

RESEARCH ARTICLE

Mindfulness-based cognitive therapy on bereavement grief: Alterations of resting-state network connectivity associate with changes of anxiety and mindfulness

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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 well-being 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 internetwork connectivity could be reformed after MBCT intervention. We recruited 19 bereaved individuals who participated the 8-week MBCT program. We evaluated (a) the large-scale changes in brain connectivity affected by the MBCT program; as well as (b) the association between connectivity changes and self-rated questionnaire. First, after MBCT, the bereaved individuals showed the reduction of the internetwork 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 internetwork reorganizations in the resting state.

KEYWORDS

bereavement, emotion regulation, functional connectivity, functional magnetic resonance imaging, grief, mindfulness-based cognitive therapy

Feng-Ying Huang and Ai-Ling Hsu are equally contributed to this work.

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1 | 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, Sharpley, McFarlane, & Sachdev, 2015; Beem, Maes, Cleiren, Schut, & Garssen, 2000; Buckley, McKinley, Tofler, & Bartrop, 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 6 months after spousal loss (Christakis & Iwashyna, 2003; Hart, Hole, Lawlor, Smith, & Lever, 2007; Lichtenstein, Gatz, & Berg, 1998; Manor & 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 & Shear, 2009) or the exacerbation of pre-existing depression (Zisook, Paulus, Shuchter, & Judd, 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 4 years in Taiwanese individuals (Tseng, Petrie, & Leon-Gonzalez, 2017; Zisook & Shear, 2009). However, such prolonged sorrow could lead to a general reduction in cognitive functions (Rosnick, Small, & Burton, 2010) and ultimately adversely affect the brain structure and functionality of the bereaved individual (Gündel, O'Connor, Littrell, Fort, & Lane, 2003; O'Connor, Gündel, McRae, & Lane, 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, Shallcross, Davis, & Mauss, 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, Williams, & Teasdale, 2013), which has been extensively documented to be beneficial for emotion regulation (Hölzel et al., 2011; Roemer, Williston, & Rollins, 2015; Teper & Inzlicht, 2013), major depression (Teasdale et al., 2000) and anxiety disorders (Goldin & 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, Cacciatori, & Hill, 2014). Recently, the MBCT effect with regard to bereavement grief was reported to enhance cognitive ability (Huang et al., 2019; Tomasino & Fabbro, 2016) and reduce depressive symptoms among elderly

bereaved persons (O'Connor, Piet, & Hougaard, 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 internetwork connectivity in the intrinsic resting state. Based on 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 internetwork 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 internetwork 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: (a) 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 (b) 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 internetwork 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.

2 | MATERIALS AND METHODS

2.1 | 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 (a) any experience on mindfulness meditation prior to this study, (b) a history of major psychiatric disorders or a use of prescription drug, (c) any known systemic or neurological diseases, and (d) MRI incompatibilities or known claustrophobia.

Prior to receiving an 8-week MBCT training course, participants completed a questionnaire battery, which included (a) Texas Revised Inventory of Grief (TRIG) (Faschingbauer, Devaul, & Zisook, 1981), (b) Generalized Anxiety Disorder-7 (GAD-7) (Spitzer, Kroenke, Williams, & Löwe, 2006), (c) the 18-item Taiwanese Depression Questionnaire (Lee, Yang, Lai, Chiu, & Chau, 2000), (d) Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004), and (e) 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.

2.2 | 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 hr each time) plus recommended daily home practice (45 min per day) during

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 4 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 toward 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 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.

2.3 | MRI acquisition and experimental design

All functional magnetic resonance imaging (fMRI) datasets were acquired on a 3T PRISMA scanner (Siemens, Erlangen, Germany) with a 20-channel head 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 $1 \times 1 \times 1 \text{ mm}^3$), 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, $3 \times 3 \text{ mm}^2$). Visual stimuli were presented via E-prime (Psychology Software Tools, Pittsburgh, PA) 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 min.

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, Bradley, & Cuthbert, 2005). The current study used datasets of the Taiwanese version of IAPS (T-IAPS) to induce the emotional arousal in participants (Tu, Lin, Suzuki, & Goh, 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 1 s duration followed by a 1 s fixation, a total of 310 face pictures were presented within the acquisition time of 620 s. 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).

2.4 | Data analysis

Data were analyzed using a custom software, IClinfMRI (Hsu et al., 2018), in a MATLAB 2014a environment (The MathWorks, Inc., Natick, MA). Preprocessing steps included motion correction, normalization to the standard Montreal Neurological Institute (MNI) space with a voxel size of $2 \times 2 \times 2 \text{ mm}^3$, de-spiking, third-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, Barnes, Snyder, Schlaggar, & Petersen, 2012) that integrated meta-analytic 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 1,037 studies and "memory" resulting from 2,744 studies (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011), respectively.

Using the analytic software of network-based statistics (NBS) (Zalesky, Fornito, & Bullmore, 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 (a) the functional connections that were altered significantly after 8-week MBCT training course across participants, as well as (b) the connections where its changes with regard to the significant changes in the self-rated questionnaire. First, the training effect was evaluated using paired t -tests on pairwise connections in participants' connectivity matrices. Considering the multiple comparisons, the significance level of $p < .05$ 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. Second, to avoid the double-dipping issue (Kriegeskorte, Simmons, Bellgowan, & Baker, 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 (five questionnaires and five sub-categories of FFMQ). To correct additional multiple comparison from 10 questionnaire scores, the correlation results were reported with significance level at FDR-corrected $p < .005$ (10,000 permutations).

3 | RESULTS

3.1 | Self-rated questionnaires

Paired t -test was conducted on the psychological variables following 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 Non-judging) were with marginal significance ($0.1 > p \geq .05$).

3.2 | Alterations of functional connectivity after MBCT

Figure 1 presents the significant changes in resting-state functional connectivity (RSFC) among the bereaved population (FDR-corrected

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

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)

Note: * $p < .05$, ** $p < .01$.

Abbreviations: DERS, Difficulties in Emotion Regulation Scale; GAD-7, Generalized Anxiety Disorder-7; FFMQ, Five Facet Mindfulness Questionnaire; MBCT, mindfulness-based cognitive therapy; TRIG, Texas Revised Inventory of Grief.

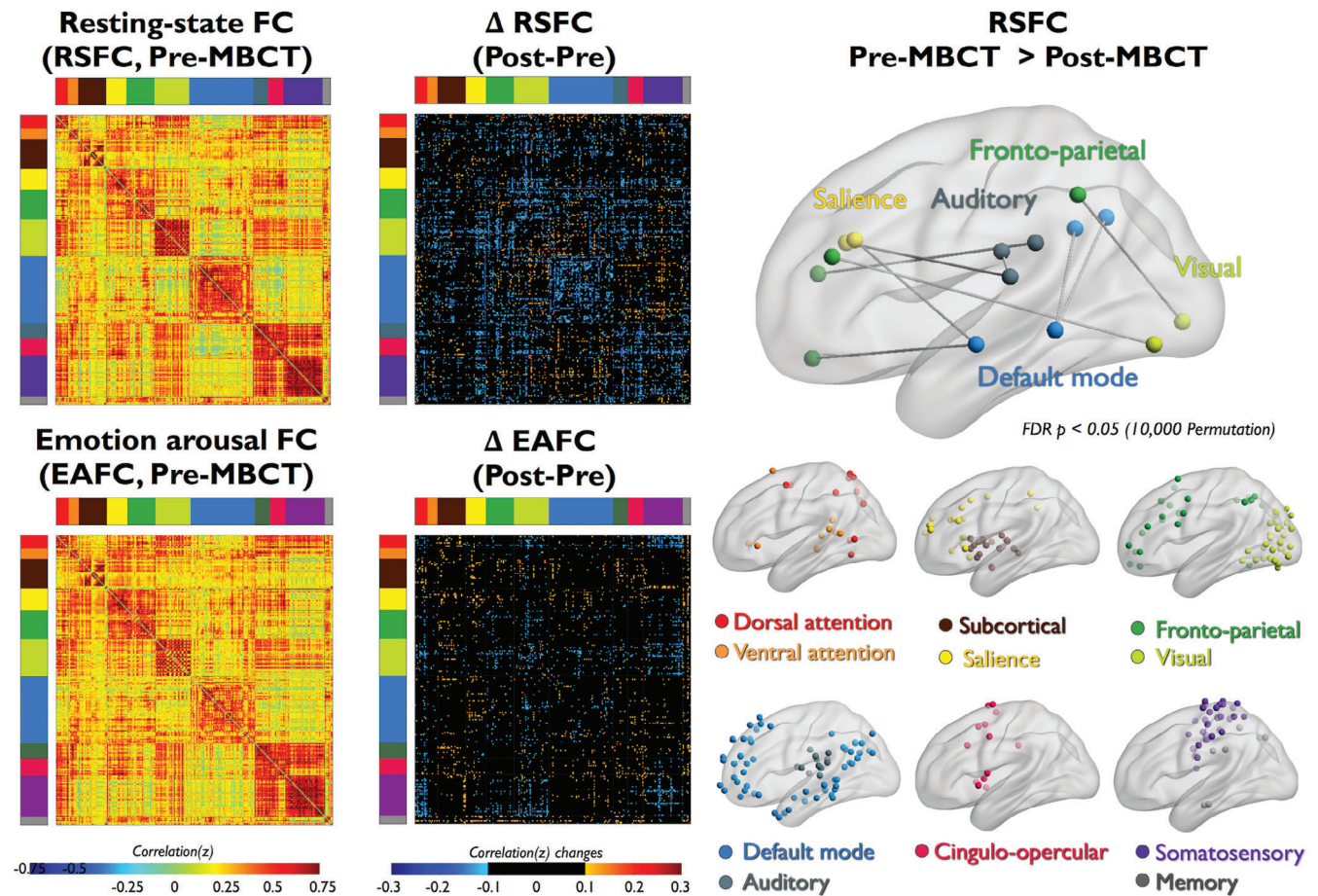


FIGURE 1 Changes of large-scale functional connections after mindfulness-based cognitive therapy (MBCT) in the bereaved population. The 245 large-scale brain nodes are categorized into 11 networks and the left panel demonstrated the correlation matrix of the baseline connectivity (left) and the connectivity 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

$p < .05$). 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 (Figure S1). Second, the overall functional connectivity during emotion arousal (EAFC) was analyzed as well (Figure 1); however, none of the edges survived the FDR threshold, indicating that the internetwork EAFC before and after MBCT remained largely unchanged during emotion engagement.

3.3 | 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 (Δ RSFC) and the changes of FFMQ scores (Δ FFMQ) after MBCT. The upper panel of Figure 2 demonstrates that the significant Δ RSFC associated with Δ FFMQ 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 Δ RSFC and Δ FFMQ ($r = .84, p < .05$). In contrast, the post-MBCT changes in cortical connectivity between the sensorimotor and visual networks demonstrated a negative correlation with Δ FFMQ ($r = -.79, p < .05$). The lower panel of Figure 2 illustrates the significant association between Δ RSFC and the sub-categories (factors) in FFMQ. Among the five factors of FFMQ, the most prominent correlation with Δ RSFC 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 Δ RSFC of caudate-CON/SMN, and they exhibited negative correlations with Δ RSFC of SMN in the posterior brain.

3.4 | 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 Δ GAD ($r = -.83, p < .05$). Relatively, Δ DERS also showed negative correlations with

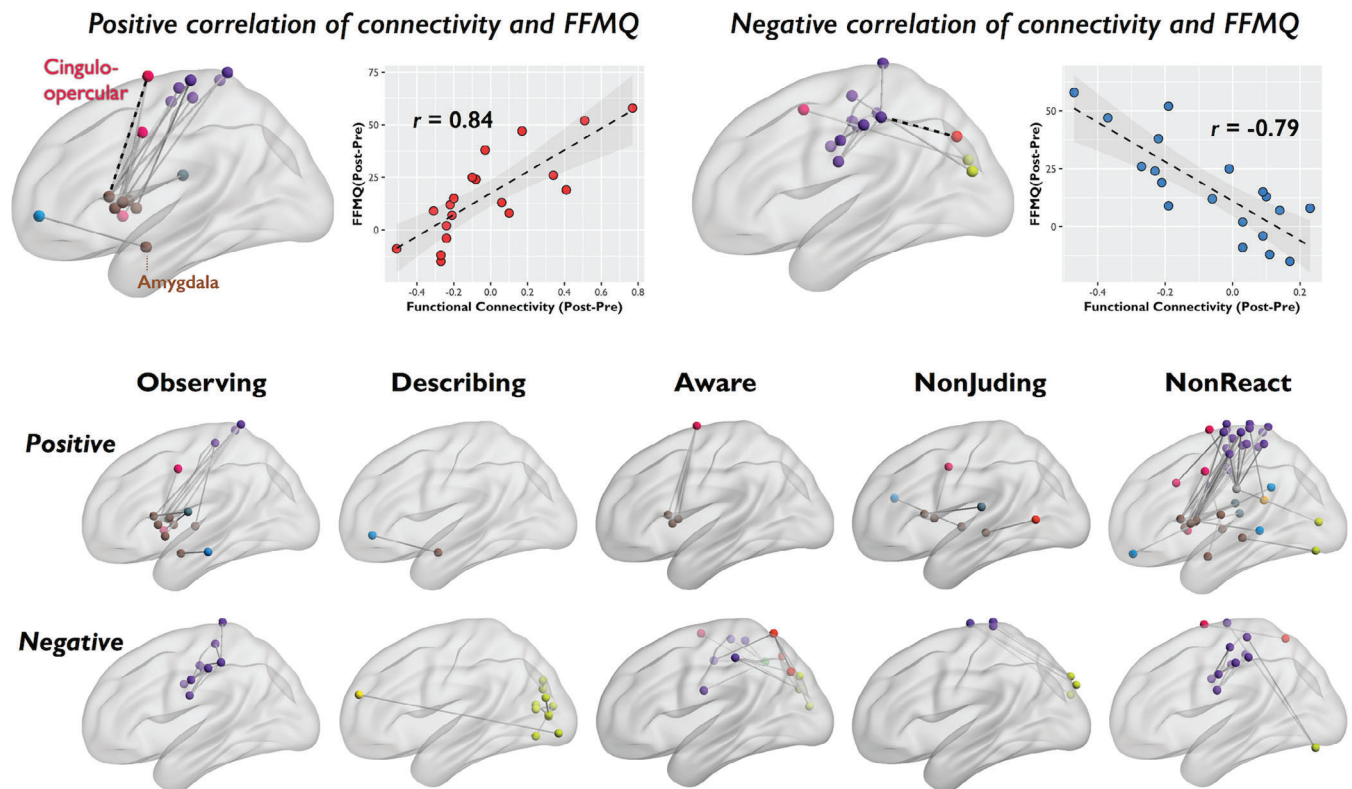


FIGURE 2 The upper panel exhibits the associations between the changes of resting-state functional connectivity (Δ RSFC) and the changes of FFMQ (Δ FFMQ) following mindfulness-based cognitive therapy (MBCT). The upper panel shows the positive correlation between the caudate-cingulo-opercular network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

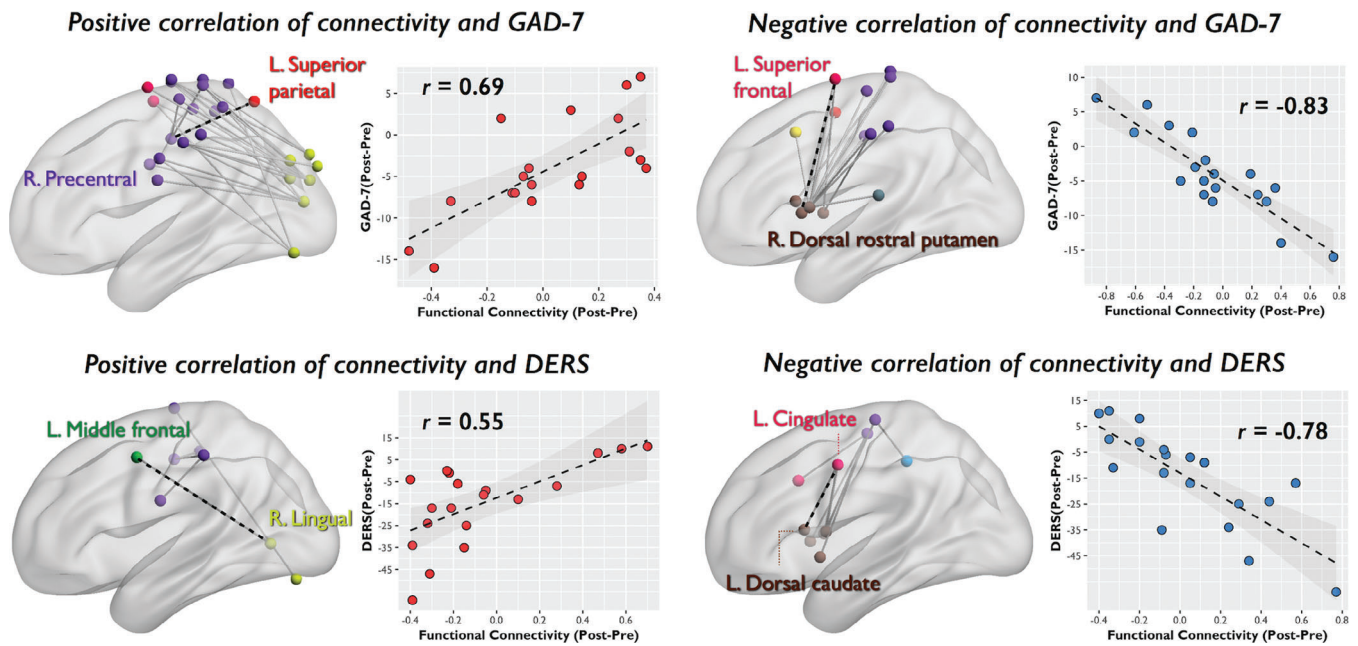


FIGURE 3 Associations between the changes in resting-state functional connectivity (Δ RSFC) and the changes in anxiety (Δ GAD-7, the upper panel), whereas the correlation between Δ RSFC and the changes in difficulty in emotion regulation (Δ DERS, the lower panel) following mindfulness-based cognitive therapy (MBCT). The caudate-cingulo-opercular network (CON) Δ RSFC and the sensorimotor network (SMN)-visual network (VN) Δ RSFC show the opposite patterns with Δ GAD-7 and Δ DERS

the cortico-subcortical connectivity changes ($r = -.78, p < .05$). The Δ DERS showed moderate positive correlation between Δ DERS and the posterior Δ RSFC (VN-SMN) ($r = .55, p < .05$). In summary, the RSFC in the posterior brain had positive contributions to both GAD and DERS after MBCT intervention, whereas the cortico-subcortical Δ RSFC showed negative contributions to the two indices.

4 | DISCUSSION

The functional changes of large-scale brain connectivity after 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 pretraining 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 internetwork 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 internetwork connection participated in emotion regulations under bereavement grief.

4.1 | MBCT for enhancing emotion flexibility in brain connectivity

Our results demonstrated the decreased RSFC after MBCT (Δ RSFC edges in Figure 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 (Δ EAFC in Figure 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 & Fabbro, 2016) or the altered RSFC_{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 internetwork effects, rather than affecting RSFC_{DMN} only, because the grief could result in multiple functionalities that transcend self-awareness, such as psychomotor retardation (Hensley & 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 internetwork analysis have been conducted in recent MBCT studies (Doll, Hölzel, Boucard, Wohlschläger, & Sorg, 2015; Hölzel et al., 2013). Figure 1 shows the

two different patterns of ΔFC after MBCT, for which the MBCT indeed reduced internetwork 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 Figure 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.

4.2 | 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 $\Delta RSFC$ between the basal ganglia and two cortical networks (SMN/CON) showed a high positive correlation ($r = .84$, Figure 2) with the $\Delta FFMQ$ (mindfulness), indicating that enhanced cortico-subcortical (inter-network) connectivity corresponds to high mindfulness levels after 8-week MBCT program. Meanwhile, the resembling $\Delta RSFC$ showed high negative correlations (Figure 3) with $\Delta GAD-7$ (anxiety, $r = -.83$) and $\Delta DERS$ (emotion, $r = -.83$). The function of the caudate nucleus is the habitual direction of attention and behavior (McNab & Klingberg, 2008). After the interventions, the brain activity of the caudate increased and its connection to DMN decreased (Bluhm et al., 2009; Tomasino & 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 $\Delta FFMQ$ into its sub-categories (Figure 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 $\Delta RSFC$ (cortico-cortical connectivity) reflected the opposite functional role, as compared with the caudate-CON $\Delta RSFC$. Figures 2 and 3 indicated that after MBCT, the reinforced RSFC between CON/SMN and visual network was accompanied by greater anxiety ($r = .69$), greater difficulty in emotion regulation ($r = .55$) and lower mindfulness levels ($r = -.79$). 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. These observations further indicated that the MBCT transfers habitual direction of attention from the external stimuli to the 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 (Figure 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, and so on. 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 (Kral et al., 2019). The other two studies conducting 8-week MBCT, however, reported the declined magnitude of intranetwork and internetwork 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. Second, 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 global 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 (Figure 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 RSFC.

4.3 | Interindividual variability during mindfulness training

Although Figure 1 shows the group Δ RSFC after MBCT, we did not observe significant correlations of the significant Δ RSFC 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 Δ RSFC_{DMN} and Δ RSFC_{FPN-SN}. Although Doll and colleagues demonstrated that RSFC_{DMN-SN} and RSFC_{FPN-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, Figures 2 and 3 demonstrate the zero-crossing in caudate-CON/SMN Δ RSFC, meaning half of the participants had positive Δ RSFC and half had negative Δ RSFC. The zero-crossing results could be the reason for the no significant findings for the Δ RSFC in Figure 1; however, the high effect size highlighted the important functional roles of caudate-CON/SMN RSFC. Such between-subject variability in Δ RSFC can have resulted from their diligence in mindfulness practices, the emotional arousal and the emotional awareness, and so on (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 among the bereaved population; however, due to the time limitations in the modern society, 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 (Figure 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.

4.4 | 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.

5 | CONCLUSION

Bereavement grief does not simply take effect in the engagement of cognitive/emotional tasks, but influences the overall brain circuits and internetwork 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 internetwork 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 intranetwork 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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DATA AVAILABILITY STATEMENT

The fMRI data of this study are not available to the public but will be available on request to the corresponding author.

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REFERENCES

- Assareh, A. A., Sharpley, C. F., McFarlane, J. R., & Sachdev, P. S. (2015). Biological determinants of depression following bereavement. *Neuroscience & Biobehavioral Reviews*, *49*, 171–181.
- Beem, E. E., Maes, S., Cleiren, M., Schut, H. A., & Garssen, B. (2000). Psychological functioning of recently bereaved, middle-aged women: The first 13 months. *Psychological Reports*, *87*, 243–254.
- Bluhm, R., Williamson, P., Lanius, R., Théberge, J., Densmore, M., Bartha, R., ... Osuch, E. (2009). Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: Decreased connectivity with caudate nucleus. *Folia psychiatricia et neurologica japonica*, *63*, 754–761.
- Buckley, T., McKinley, S., Tofler, G., & Bartrop, R. (2010). Cardiovascular risk in early bereavement: A literature review and proposed mechanisms. *International Journal of Nursing Studies*, *47*, 229–238.
- Buckley, T., Sunari, D., Marshall, A., Bartrop, R., McKinley, S., & Tofler, G. (2012). Physiological correlates of bereavement and the impact of bereavement interventions. *Dialogues in Clinical Neuroscience*, *14*, 129–139.
- Chiesa, A. (2013). The difficulty of defining mindfulness: Current thought and critical issues. *Mindfulness (N Y)*, *4*, 255–268.
- Christakis, N. A., & Iwashyna, T. J. (2003). The health impact of health care on families: A matched cohort study of hospice use by decedents and mortality outcomes in surviving, widowed spouses. *Social Science & Medicine*, *57*, 465–475.
- Creswell, J. D., Taren, A. A., Lindsay, E. K., Greco, C. M., Gianaros, P. J., Fairgrieve, A., ... Ferris, J. L. (2016). Alterations in resting-state functional connectivity link mindfulness meditation with reduced interleukin-6: A randomized controlled trial. *Biological Psychiatry*, *80*, 53–61.
- Davidson, R. J. (2010). Empirical explorations of mindfulness: Conceptual and methodological conundrums. *Emotion*, *10*, 8–11.
- Di Martino, A., Scheres, A., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Shehzad, Z., ... Milham, M. P. (2008). Functional connectivity of human striatum: A resting state fMRI study. *Cerebral Cortex*, *18*, 2735–2747.
- Doll, A., Hölzel, B. K., Boucard, C. C., Wohlschläger, A. M., & Sorg, C. (2015). Mindfulness is associated with intrinsic functional connectivity between default mode and salience networks. *Frontiers in Human Neuroscience*, *9*, 37–232.
- Faschingbauer, T. R., Devaul, R., & Zisook, S. (1981). *The Texas inventory of grief—Revised*. Houston, Texas: Honeycomb Publishing Co.
- Goldin, P. R., & Gross, J. J. (2010). Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion*, *10*, 83–91.
- Gratz, K. L., Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. *Journal of Psychopathology and Behavioral Assessment*, *26*(1), 41–54.
- Gündel, H., O'Connor, M.-F., Littrell, L., Fort, C., & Lane, R. D. (2003). Functional neuroanatomy of grief: An fMRI study. *The American Journal of Psychiatry*, *160*, 1946–1953.
- Hart, C. L., Hole, D. J., Lawlor, D. A., Smith, G. D., & Lever, T. F. (2007). Effect of conjugal bereavement on mortality of the bereaved spouse in participants of the Renfrew/Paisley study. *The Journal of Epidemiology and Community Health*, *61*, 455–460.
- Hensley, P. L., & Clayton, P. J. (2008). Bereavement: Signs, symptoms, and course. *Psychiatric Annals*, *38*, 649–654.
- Hölzel, B. K., Hoge, E. A., Greve, D. N., Gard, T., Creswell, J. D., Brown, K. W., ... Lazar, S. W. (2013). Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. *NeuroImage: Clinical*, *2*, 448–458.
- Hölzel, B. K., Lazar, S. W., Gard, T., Schuman-Olivier, Z., Vago, D. R., & Ott, U. (2011). How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. *Perspectives on Psychological Science*, *6*, 537–559.
- Hsu, A.-L., Hou, P., Johnson, J. M., Wu, C. W., Noll, K. R., Prabhu, S. S., ... Liu, H.-L. (2018). IClintfMRI software for integrating functional MRI techniques in presurgical mapping and clinical studies. *Frontiers in Neuroinformatics*, *12*, 839–814.
- Huang, F.-Y., Hsu, A.-L., Hsu, L.-M., Tsai, J.-S., Huang, C.-M., Chao, Y.-P., ... Wu, C. W. (2019). Mindfulness improves emotion regulation and executive control on bereaved individuals: An fMRI study. *Frontiers in Human Neuroscience*, *12*, 541.
- Huang, F.-Y., Wu, C. W., Bhikshu, H., Shih, G., Chao, Y.-P., & Dai, C.-T. (2015). Validation of the Taiwanese version of the five facet mindfulness questionnaire (T-FFMQ). *Psychological Testing*, *62*, 231–260.
- Kim, Y. W., Lee, S.-H., Choi, T. K., Suh, S. Y., Kim, B., Kim, C. M., ... Yook, K.-H. (2009). Effectiveness of mindfulness-based cognitive therapy as an adjuvant to pharmacotherapy in patients with panic disorder or generalized anxiety disorder. *Depression and Anxiety*, *26*, 601–606.
- King, A. P., Block, S. R., Sripada, R. K., Rauch, S., Giardino, N., Favorite, T., ... Liberzon, I. (2016). Altered default mode network (DMN) resting state functional connectivity following a mindfulness-based exposure therapy for posttraumatic stress disorder (PTSD) in combat veterans of Afghanistan and Iraq. *Depression and Anxiety*, *33*, 289–299.
- Kral, T. R. A., Imhoff-Smith, T., Dean, D. C., Grupe, D., Adluru, N., Patsenko, E., ... Davidson, R. J. (2019). Mindfulness-based stress reduction-related changes in posterior cingulate resting brain connectivity. *Social Cognitive and Affective Neuroscience*, *14*, 777–787.
- Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S. F., & Baker, C. I. (2009). Circular analysis in systems neuroscience: The dangers of double dipping. *Nature Neuroscience*, *12*, 535–540.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). International Affective Picture System (IAPS): Instruction manual and affective ratings, Technical Report A-8. Gainesville: The Center for Research in Psychophysiology, University of Florida.
- Lee, Y., Yang, M. J., Lai, T. J., Chiu, N. M., & Chau, T. T. (2000). Development of the Taiwanese depression questionnaire. *Chang Gung Medical Journal*, *23*, 688–694.
- Li, J., Biswal, B. B., Wang, P., Duan, X., Cui, Q., Chen, H., & Liao, W. (2019). Exploring the functional connectome in white matter. *Human Brain Mapping*, *40*, 4331–4344.

- Lichtenstein, P., Gatz, M., & Berg, S. (1998). A twin study of mortality after spousal bereavement. *Psychological Medicine*, 28, 635–643.
- Manor, O., & Eisenbach, Z. (2003). Mortality after spousal loss: Are there socio-demographic differences? *Social Science & Medicine*, 56, 405–413.
- McNab, F., & Klingberg, T. (2008). Prefrontal cortex and basal ganglia control access to working memory. *Nature Neuroscience*, 11, 103–107.
- O'Connor, M., Piet, J., & Hougaard, E. (2014). The effects of mindfulness-based cognitive therapy on depressive symptoms in elderly bereaved people with loss-related distress: A controlled pilot study. *Mindfulness (N Y)*, 5, 400–409.
- O'Connor, M.-F., Gündel, H., McRae, K., & Lane, R. D. (2007). Baseline vagal tone predicts BOLD response during elicitation of grief. *Neuropsychopharmacology*, 32, 2184–2189.
- Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, 59, 2142–2154.
- Roemer, L., Williston, S. K., & Rollins, L. G. (2015). Mindfulness and emotion regulation. *Current Opinion in Psychology*, 3, 52–57.
- Rosnick, C. B., Small, B. J., & Burton, A. M. (2010). The effect of spousal bereavement on cognitive functioning in a sample of older adults. *Neuropsychology, development, and cognition. Section B, Aging Neuropsychology and Cognition*, 17, 257–269.
- Scott, C. (2015). *DSM-5® and the Law: Changes and Challenges*, New York, NY: Oxford University Press.
- Scult, M. A., Fresco, D. M., Gunning, F. M., Liston, C., Seeley, S. H., García, E., & Mennin, D. S. (2019). Changes in functional connectivity following treatment with emotion regulation therapy. *Frontiers in Behavioral Neuroscience*, 13, 10.
- Segal, Z. V., Williams, J. M. G., & Teasdale, J. D. (2013). *Mindfulness-based cognitive therapy for depression, 2nd edn*. New York, NY: Guilford Publications.
- Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, 166, 1092–1097.
- Taylor, M. P., Reynolds, C. F., Frank, E., Dew, M. A., Mazumdar, S., Houck, P. R., & Kupfer, D. J. (1999). EEG sleep measures in later-life bereavement depression. A randomized, double-blind, placebo-controlled evaluation of nortriptyline. *The American Journal of Geriatric Psychiatry*, 7, 41–47.
- Teasdale, J. D., Segal, Z. V., Williams, J. M., Ridgeway, V. A., Soulsby, J. M., & Lau, M. A. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *The Journal of Consulting and Clinical Psychology*, 68, 615–623.
- Teper, R., & Inzlicht, M. (2013). Meditation, mindfulness and executive control: The importance of emotional acceptance and brain-based performance monitoring. *Social Cognitive and Affective Neuroscience*, 8, 85–92.
- Thielemann, K., Cacciatori, J., & Hill, P. W. (2014). Traumatic bereavement and mindfulness: A preliminary study of mental health outcomes using the ATTEND model. *Clinical Social Work Journal*, 42, 260–268.
- Tomasino, B., & Fabbro, F. (2016). Increases in the right dorsolateral prefrontal cortex and decreases the rostral prefrontal cortex activation after-8 weeks of focused attention based mindfulness meditation. *Brain and Cognition*, 102, 46–54.
- Tommasin, S., Mascali, D., Gili, T., Assan, I. E., Moraschi, M., Fratini, M., ... Giove, F. (2017). Task-related modulations of BOLD low-frequency fluctuations within the default mode network. *Frontiers of Physics*, 5, 1347.
- Troy, A. S., Shallcross, A. J., Davis, T. S., & Mauss, I. B. (2013). History of mindfulness-based cognitive therapy is associated with increased cognitive reappraisal ability. *Mindfulness (N Y)*, 4, 213–222.
- Tseng, F.-M., Petrie, D., & Leon-Gonzalez, R. (2017). The impact of spousal bereavement on subjective wellbeing: Evidence from the Taiwanese elderly population. *Economics and Human Biology*, 26, 1–12.
- Tu, Y.-Z., Lin, D.-W., Suzuki, A., & Goh, J. O. S. (2018). East Asian young and older adult perceptions of emotional faces from an age- and sex-fair east Asian facial expression database. *Frontiers in Psychology*, 9, 2358.
- Yan, F.-X., Wu, C. W., Cheng, S.-Y., Lim, K.-E., Hsu, Y.-Y., & Liu, H.-L. (2013). Resting-state functional magnetic resonance imaging analysis with seed definition constrained by regional homogeneity. *Brain Connectivity*, 3, 438–449.
- Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, 8, 665–670.
- Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: Identifying differences in brain networks. *NeuroImage*, 53, 1197–1207.
- Zhao, X.-R., Chen, Z.-F., Kang, C.-Y., Liu, R.-X., Bai, J.-Y., Cao, Y.-P., ... Zhang, Y.-L. (2019). Mindfulness-based cognitive therapy is associated with distinct resting-state neural patterns in patients with generalized anxiety disorder. *Asia-Pacific Psychiatry*, 32, e12368.
- Zimmerman, B., Finnegan, M., Paul, S., Schmidt, S., Tai, Y., Roth, K., ... Husain, F. T. (2019). Functional brain changes during mindfulness-based cognitive therapy associated with tinnitus severity. *Frontiers in Neuroscience*, 13, 747.
- Zisook, S., Paulus, M., Shuchter, S. R., & Judd, L. L. (1997). The many faces of depression following spousal bereavement. *The Journal of Affective Disorders*, 45, 85–94 Discussion 94–5.
- Zisook, S., & Shear, K. (2009). Grief and bereavement: What psychiatrists need to know. *World Psychiatry*, 8, 67–74.

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