. Also, the study participants reported they experienced the 4-stage CPGHE protocol as beneficial. The blood samples collected from the research participants were delivered to genomics labs and processed for gene expression data results without incident.

The 4-stage CPGHE protocol’s objective is to facilitate problem solving and emotional healing by activating experience dependent gene expression that modulates a variety of biological mechanisms connecting mind and body pathways. The protocol’s goal is to enable emotional healing by supporting the subject’s ability to solve existential issues. The combination of the CPGHE protocol with gene expression analysis has been attempted before with human subjects (Rossi et al., 2011). These human subjects were relatively

healthy with a background in hypnotherapy and meditation. This feasibility study was the first attempt to utilize the CPGHE protocol with breast cancer patients.

The CPGHE protocol defines mental engagement as a type of “time distortion,” a concept studied by psychologists who use therapeutic hypnosis with their clients (Rossi, 2012). For example, a therapeutic hypnosis session may be 20 minutes in duration but the client estimates the session at 5 minutes. The client’s ability to engage or become absorbed in the session distorts time.

This deep engagement is also understood by the CPGHE protocol as a creative and focused mental activity that potentially affects activity-dependent gene expression linked to brain plasticity associated with learning and memory (Rossi, 2012). Participant 1’s mental engagement score was highest at 213%. This participant was the only one who evidenced down-regulation in the NF-kB signaling pathway. The NF-kB signaling pathway supports pro-inflammatory gene expression associated with stress. Participant 1 may have utilized the CPGHE protocol as a calming experience down-regulating the pro-inflammatory NF-kB gene expression. The calming CPGHE experience may have also supported Participant 1’s creative and focused mental activity evidenced by the up-regulation of EGR1 and BDNF gene expression associated with brain plasticity and learning.

Participant 1, from the low dose group, also reported a 25% stress reduction after the CPGHE session. On the other end of the spectrum, Participant 3, from the high dose group, reported a stress *increase* of 27% after the first CPGHE session and 0% stress reduction after the second CPGHE session. Participant 3’s reported stress levels are evidenced by the absence of NF-kB down-regulation and the absence of the EGR1, Arc, and BDNF up-regulated gene expression.

4.1. Limitations

The limitation of this study was the small number of participants. The small number of participants would not allow the testing of a hypothesis or any establishment of statistical significance of the study’s results. Additionally, the small number of participants was underpowered and would not allow for a reasonable test of a significant correlation between the self-reported data collected with the CSA and the gene expression results. The CSA form is not a validated instrument to measure perceived stress, mental engagement or cognitive function. Since this was a feasibility study, the number of participants was fixed by the gene expression technology chosen for the study.

4.2. Conclusions

Breast cancer patients were recruited, consented, and enrolled into this feasibility study with only minor attrition and participated in the data collection and the intervention without adverse events. Eight BCPs were identified as eligible and referred, and subsequently five consented to participate in the study. One participant dropped out of the study due to illness. All the research participants cooperated and engaged the 4-stage CPGHE protocol but not all fully experienced the objectives of the protocol. The blood samples from BCPs were collected without incident and delivered to the CHLA genomics lab for RNA extraction. The

CHLA lab delivered the extracted RNA to the UNLV genomics lab for the DNA microarray process. The DNA microarray results provided data for gene expression analysis.

In this completed feasibility study, the participants experienced each stage for an average of seven minutes. In a subsequent study, this average could be increased to fifteen minutes to provide more time for the participant to experience the intentions of each stage. This time increase may support the up-regulation of Arc gene expression, absent in all study participants and fidelity to CPGHE protocol stages. One CPGHE session with longer duration time for each stage may be sufficient to collect more data to detect differences in the effects of the 4-stage protocol on breast cancer patients. For next steps in the study of the CPGHE protocol effects on BCPs, the first author recommends increasing the number of enrolled BCPs, one CPGHE session of sufficient length, cortisol and melatonin measurements, and the use of RNA sequencing techniques instead of DNA microarrays in order to collect more gene expression data.

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Highlights

- This study explored the feasibility of recruiting and enrolling breast cancer patients into a study using the mind-body therapy, the 4-stage Creative Psychosocial Genomic Healing Experience (CPGHE) protocol.
- Study participants' adherence and implementation fidelity to the 4-stage CPGHE protocol were assessed.
- Feasibility of utilizing gene expression as a biomarker processed from collected peripheral blood samples of breast cancer patients.
- Breast cancer patients enrolled and participated with minimal attrition and found the CPGHE protocol beneficial.

Table 1

Group 1 (Low Dose): CPGHE Mental Engagement: First and Only Session

Group 1 (n=2)	Real CPGHE Session Time: Minutes	Estimated CPGHE Session Time: Minutes	Mental Engagement (Real Time/Estimated Time x 100)
Participant 1	32 minutes	15 minutes	213%
Participant 2	27 minutes	30 minutes	90%

Table 2

Group 2 (High Dose): CPGHE Mental Engagement: First Session

Group 2 (n=2)	Real CPGHE First Session Time: Minutes	Estimated CPGHE First Session Time: Minutes	Mental Engagement (Real Time/ Estimated Time x 100)
Participant 3	27 minutes	18 minutes	150%
Participant 4	32 minutes	30 minutes	106%

Table 3

Group 2: CPGHE Mental Engagement: Second Session

Group 2 (n=2)	Real CPGHE Second Session Time: Minutes	Estimated CPGHE Second Session Time: Minutes	Mental Engagement (Real Time/ Estimated Time x 100)
Participant 3	27 minutes	30 minutes	90%
Participant 4	27 minutes	23 minutes	117%

Table 4

Group 1 (Low Dose): Self-Reported Stress Levels: First and Only Session

Group 1 (n=2)	Initial Stress: 0%– 100% Pre-CPGHE Intervention	End Stress: 0%– 100% Post- CPGHE Intervention	Stress Reduction: % Post-CPGHE Intervention
Participant 1	50%	25%	25%
Participant 2	10%	0%	10%

Table 5

Group 2 (High Dose): Self-Reported Stress Levels: First Session

Group 2 (n=2)	Initial Stress: 0%– 100% Pre-CPGHE Intervention	End Stress: 0%– 100% Post-CPGHE Intervention	Stress Reduction: % Post- CPGHE Intervention
Participant 3	1%	28%	27% (increase)
Participant 4	50%	12%	38%

Table 6

Group 2: Self-Reported Stress Levels: Second Session

Group 2 (n=2)	Initial Stress: 0%– 100% Pre-CPGHE Intervention	End Stress: 0%– 100% Post- CPGHE Intervention	Stress Reduction: % Post-CPGHE Intervention
Participant 3	20%	20%	0%
Participant 4	50%	25%	25%