Wu Changwei (Orcid ID: 0000-0001-8968-9366)

Mindfulness-based Cognitive Therapy on Bereavement Grief: Alterations of Resting-state Network Connectivity Associate with Changes of Anxiety and Mindfulness

Feng-Ying Huang[1†], Ai-Ling Hsu[2†], Yi-Ping Chao[3], Chloe Mu-Hsuan Shang[4], Jaw-Shiun Tsai[5,6], Changwei W. Wu[2,7*]

[1]Department of Education, National Taipei University of Education, Taipei, Taiwan

[2]Brain and Consciousness Research Center, Shuang Ho Hospital-Taipei Medical University, New Taipei, Taiwan;

[3]Graduate Institute of Medical Mechatronics, Chang Gung University, Taoyuan, Taiwan;

[4]Department of Psychology, University of Michigan, Ann Arbor, MI, USA;

[5]Department of Family Medicine, College of Medicine and Hospital, National Taiwan University, Taipei, Taiwan;

[6]Center for Complementary and Integrated Medicine, National Taiwan University Hospital, Taipei, Taiwan;

[7]Graduate Institute of Mind, Brain and Consciousness, Taipei Medical University, Taipei, Taiwan;

[†] The two authors are equally contributed to this work.

[*]Please address correspondence to Changwei W. Wu, PhD, 12 Floor, 172-1, Section 2, Keelung Road, Taipei, Taiwan 10675; phone: +886-2- 6638-2736 ext 1234; e-mail: sleepbrain@tmu.edu.tw.

Running title: MBCT-induced connectivity change on bereavement grief

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Abstract

Bereavement, the experience of losing a loved one, is one of the most catastrophic but inevitable events in life. It causes grief and intense depression-like sadness. Recent studies have revealed the effectiveness and proficiency of mindfulness-based cognitive therapy (MBCT) in emotional regulation among bereavement populations. MBCT improves the wellbeing of the bereaved by enhancing cognitive performances. Regarding the neural correlates of bereavement grief, previous studies focused on the alleviation of emotion-cognition interferences at specific brain regions. Here, we hypothesized that the bereavement grief fundamentally triggers global alterations in the resting-state brain networks and part of the inter-network connectivity could be reformed after MBCT intervention. We recruited 19 bereaved individuals who participated the 8-week MBCT. We evaluated (1) the large-scale changes in brain connectivity affected by the MBCT program; as well as (2) the association between connectivity changes and self-rated questionnaire. First, after MBCT, the bereaved individuals showed the reduction of the inter-network connectivity in the salience, default-mode and fronto-parietal networks in the resting state but not under emotional arousal, implying the alleviated attention to spontaneous mind wandering after MBCT. Second, the alterations of functional connectivity between subcortical (e.g., caudate) and cortical networks (e.g., cingulo-opercular/sensorimotor) were associated with the changes of the mindfulness scale, the anxiety and the emotion regulation ability. In summary, MBCT could enhance spontaneous emotion regulation among the bereaved individuals through the inter-network reorganizations in the resting state.

Keywords: Mindfulness-based cognitive therapy (MBCT), emotion regulation, grief, bereavement, functional magnetic resonance imaging (fMRI), functional connectivity.

Introduction

Bereavement grief, the emotional response following the death of a loved one, incorporates various physical, psychological, and behavioral symptoms that have been reported to worsen individuals' physical and psychological health [Assareh et al., 2015; Beem et al., 2000; Buckley et al., 2010]. Intensity and interference symptoms may involve serious negative and sorrowful feelings with regard to the deceased ones, and the grief is often accompanied by excessive self-blame and anger, mixed up with previous memories, as well as worries and fears about living alone in the future without the deceased. Although most bereaved persons can adjust to the loss with time, an increased mortality rate on bereavement has been reported in widowhood, which peaks during the first six months after spousal loss [Christakis and Iwashyna, 2003; Hart et al., 2007; Lichtenstein et al., 1998; Manor and Eisenbach, 2003]. Spousal and late-life bereavement have been reported to be accompanied by inevitable sadness, sleep disturbance, depression and anxiety [Taylor et al., 1999; Zisook and Shear, 2009] or the exacerbation of pre-existing depression [Zisook et al., 1997]. According to the bereaved individuals' reports, the painful grief perception surges in the form of uncontrollable waves in their daily lives [Scott, 2015]. Generally, bereaved individuals have to pass through a long-term grieving process until they accept an adjustment to a life without their loved ones, which may take up to four years in Taiwanese individuals [Tseng et al., 2017; Zisook and Shear, 2009]. However, such prolonged sorrow could lead to a general reduction in cognitive functions [Rosnick et al., 2010] and ultimately adversely affect the brain structure and functionality of the bereaved individual [Gündel et al., 2003; O'Connor et al., 2007].

Early effective intervention for the bereaved populations that encounters challenges following bereavement adjustment is vital for the prevention of the associated physical and psychological disorders. Mindfulness-based cognitive therapy (MBCT) was reported to offer greater emotion-regulation ability than traditional cognitive behavioral therapy (CBT) in anxiety disorders [Troy et al., 2013]. Mindfulness has been described as "the present awareness that emerges through paying attention purposely to what is happening in the present moment with acceptance and nonjudgmentally, and to things as they are" [Segal et al., 2013], which has been extensively documented to be beneficial for emotion regulation [Hölzel et al., 2011; Roemer et al., 2015; Teper and Inzlicht, 2013], major depression [Teasdale et al., 2000] and anxiety disorders [Goldin and Gross, 2010; Kim et al., 2009]. In an empirical study, practicing mindfulness allowed the bereaved individuals to stop overwhelming ruminations and emotional interferences over cognition in their daily life. Therefore, their traumatic bereavement symptoms declined following MBCT [Thieleman et al., 2014]. Recently, the MBCT effect with regard to bereavement grief was reported to enhance cognitive ability [Huang et al., 2019; Tomasino and Fabbro, 2016] and reduce depressive symptoms among elderly bereaved persons [O'Connor et al., 2014]. However, beyond the empirical effectiveness of MBCT on emotion and cognition, research regarding the neurophysiological mechanisms underlying the MBCT-induced bereavement relief remains elusive. We demonstrated the improved performance of executive control in a bereaved population following MBCT, along with the decreased posterior cingulate cortex (PCC) activity [Huang et al., 2019]. Other mechanisms of mindfulness-based neuroplasticity require further investigations, particularly for the populations with intensive bereavement grief.

In search of the neural substrates of bereavement grief, previous studies focused on the induction of transient grief and the reduction of cognitive performance [Gündel et al., 2003; O'Connor et al., 2007]. However, considering the debilitating effects of long-lasting sorrow on moments in daily life, we speculated that the experimental strategy of evoking emotion might not faithfully reflect brain alterations in the bereaved populations. In other words, the persistent bereavement grief does not simply take effect while performing emotional tasks, but consistently affects the overall brain circuits and the inter-network connectivity in the intrinsic resting state. Based on our experiences, bereaved individuals subjectively expressed that their baseline condition changed from an uncontrollable grief attachment into an acceptance of grief after the MBCT course. Therefore, we speculated that the MBCT moderated the hyper-intense brain circuits in the resting state in the bereaved individuals, rather than soothing their brain circuits in the emotion-aroused states. Previous literature has observed the mindfulness-related changes of resting-state brain functions on stressful populations, which are partly consistent with such conjecture. For example, King et al. demonstrated the increased functional connectivity between PCC and dorsolateral prefrontal cortex (DLPFC) in patients with post-traumatic stress disorder after a 16-week mindfulness-based exposure training [King et al., 2016]; Scult et al. also observed the enhanced PCC-DLPFC connectivity strength in 21 patients with general anxiety disorder (GAD) following a 20-week mindful emotion regulation therapy [Scult et al., 2019]. In addition, another study revealed the decreased magnitude of PCC-seeded inter-network connectivity (PCC-insula and PCC-dorsal anterior cingulate cortex), without prominent changes of PCC-DLPFC connectivity, after an 8-week MBCT in 32 GAD patients [Zhao et al., 2019]. Accordingly, the mindfulness-based interventions (MBI) may lead to multiple scenarios of inter-network neuroplasticity to stressful populations in the resting state. In the current study, we specifically targeted on the bereaved population to evaluate the MBCT intervention effect on their brain networks in both resting and emotional states.

In the current study, we aimed at two objectives: (1) disclosing the changes in functional connectivity (under both resting state and emotional arousal) induced by an 8-week MBCT in a population with bereavement grief, and (2) exploring the associations between the connectivity alterations and subjective-perception changes (assessed by questionnaires). Apart from adopting the seed-correlation strategy on a single network, such as the default-mode network (DMN), we adopted a global search of inter-network connectivity. Employing a 2-by-2 factorial design (state-by-training), we disclosed the longitudinal changes in the global brain-network interactions under both the resting state and emotion arousals following MBCT. Finally, we evaluated the relationships between the MBCT-induced neuroplasticity (connectivity changes), and the associated score changes in self-rated questionnaires (anxiety, difficulty in emotion regulation, and mindfulness) were evaluated to unravel the key alterations in brain circuits that are most correlated with subjective perceptions of grief and mindfulness.

Materials and Methods

Participants

The prospective study was approved by the Research Ethics Office of the National Taiwan University and written informed consent was obtained from each participant. A total of 23 bereaved volunteers (2 men and 21 women; age range, 25-66 years) who had experienced the death of at least one first-degree relative within 6 months to 4 years and self-rated with unresolved grief were recruited in this study. They were native Mandarin speakers and were recruited through general advertisements at the National Taipei University of Education's internet forums and in local communities in Taipei city by word-of-mouth. The exclusion criteria were (1) any experience on mindfulness meditation prior to this study; (2) a history of major psychiatric disorders or a use of prescription drug; (3) any known systemic or neurological diseases, and (4) MRI incompatibilities or known claustrophobia.

Prior to receiving an 8-week MBCT training course, participants completed a questionnaire battery, which included (1) Texas Revised Inventory of Grief (TRIG) [Faschingbauer et al., 1981]; (2) Generalized Anxiety Disorder-7 (GAD-7) [Spitzer et al., 2006], (3) the 18-item Taiwanese Depression Questionnaire [Lee et al., 2000], (4) Difficulties in Emotion Regulation Scale (DERS) [Gratz and Roemer, 2004], and (5) Taiwanese version of Five Facet Mindfulness Questionnaire (FFMQ) [Huang et al., 2015]. Participants were compensated for their participation. Four participants dropped out (two moved out of town prior to the beginning of the training course, one did not complete the training course, and one did not receive the imaging scan after the training course). Therefore, complete datasets were available from 19 bereaved volunteers (mean age = 48.3 ± 10.9 years; one male) for imaging data analysis. The fMRI data of this study are not available to the public but will be available on request to the corresponding author.

Mindfulness-based Cognitive Therapy

The intervention adopted was the group-based MBCT program [Segal et al., 2013], which consisted of one meeting per week (2.5 hours each time) plus recommended daily home practice (45 minutes per day) during the 8 weeks. The main focus of the MBCT is to learn to interact with inner experiences such as grief, feelings, and thoughts by using a "being mode of mind" and to let feelings or thoughts remain in the mind without attempting to push them away [Segal et al., 2013]. Throughout the intervention process, the first four weeks of the course allowed the bereaved participants to practice basic skills of mindfulness, recognize how the mind moving from one object to another, and how such mental inertia proliferates the grief. In addition, bereavement participants learned to direct their attention to the present moment, especially by focusing their attention on the breath and body sensations through mindfulness practices. By being able to let go of a problem-solving approach towards negative emotions and cognitive contents, bereaved participants would possibly step out from habitual and automatic ways of acting. Grounded on the above-mentioned abilities, the aim of the 5–8 week course was to sharpen bereaved participants' mindfulness practices to enable them to become skillful in "handling mood shifts" when dealing with difficult situations without being easily entangled by cognitive content. Another goal was to prevent falling into an automated aversive reaction based on an ability to cultivate self-compassion and self-care in their daily life [Segal et al., 2013]. Participants were led by a group therapist with skills training and in-class practice in guided meditation, experiential exercises, and discussions of the participants' daily practices. All the procedures were guided by a grief therapist certificated to facilitate mindfulness interventions. Specific in-class guided meditation included the raisin exercise, mindfulness of breathing, body scans, sitting meditation, 3-min breathing space, mindful walking and listening and yoga. Inquiries and reflection of in-class practices following every skill instruction were immediately evaluated. In addition to the group sessions, participants were instructed to practice mindfulness exercises aided by standard audio-recordings throughout the day and to record their daily practice times at home, which were evaluated in the weekly course sessions. Furthermore, an extra 2-hr introduction session of “acknowledgment of grief and theory of psycho-physical reactions to loss” specifically designed for bereaved individuals was conducted before the standard MBCT program.

MRI Acquisition and Experimental Design

All functional magnetic resonance imaging (fMRI) datasets were acquired on a 3T PRISMA scanner (Siemens, Erlangen, Germany) scanner with a 20-channel brain coil at the National Taiwan University. The protocol included a high-resolution T_1-weighted scan using 3D-MPRAGE sequence (TR/ TE, 1900 ms / 2.28 ms; inversion time, 900 ms; flip angle = 9°; 176 slices with resolution of 1 × 1 × 1 mm^3), followed by fMRI scans using T_2^*-weighted gradient-echo echo-planar imaging sequence (repetition time / echo time = 2000 ms / 35 ms; flip angle = 84°, 33 slices with 4-mm thickness and no gap; in-plane resolution, 3 × 3 mm^2). Visual stimuli were presented via E-prime (Psychology Software Tools, Pittsburgh, PA, USA) with a back-projection system (800 × 600 resolution). Participants were instructed to passively view the stimuli using a mirror mounted on the head-coil and the viewing field was 8.4° (H) by 6.3° (V) at a viewing distance of 420 cm. During the resting-state sessions, the participants will be instructed to fixate at a centrally displayed cross for the entire session, not to fall asleep, not to move head, and not to think of anything in particular for 5 minutes.

The fMRI sessions comprised two parts: one resting-state scan in the first place followed by a facial-expression scan. For the resting-state scan, participants were asked to keep their eyes open, not to move their head, not to fall asleep, and not to think of anything in particular during the 6-min acquisition (180 volumes). The facial expression task was used to probe the alteration of functional connectivity under emotion arousal. The International Affective Picture System (IAPS) is a standardized instrument for the induction of emotional states [Lang et al., 2005]. The current study used datasets of the Taiwanese version of IAPS (T-IAPS) to induce the emotional arousal in participants [Tu et al., 2018]. Therefore, 30 pictures of negative facial expression and 30 pictures of neutral facial expression were drawn randomly from the T-IAPS as continuous visual stimuli in the emotion-arousal session. Each picture was presented with one-second duration followed by a one-sec fixation, a total of 310 face pictures were presented within the acquisition time of 620 seconds. During the scan time, the participants were instructed to view the facial expression pictures passively without the resting period. In the following analysis, we regarded the dataset with the continuous task in another state of emotional arousal and used this dataset as an alternative resting state for the connectivity analysis, resembling the method used in the literature [Tommasin et al., 2017].

Data analysis

Data were analyzed using a custom software, IClinfMRI [Hsu et al., 2018], in a MATLAB 2014a environment (The MathWorks, Inc., Natick, MA, USA). Preprocessing steps included motion correction, normalization to the standard Montreal Neurological Institute (MNI) space with a voxel size of 2 × 2 × 2 mm^3, de-spiking, 3rd order detrending, regressing out covariates (including six motion parameters and two averaged fluctuations over masks of white matter and cerebrospinal fluid), band-pass filtering of 0.01–0.08 Hz, and spatial smoothing using a Gaussian kernel at 4-mm full width at half-maximum.

To investigate group differences in large-scale functional networks, we adopted a scheme that summarized a complex functional organization of the human brain into the 11 networks, namely dorsal attention (DAN), ventral attention (VAN), subcortical (SUB), salience (SN), frontal-parietal (FPN), visual (VN), default mode (DMN), auditory (AN), cingulo-opercular (CON), somatosensory (SMN), and memory networks (MN). These networks were modeled using 245 spherical regions of interests (ROIs) with a 5-mm radius. Among the ROIs, 229 were adopted in a study [Power et al., 2012] that integrated metaanalytic task-based fMRI findings and rs-fMRI findings as spherical ROIs spanning both cerebral and subcortical areas at the Montreal Neurologic Institute (MNI) space. Twelve ROIs were adopted in a study that comprehensively modeled the basal ganglia circuitry by using rs-fMRI functional connectivity analysis [Di Martino et al., 2008]. To supplement additional regions for subcortical network beyond the Power's template, two ROIs at the amygdala and two ROIs at the hippocampus were prescribed from Neurosynth using the term "emotion" resulting from 1037 studies and "memory" resulting from 2744 studies [Yarkoni et al., 2011], respectively.

Using the analytic software of Network-Based Statistics (NBS) [Zalesky et al., 2010], a 245 by 245 inter-regional matrix of functional connectivity was computed for each subject using Pearson correlation between the time series of each ROI pair and then transformed using Fisher r to z transformation. The functional matrices were then used in a second-level random effects analysis to identify (1) the functional connections that were altered significantly after the 8-week MBCT training course across participants, as well as (2) the connections where its changes with regard to the significant changes in the self-rated questionnaire. Firstly, the training effect was evaluated using paired t-tests on pairwise connections in participants' connectivity matrices. Considering the multiple comparisons, the significance level of $p < 0.05$ was corrected by a false discovery rate (FDR) with 10,000 permutations. Of note, the paired t-test FDR is a connection-based controlling procedure based on the nonparametric p-value across permutations. Secondly, to avoid the double-dipping issue [Kriegeskorte et al., 2009] that performing the statistical tests only on those significant connections, we performed the regression analysis to examine the relation between the changes in functional connectivity and that in the 10 self-rated questionnaire scores (the 5 questionnaires and the 5 sub-categories of FFMQ). To correct additional multiple comparison from the 10 questionnaire scores, the correlation results were reported with significance level at FDR-corrected $p < 0.005$ (10,000 permutations).

Results

Self-rated Questionnaires

Paired *t*-test was conducted on the psychological variables following the 8-week intervention of MBCT, and **Table 1** shows the summary of the self-rated scores among the bereaved individuals. Compared with the pre-MBCT scores, the grief (TRIG), negative emotions (GAD-7 and Depression), and the difficulty of emotion regulation (DERS) decreased significantly after MBCT, whereas the mindfulness level (total FFMQ score) increased significantly. Specifically, among the five sub-categories of FFMQ, the Observing and Non-react increased with significance and the other three factors (Describing, Aware, and Nonjudging) were with marginal significance ($0.1 > p \geq 0.05$).

Alterations of Functional Connectivity after MBCT

Figure 1 presents the significant changes in resting-state functional connectivity (RSFC) among the bereaved population (FDR-corrected $p < .05$). After the 8-week MBCT, we observed reduced connectivity across networks, without significant post-MBCT enhancements in RSFC. The changes of functional connectivity after MBCT appeared as multiple edges, including the salience-auditory, salience-DMN, FPN-visual, FPN-DMN, and within-DMN connectivity. However, the mindfulness training effect of these specific RSFC edges seemed unstable across NBS tests (**Fig. S1**). Secondly, the overall functional connectivity during emotion arousal (EAFC) was analyzed as well (**Fig. 1**); however, none of the edges survived the FDR threshold, indicating that the inter-network EAFC before and after MBCT remained largely unchanged during emotion engagement.

FFMQ-related RSFC changes after MBCT

We applied the correlation analysis to the entire connectivity matrix and illustrated the prominent associations (shown in edges) between the connectivity changes (ΔRSFC) and the changes of FFMQ scores (ΔFFMQ) after MBCT. The upper panel of **Fig. 2** demonstrates that the significant ΔRSFC associated with ΔFFMQ appeared at the cortico-subcortical connectivity between caudate and CON/SMN. One of the significant edges, the linkage between CON and caudate, showed a positive correlation between the ΔRSFC and ΔFFMQ ($r = 0.84$, $p < .05$). By contrast, the post-MBCT changes in cortical connectivity between the sensorimotor and visual networks demonstrated a negative correlation with ΔFFMQ ($r = -0.79$, $p < .05$). The lower panel of **Fig. 2** illustrates the significant association between ΔRSFC and the sub-categories (factors) in FFMQ. Among the five factors of FFMQ, the most prominent correlation with ΔRSFC was “Non-react”, which showed a positive relation with caudate-CON/SMN. Similarly, the score changes in “Observing” and “Aware” also contributed to the positive correlations with ΔRSFC of caudate-CON/SMN, and they exhibited negative correlations with ΔRSFC of SMN in the posterior brain.

Anxiety-related RSFC changes after MBCT

The association analysis was also applied to GAD-7 and DERS. **Figure 3** demonstrates that the cortical connectivity changes in the posterior brain had positive correlation with the anxiety changes after MBCT ($r = 0.69$, $p < .05$). Meanwhile the cortico-subcortical connectivity changes showed negative correlations with ΔGAD ($r = -0.83$, $p < .05$). Relatively, ΔDERS also showed negative correlations with the cortico-subcortical connectivity changes ($r = -0.78$, $p < .05$). The ΔDERS showed moderate positive correlation between ΔDERS and the posterior ΔRSFC (VN-SMN) ($r = 0.55$, $p < .05$). In summary, the RSFC in the posterior brain had positive contributions to both GAD and DERS after MBCT intervention, whereas the cortico-subcortical ΔRSFC showed negative contributions to the two indices.

Discussion

The functional changes of large-scale brain connectivity after the 8-week MBCT were evaluated among participants with bereavement grief. The MBCT-related brain connectivity alterations were tested in both resting state and emotion-induced state. We evaluated all functional indices by observing changes in the indices for evaluating the MBCT intervention effect, in contrast to their pre-training conditions. The results indicated significant reductions in TRIG, GAD-7 and DERS and increases in FFMQ, denoting the alleviation of emotion entanglements among the bereaved individuals after MBCT. With regard to brain connectivity, the results indicated that MBCT reduced specific functional connectivity (intra-DMN connectivity and inter-network connectivity between salience, auditory, fronto-parietal, and visual networks) in the resting state, but not in the emotion-induced state. Furthermore, the RSFC between the caudate and CON/SMN exhibited a positive correlation with FFMQ and negative correlation with GAD-7 and DERS, implying the specific inter-network connection participated in emotion regulations under bereavement grief.

MBCT for enhancing emotion flexibility in brain connectivity

Our results demonstrated the decreased RSFC after MBCT (ΔRSFC edges in **Fig. 1**, Post < Pre) in the bereaved participants; however, there were no significant differences between the pre-MBCT and post-MBCT states based on the brain connections observed in the emotion condition (ΔEAFC in **Fig. 1**). This findings could be counter-intuitive because a majority of previous findings reported the reduction in emotion-induced brain activity [Huang et al., 2019; Tomasino and Fabbro, 2016] or the altered $\mathrm{RSFC}_{\mathrm{DMN}}$ (such as reduced intra-DMN and enhanced PCC-DLPFC connectivity) following the mindfulness training [Creswell et al., 2016; King et al., 2016; Zimmerman et al., 2019]. Nevertheless, considering emotion arousal in bereaved individuals generally takes place consistently in the course of their daily life, even without external triggers of specific names or facial expressions, we conjectured that the global brain connectivity in the resting state could better express such behavioral alterations in bereavement grief. The brain functional alterations have global inter-network effects, rather than affecting $\mathrm{RSFC}_{\mathrm{DMN}}$ only, because the grief could result in multiple functionalities that transcend self-awareness, such as psychomotor retardation [Hensley and Clayton, 2008], sleep disturbance, and neuroendocrine activations [Buckley et al., 2012]. In other words, the bereavement grief could have far more impacts on brain networks associated with psychiatric complications (such as DMN), where such large-scale inter-network analysis have been conducted in recent MBCT studies [Doll et al., 2015; Hölzel et al., 2013]. **Figure 1** shows the two different patterns of ΔFC after MBCT, for which the MBCT indeed reduced inter-network connectivity in the resting state (RSFC); however, the MBCT did not significantly affect the connectivity in the emotion-induced state (EAFC). The finding supported our speculation that the function of MBCT is to minimize the hyper-intense brain circuits in the resting state in bereaved individuals. In addition, our results (top-right panel in **Fig. 1**) demonstrated the significant RSFC reduction in DMN itself and the interactions among salience, FPN, and sensory (visual/auditory) networks, which in turn explained the reduction in self-reference and external attention following MBCT. The finding suggests that after MBCT, the mental state of bereaved individuals is not easily engaged to spontaneous emotion fluctuations under an intrinsic resting state. The results are consistent with subjective experiences where the bereaved individuals often reported the general acceptance of grief in their daily life; however, emotional arousal remained high when viewing a photo or the name of their deceased relatives. In short, the MBCT does not diminish the emotions, but shifts attention away from emotion perception in the resting state in the bereaved population.

Role of cortico-subcortical connectivity changes after MBCT

Regarding the MBCT effect on both brain connectivity and subjective perceptions, we evaluated the associations between connectivity changes and the score changes of self-rated questionnaires (TRIG, DERS, GAD-7 and FFMQ). Notably, the ΔRSFC between the basal ganglia and two cortical networks (SMN/CON) showed a high positive correlation ($r = 0.84$, **Fig. 2**) with the ΔFFMQ (mindfulness), indicating that enhanced cortico-subcortical (inter-network) connectivity corresponds to high mindfulness levels after 8-week MBCT program. Meanwhile, the resembling ΔRSFC showed high negative correlations (**Fig. 3**) with ΔGAD-7 (anxiety, $r = -0.83$) and ΔDERS (emotion, $r = -0.83$). The function of the caudate nucleus is the habitual direction of attention and behavior [McNab and Klingberg, 2008]. After the meditation training, the brain activity of the caudate increased and its connection to DMN decreased [Bluhm et al., 2009; Tomasino and Fabbro, 2016]. The CON represents the sustained attention and the SMN indicates the somatosensory perceptions. Collectively, such findings might imply the re-direction of attention to the interoceptive awareness. Breaking the ΔFFMQ into its sub-categories (**Fig. 2**, lower panel), we observed similar cortico-subcortical connectivity was particularly prominent in Observing and Non-React, which partly supports the plausible scenario of attention shift after MBCT. Conversely, the other SMN-VN ΔRSFC (cortico-cortical connectivity) reflected the opposite functional role, as compared with the caudate-CON ΔRSFC. **Figures 2** and **3** indicated that after MBCT, the reinforced RSFC between CON/SMN and visual network was accompanied by greater anxiety ($r = 0.69$), greater difficulty in emotion regulation ($r = 0.55$) and lower mindfulness levels ($r = -0.79$). In short, the caudate-CON/SMN connectivity facilitated emotion regulation, while the SMN-VN connectivity impaired the emotion regulation, as analogies of an accelerator and a break in emotion regulation, respectively. In short, these observations further indicated that the MBCT transfers habitual direction of attention from the external stimuli to internal perception in bereaved individuals.

Previous neuroimaging studies performing MBI have reported the enhanced connectivity strengths between PCC and DLPFC using the seed-correlation analysis [King et al., 2016; Kral et al., 2019; Scult et al., 2019]; however, adopting the same strategy with different seed locations, the PCC-DLPFC connectivity strengths after MBCT were insignificantly increased in the bereaved population (**Fig.S2**). Through a literature review, we speculated that the post-MBI PCC-DLPFC connectivity change is potentially influenced by the following factors, such as MBI duration, type, age, etc. First, the training type and duration of MBI could be influential to the changes of functional connectivity. For example, King et al. observed the enhanced PCC-DLPFC connectivity following a 16-week mindfulness-based exposure training [King et al., 2016], and Scult et al. found the increased connection between PCC and DLPFC/premotor area after a 20-week span of mindfulness emotion regulation therapy [Scult et al., 2019]. Using the standard protocol of 8-week MBSR training, Kral et al. observed the enhanced PCC-DLPFC connectivity with small effect size (beta: 0.05) [Kral et al., 2019]. The other two studies conducting 8-week MBCT, however, reported the declined magnitude of intra- and inter-network PCC-seeded connectivity without prominent changes of PCC-DLPFC connectivity [Zhao et al., 2019; Zimmerman et al., 2019]. Therefore, the program duration and consistent practices seemed to be crucial on the connectivity enhancement. Secondly, the MBI-induced RSFC changes might be subject to the age of recruited participants. For example, the enhanced PCC-DLPFC connectivity was reported from relatively young population [King et al., 2016; Scult et al., 2019], whereas the small or no effect of connectivity enhancement was reported from the middle-aged population [Kral et al., 2019; Zimmerman et al., 2019]. Another plausible factor on the mismatched connectivity findings could be the prescription of seed locations, which could lead to distinct results of intra-DMN connectivity [Yan et al., 2013]. At last, the types of participants could impact the mindfulness-based alterations of functional connectivity. Among the limited literature targeting on the MBI-induced RSFC changes of the stressful persons, this is the first work evaluating the RSFC changes following MBCT in the bereavement grief. Further MBI-based longitudinal studies are warranted to validate our findings on the bereaved individuals.

Additionally, a recent study denoted the functional role of white matter signals in brain connectome [Li et al., 2019], where the inclusion of white matter signals might influence our findings. Therefore, we re-analyzed our data without the inclusion of white matter signals in the fMRI preprocessing, which did not alter our findings in the current datasets (**Fig. S3**). The consideration of white matter signals and its function in the mindfulness training is beyond the scope of the current study, which awaits future investigations to uncover its role in RSBC.

Inter-individual variability during mindfulness training

Although **Fig. 1** shows the group ΔRSFC after MBCT, we did not observe significant correlations of the significant ΔRSFC with any changes of the self-rated questionnaire, which could be due to the following two reasons. First, the score changes of the self-rated questionnaires in the current study could not reflect the $\Delta RSFC_{DMN}$ and $\Delta RSFC_{FPN\text{-}SN}$. Although Doll and colleagues demonstrated that $RSFC_{DMN\text{-}SN}$ and $RSFC_{FPN\text{-}SN}$ had positive correlations with mindfulness scores [Doll et al., 2015], the authors demonstrated the association between RSFC and trait mindfulness on meditation-naïve volunteers, where the strategy was different from the longitudinal approach adopted in the present study. In other words, the comparison between pre-/post-MBCT could better illustrate the MBI intervention effect and the improvement of the mental health of the bereaved individuals, independent of their individual trait differences in mindfulness. Second, although the goal of MBCT is to cultivate acceptance in a non-judgmental way with regard to negative emotions or thoughts and to perceive our inertial mental habitual patterns without getting involved in automated reaction patterns, such practices were not easy for the participants with major bereavements, resulting in high between-subject variability. Similarly, **Figs. 2** and **3** demonstrate the zero-crossing in caudate-CON/SMN ΔRSFC, meaning half of the participants had positive ΔRSFC and half had negative ΔRSFC. The zero-crossing results could be the reason for the no significant findings for the ΔRSFC in **Fig. 1**; however, the high effect size highlighted the important functional roles of caudate-CON/SMN RSFC. Such between-subject variability in ΔRSFC can have resulted from their diligence in mindfulness practices, the emotional arousal and the emotional awareness, etc. [Thieleman et al., 2014]. Most importantly, the MBCT course was administered to a group rather than to individuals. Therefore, the instructor could not adequately cater to each individual with regard to mindfulness training and ensuring that each participant grasped the concepts. In other words, individual training is preferred for an MBCT course; however, due to the time limitations in the modern society, the 8-week group-based MBCT is the default approach. Bereavement involves major changes in family systems. For example, the participants endured greater burdens in the form of requiring caregivers to look after the rest of family members who were suffering from major depression. Some of the participants had even been forced to take on additional burdens caused by other family members. Such familial burdens introduce additional confounding factors in the mourning process, particularly within the Taiwanese family system. Therefore, cultural factors may delay the grief reconciliation among bereaved participants.

It is noticed that only one male participant showed his willingness to participate the MBCT program, which lead to the imbalanced gender distribution of our datasets. We found the exclusion of the male participant did not cause an impact on the findings (**Fig. S4** – **S6**); therefore, our results can be inferred to the MBCT-induced connectivity change of female brain. Future investigations are warranted to disclose the general impact of MBCT on the resting-state brain connectivity for both genders.

Limitations

The current study has limitations that ought to be considered. First, we did not include an active or waiting-list control group for comparison. Considering the ethical concerns that the grieving and bereaved individuals looked forward to the immediate alleviation of emotion entanglements, none of them was willing to be enrolled in the control group without any assistance of emotion regulation. Nevertheless, a previous study has reported Taiwanese bereavements took approximately 4 years before the depression scale could revert to the baseline [Tseng et al., 2017]. However, the MBCT could alleviate the bereavement grief within 2 months, which validates the effectiveness of MBCT and suggests that the outcome was not a random effect. Second, we asked the participants to passively view the facial expression pictures in the emotional arousal state, but we did not record the responses of subjective emotion level during or after performing the emotional arousal task. Because the emotional arousal after the consecutive presentation of emotional facial expressions has been documented in the literature [Lang et al., 2005; Tu et al., 2018], we assumed that the emotion was successfully induced in our task, which was orally confirmed by the bereaved participants. Third, the baseline FFMQ assessment before the MBCT course might be with poor precision [Chiesa, 2013; Davidson, 2010], for the possibility that the bereaved participants with high levels of emotional entanglements did not adequately comprehend the mindfulness questionnaire. This concern does not arise with regard to the anxiety levels, and previous studies have reported significant negative correlation between FFMQ and anxiety levels [Chiesa, 2013; Davidson, 2010]. Therefore, we double-checked the consistency between FFMQ scores and the GAD-7 among our datasets, and there was high consistency between the two indices, demonstrating the reliability of the baseline FFMQ scores in the present study.

Conclusion

Bereavement grief does not simply take effect during cognitive/emotional tasks, but may influence the overall brain circuits and inter-network connectivity in the intrinsic resting state. To prove the hypothesis, we performed a whole-brain functional connectivity analysis (by NBS) in both the resting state and the emotion-induced state in the participants with bereavement grief. Results showed that the MBCT intervention effect was reflected on the significant RSFC changes (intra-DMN connectivity and inter-network connectivity between salience, auditory, fronto-parietal, and visual networks), but not on the functional connectivity under emotion inducement. With regard to the neural correlates of emotion regulation, we revealed the strong MBCT effect on both cortico-subcortical and cortico-cortical connectivity: the caudate-CON/SMN connectivity accentuated emotion regulation, while the SMN-VN connectivity impaired emotion regulation. However, the intra-network connectivity changes of DMN, SN, and FPN did not present a strong correlation with mindfulness, anxiety, and emotion regulation in the bereaved population. Future studies are warranted to investigate the modulation of brain circuits in the populations with intense emotion entanglements.

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Figure Legends

Figure 1. Changes of large-scale functional connections after MBCT in the bereaved population. The 245 large-scale brain nodes are categorized into 11 networks and the left panel demonstrated the correlation matrix of the baseline connectivity (left) and the connectivity contrast (Post-Pre, right) in the resting state (upper row) and the emotion induction state (lower row). The node-edge figure in the up-right panel denotes the general observation of connectivity changes after MBCT, in which all edges presented shows the reduction of resting-state functional connectivity after MBCT in the bereaved population.

Figure 2. The upper panel exhibits the associations between the changes of resting-state functional connectivity (ΔRSFC) and the changes of FFMQ (ΔFFMQ) following MBCT. The upper panel shows the positive correlation between the caudate-CON ΔRSFC and the overall ΔFFMQ; whereas the SMN-VN ΔRSFC shows the negative correlation with overall ΔFFMQ. The lower panel demonstrates that the significant neural correlates of ΔRSFC and the subcategories of ΔFFMQ, among which the 'Observing' and 'Non-React' show high consistency with the neural correlates of overall FFMQ. (FFMQ: five-facet mindfulness questionnaire; CON: cingulo-opercular network; SMN: sensorimotor network; VN: visual network)

Figure 3. Associations between the changes in resting-state functional connectivity (ΔRSFC) and the changes in anxiety (ΔGAD-7, the upper panel), whereas the correlation between ΔRSFC and the changes in difficulty in emotion regulation (ΔDERS, the lower panel) following MBCT. The caudate-CON ΔRSFC and the SMN-VN ΔRSFC show the opposite patterns with ΔGAD-7 and ΔDERS. (CON: cingulo-opercular network; SMN: sensorimotor network; VN: visual network)

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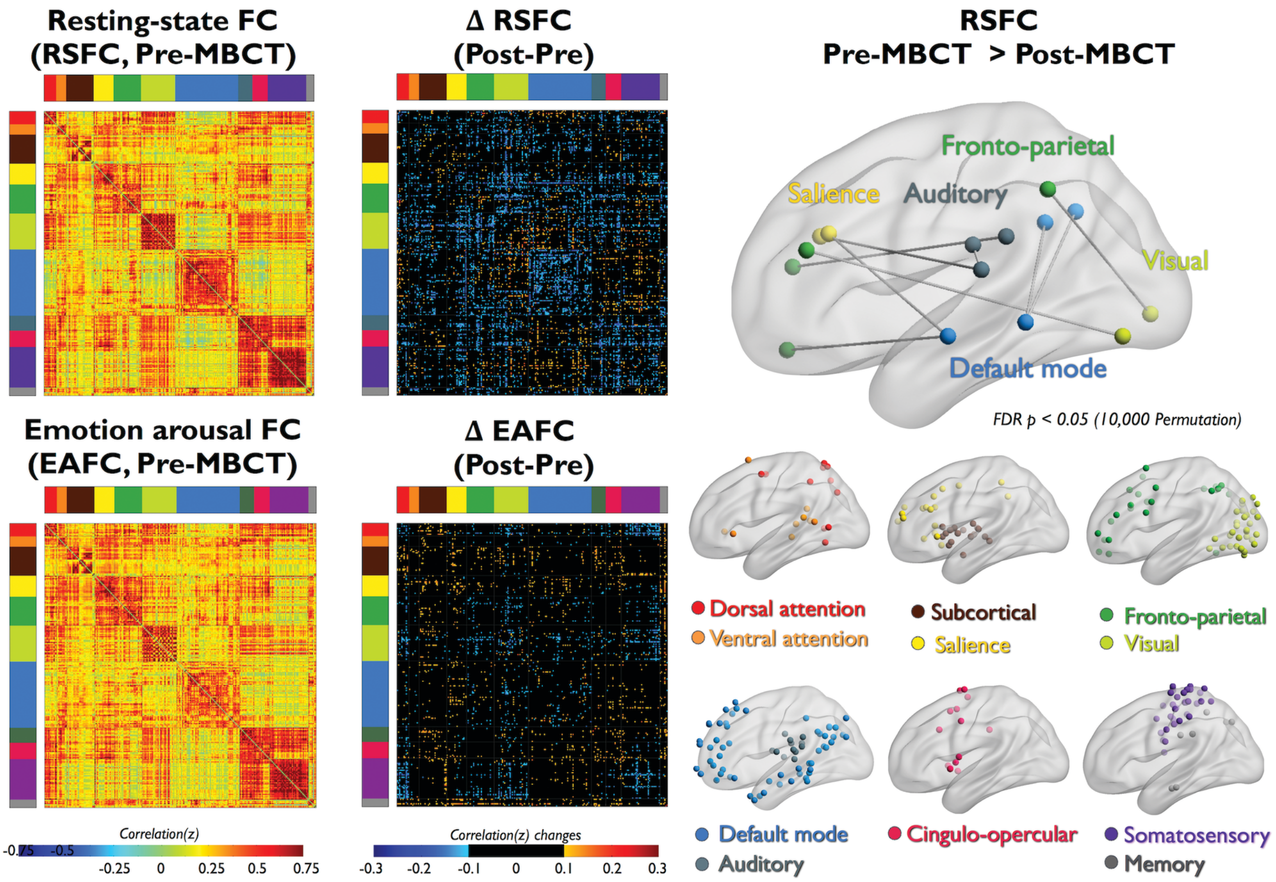

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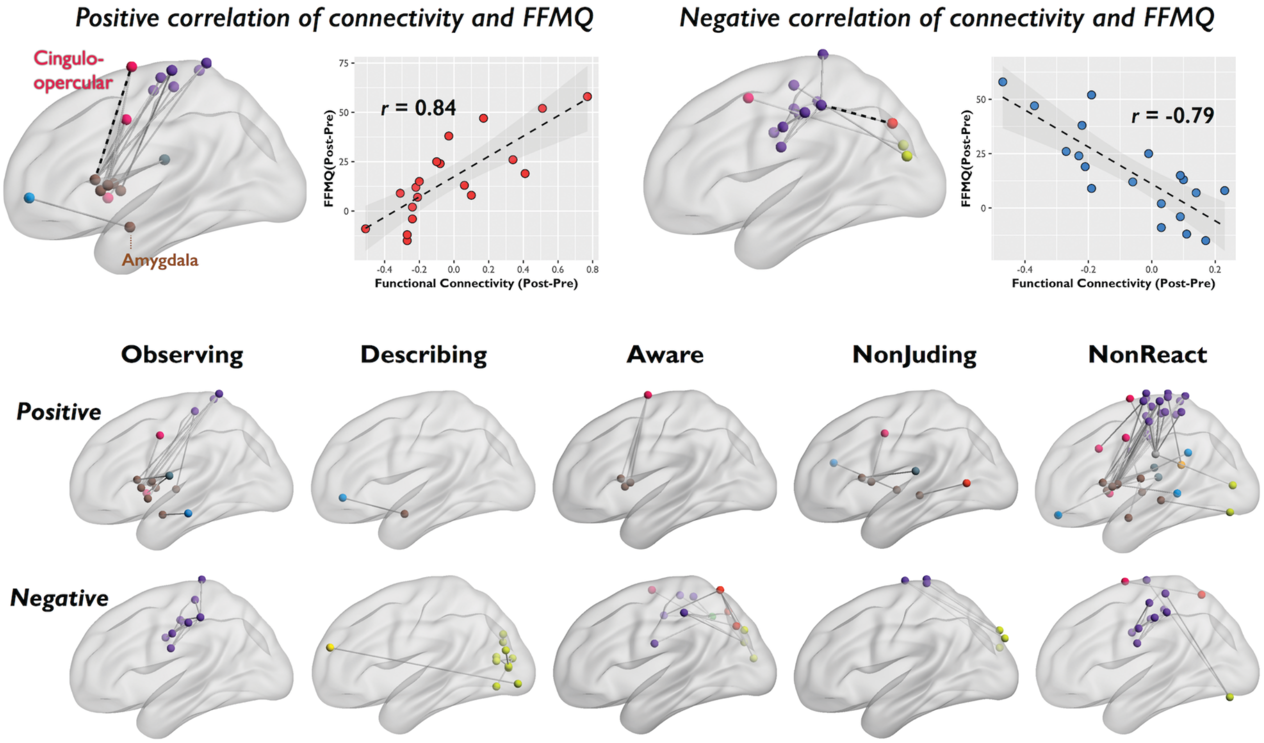

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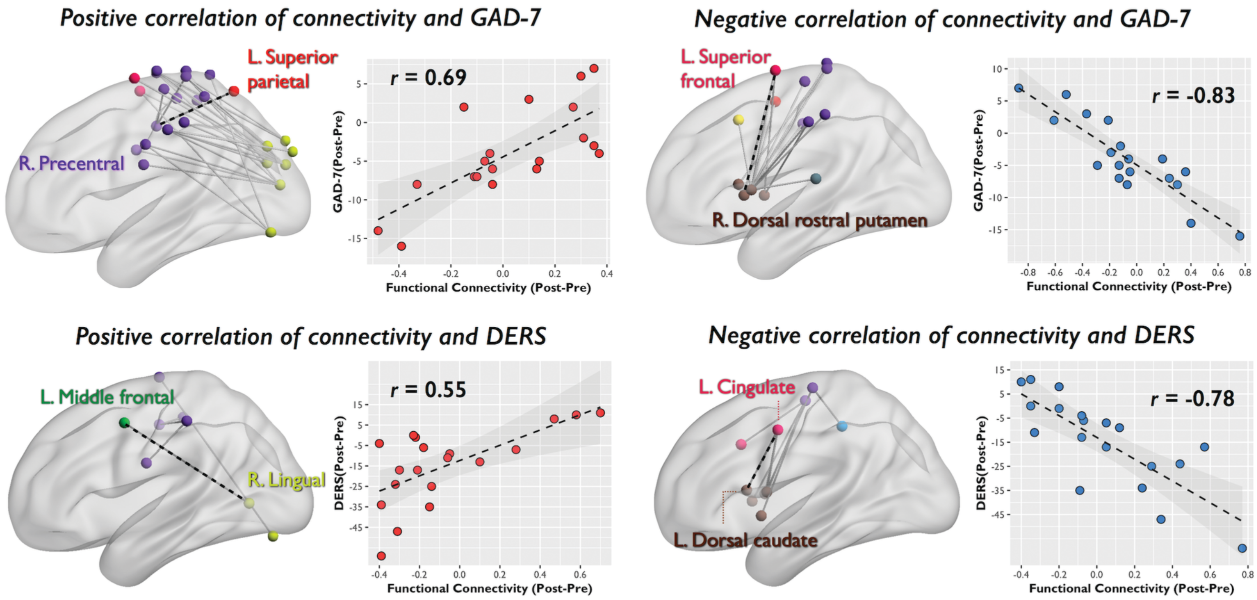

Positive correlation of connectivity and GAD-7

Negative correlation of connectivity and GAD-7

Positive correlation of connectivity and DERS

Negative correlation of connectivity and DERS

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TABLE 1 Descriptive statistics of self-reported questionnaires between pre- and post-MBCT on the 19 participants with bereavement grief (means and standard error of the means).

Questionnaire	**Pre-MBCT**		**Post-MBCT**		**Paired *t*-test**	
	Mean	SEM	Mean	SEM	*t*-value	*p*-value
TRIG	48.74	2.97	36.74	2.67	-3.83^{**}	.001
GAD-7	10.53	1.23	6.58	1.25	-2.86^{*}	.01
Depression	23.95	2.61	13.26	2.74	-5.11^{**}	<.001
DERS	104.89	4.10	90.16	4.31	-3.39^{**}	.003
FFMQ	110.05	3.90	126.63	5.78	3.44^{**}	.003
Observing	22.53	1.07	27.89	0.89	5.20^{**}	<.001
Describing	24.63	1.10	26.26	1.52	1.85	.08
Aware	23.26	1.44	25.58	1.57	1.75	.09
Nonjudging	21.63	1.14	24.63	1.72	1.85	.08
Non-react	18.00	1.01	22.26	2.43	3.96^{**}	.001

$^{*}p < 0.05$, $^{**}p < 0.01$