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Meditative practice and behavioral neuroscience

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Meditative practice and behavioral neuroscience

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Editorial: Meditative practice and behavioral neuroscience

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Editorial on the Research Topic
Meditative practice and behavioral neuroscience

Mental wellbeing is paramount in today's global society, emphasized by advancements in brain research and algorithms. Major global players, including the US, EU, and China, are heavily investing in this domain. Yet, understanding concepts like consciousness and the mind-body problem remains elusive. Disorders like depression and epilepsy still challenge us. Ancient practices might offer insights into these modern dilemmas. This issue delves into the mind-body connection through a neuroscientific lens.

The elusive nature of mind sometimes clashes with scientific objectivity, necessitating a balance between subjectivity and objectivity. Recognizing the intrinsic mind-body connection, which has been present since life's inception, is crucial. This calls for a holistic research approach, and meditation, an age-old mental training practice, might be the key. This issue emphasizes meditative practices within the realm of behavioral neuroscience. Meditation, spanning various forms like Yoga, religious chanting, and contemporary mindfulness, has been practiced for millennia. Intensive training in meditation by practitioners, especially Buddhists and Hindus, can lead to profound mental states like enlightenment. While reaching such states is challenging, meditation's benefits, such as improved mental clarity and problem-solving, are well-documented. The rising popularity of mindfulness meditation, supported by scientific validation, underscores the need to further decipher its mechanisms.

A practical approach involves examining meditation from a brain-heart perspective. This dual training, linking brain and cardiac activities, might be key, especially in today's world where mental and physical aspects are often segregated. For instance, office workers might focus mentally, neglecting their body's needs. Persistent mind-body separation can be detrimental. Meditation can bridge this gap, enhancing overall wellbeing. Several studies in this issue found increased mind-body interaction post-meditation (Gan et al.; Gao, Sun et al.; Wong et al.), suggesting that studying the brain-heart connection can provide insights into the mind-body problem.

This issue encompasses diverse research areas, from epilepsy to mindfulness, utilizing various neuroimaging tools like EEG, fMRI, and fNIRS. The goal is to probe brain function using both objective tools and subjective mind states, especially during meditation. In this Research Topic, the emphasis is on mental wellbeing and brain-heart connection, which are related to mind-body problem in a broader sense. Its intricate relationship with meditation is evident. Given the prominent proportion of mindfulness-related research, a significant portion of the research, such as the studies on "*Enhanced resting-state* *functional connectivity*" (Gan et al.) and "Enhancing Chinese preschoolers' executive function via mindfulness training" (Xie et al.), delves deep into the realm of mindfulness application. These studies, along with others on "Interoceptive awareness" (Guu et al.) and "Increased neurocardiological interplay after mindfulness meditation" (Gao, Sun et al.), investigate mindfulness from varied yet interconnected angles, highlighting its central role in meditation-related neuroscientific exploration.

However, the scope of this issue isn't limited to mindfulness alone. Traditional meditation techniques, deeply rooted in Buddhist theories, also find their place. The "Loving-kindness meditation (LKM) modulates brain-heart connection" (Wong et al.) is particularly noteworthy. This EEG case study not only offers a unique perspective on the physiological effects of LKM but also underscores the potential of wearable technology in gathering extensive data. The "Neurophysiology of the intervention strategies of Awareness Training Program" (Gao, Leung et al.) further complements the exploration of traditional Buddhist practices, emphasizing the impact of such interventions on emotion regulation.

While the majority of the research is centered around meditation and its various forms, the issue also recognizes the importance of broadening its neuroscientific spectrum. Studies like "Inhibitory dysfunction in temporal lobe epilepsy (TLE) patients" (Yu et al.) and "Classification of temporal lobe epilepsy based on neuropsychological tests" (Meng et al.) delve into the realm of epilepsy. By incorporating these, the issue ensures comprehensive coverage, intertwining normative meditation practices with clinical neurological conditions.

Furthermore, the bridging of traditional neuroscience with modern machine learning techniques is evident in the "EEG-based investigation of effects of mindfulness meditation training" (Shang et al.). Indeed, advances in the neuroscience of epilepsy and in machine learning, which is the foundation for AI, can eventually aid in a more evidence-based classification of mindfulness meditation. This classification can also have an impact on the neural measures in clinical psychology practice (Ngan and Cheng). All of this research not only offers fresh insights into the effects of mindfulness meditation but also paves the way for more objective studies.

The potential for large-scale data collection on meditators, especially with the use of wearable devices (Wong et al.), presents both opportunities and challenges. It is believed that AI, like large language models and big data, can provide invaluable insights into which neural indices can best estimate meditation (Ngan and Cheng; Shang et al.). Current cumulative research can pave the way for advanced research methods. Given the reservations of some meditators about their privacy and their occasional hesitance to participate in studies, ethical considerations have to be considered carefully during data gathering and analysis. It is essential to adhere to established ethical guidelines and best practices on personal and sensitive information.

Despite the progress made in this Research Topic, significant challenges remain to be addressed. One of the primary challenges is bridging the gap, especially in terms of theories and terminology, between modern neuroscience and ancient practices, such as those in the Buddhist tradition. The differing theoretical frameworks and foundational concepts often lead to communication barriers. Furthermore, there are methodological challenges in identifying and defining the subjective experiences of advanced meditators and verifying their profound mental states.

Overall, this edition provides a comprehensive perspective and paves the way for upcoming innovations in mental health. It gives an example of the blending of ancient traditions with neuroscientific research techniques, including the use of advanced neuroimaging techniques. This publication signifies a notable advancement in understanding meditation, fostering optimism that as we delve deeper. Based on a more objective methodology, it is estimated that scientists can gain clearer insights into human psychology and spirituality to enhance modern-day mental health practices.

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Enhanced Resting-State Functional Connectivity With Decreased Amplitude of Low-Frequency Fluctuations of the Salience Network in Mindfulness Novices

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Mindfulness and accordant interventions are often used as complementary treatments to psychological or psychosomatic problems. This has also been gradually integrated into daily lives for the promotion of psychological well-being in non-clinical populations. The experience of mindful acceptance in a non-judgmental way brought about the state, which was less interfered by a negative effect. Mindfulness practice often begins with focused attention (FA) meditation restricted to an inner experience. We postulate that the brain areas related to an interoceptive function would demonstrate an intrinsic functional change after mindfulness training for the mindful novices along with paying more attention to internal processes. To further explore the influence of mindfulness on the organization of the brain regions, both functional connectivity (FC) in the voxel and the region of interest (ROI) level were calculated. In the current study, 32 healthy volunteers, without any meditation experiences, were enrolled and randomly assigned to a mindfulness-based stress reduction group (MBSR) or control group (CON). Participants in the MBSR group completed 8 weeks of mindfulness-based stress reduction (MBSR) and rated their mindfulness skills before and after MBSR. All subjects were evaluated *via* resting-state functional MRI (rs-fMRI) in both baselines and after 8 weeks. They also completed a self-report measure of their state and trait anxiety as well as a positive and negative affect. Pre- and post-MBSR assessments revealed a decreased amplitude of low-frequency fluctuations (ALFF) in the right anterior cingulate gyrus (ACC.R), left anterior and posterior insula (aIC.L, pIC.L), as well as left superior medial frontal gyrus (SFGmed.L) in MBSR practitioners. Strengthened FC between right anterior cingulate cortex (ACC.R) and aIC.R was observed. The mean ALFF values of those regions were inversely and positively linked to newly acquired mindful abilities. Along with a decreased negative affect score, our results suggest that the brain regions related to attention and interoceptive function were involved at the beginning of mindfulness. This study provides new clues in elucidating the time of evaluating the brain mechanisms of mindfulness novices.

Keywords: emotion regulation, functional connectivity (FC), mindfulness, amplitude of low-frequency fluctuation (ALFF), functional magnetic resonance imaging (fMRI)

INTRODUCTION

By cultivating a state of sustained attention to internal processes in the present moment with acceptance and without judgment (Kabat-Zinn, 1990), mindfulness and accordant interventions have shown benefits with various psychological or psychosomatic problems when they are used as complementary treatments (Goyal et al., 2014). Mindfulness has been proven to be effective in alleviating chronic pain (Priddy et al., 2018), relieving the symptoms of depression (Marchand, 2012), anxiety (MacDonald and Olsen, 2020), or even reducing substance cravings of addiction (Enkema and Bowen, 2016). Moreover, mindfulness becomes popularized in recent years as an aid to help with the promotion of psychological well-being in non-clinical populations (Kingston et al., 2007). Mindfulness meditators often report less acceptance (Brown and Ryan, 2003), more acceptance, and a better regulation of negative affect (Wenzel et al., 2020). For these reasons, mindful practices have been incorporated into daily lives rather than as independent psychological interventions. The benefits of mindfulness have often been considered in their association with emotion regulation (Guendelman et al., 2017). This study convinces us that both attention and attitude were involved in the contribution of mindfulness to emotion regulation (Cavicchioli et al., 2018). By reappraising and focusing on the present moment, individuals become aware of their momentary sensations in the background of broadened attention and learn to adapt into new situations. Moreover, the experience of accepting feelings that arise, in a non-judgmental way, makes it easier to adapt to undesirable situations (Murphy and Lahtinen, 2015). The state of well-being could be achieved simply by accepting instead of fighting to control emotions. Corresponding to this notion, a recent study showed a significant association between mindfulness ability (especially non-judgmental acceptance facet) and the lesser use of emotion regulation strategies. It also proved and indicated that mindfulness may facilitate better well-being by lessening the need for strenuous emotion regulation.

Accordingly, mindfulness practice can generally be divided into two categories, i.e., focused attention (FA) and open monitoring (OM) (Lutz et al., 2008; Britton et al., 2018). FA practice is normally considered as an attentional skill in which selective attention of a chosen object, such as the sensation of breathing. Nevertheless, OM emphasizes de-selection, non-reactive monitoring of internal and external sensation, and entails non-judgmental awareness of experience. Basically, the attention regulation is the common link for both kinds of methods, which are comprehensively combined in traditional practice. In mindfulness practice, FA and OM are used jointly in enhancing the process of detecting mind wandering, configuring attention resources, and reducing habitual behavior. Normally, FA improves attentional resources in the first place, which in turn may reduce emotional interference (Farb et al., 2012). The process could be summarized as an interaction between attention regulation (Hasenkamp and Barsalou, 2012) and rising awareness (Kwee, 1995; Raffone et al., 2010; Keng et al., 2011; Vago and Silbersweig, 2012). A non-judgmental would lead to a certain perspective change, nominated as "decentering" (Fresco et al., 2007). With repeat practice, automatic attentional habits were gradually noticed. Concomitantly, metacognitive awareness was cultivated, which led to a reasonable distribution of attentional resources. Ultimately, concurrent monitoring of multiple present-moment experiences took place (Carmody, 2009). Detachment, decentering, or deautomatization was entailed by the previously mentioned procedure and rumination was reduced (Gu et al., 2015), increased levels of mindful attention and awareness were finally achieved (Shapiro et al., 2008). The underlying brain function may shed light on the mechanisms of mindfulness (Brown et al., 2007; Duquette, 2017).

Meanwhile, an accumulating body of evidence in neuroimaging is revealing the effects of mindfulness on the structure of the brain (Grant et al., 2010; Lazar et al., 2011; Kurth et al., 2014; Lu et al., 2014), activation (Farb et al., 2007; Braden et al., 2016; Tomasino and Fabbro, 2016), or neural connectivity (Doll et al., 2015; Murakami et al., 2015; Taren et al., 2015; Anthony et al., 2016) after 8 weeks of mindful induction (Gotink et al., 2016). Attention (Tsai and Chou, 2016) networks were particularly highlighted (Dickenson et al., 2013; Peters et al., 2016; Tomasino and Fabbro, 2016). Distinctive parts of the brain were regulated by the three subfunctions of attention (Tsai and Chou, 2016). While the involvement of subnetworks is sequential according to how much effort is needed for the maintenance of the different states (Tang et al., 2012). Recent studies have also revealed intrinsic functional connectivity (FC). Inter- and/or intra-attention networks were modified with mindfulness (Doll et al., 2015; Roland et al., 2015). To be specific, much effort was required to achieve the meditative state at the beginning. The lateral prefrontal cortex (PFC) and parietal cortex are mostly involved in voluntary control (Farb et al., 2007; Tang et al., 2009, 2012), whereas with the anterior cingulate cortex (ACC) less effort is invested (Tang et al., 2009, 2012; Hölzel et al., 2011; Tang, 2011). In the middle stage of meditation, practitioners began to notice distractions of the wandering mind that was decreased as awareness increased. With an appropriate effort, the participants' meditation skills and attention control increased. Hence, the brain regions related to awareness and attention switched, namely the salience network (SN), dorsolateral prefrontal cortex (dlPFC), and posterior parietal lobule could be activated (Hasenkamp and Barsalou, 2012; Malinowski, 2012; Tang et al., 2012). Along with the practice, one became proficient in the awareness of distraction and the switching of attention. Theoretically, the maintenance of a mindful state may be achieved with little or no effort in the advanced stage. One is mindful of the present moment, whether it includes a particular object or all salient stimuli. Thus, attention is focused and broadened and "conflict monitoring is used to a lesser degree" (Barinaga, 2003). With the decrease of attention control, the obtaining and maintenance of mindfulness state became much fluent. The state may be supported by the ACC, left insula, and striatum (Tang et al., 2012). Besides, the midline structure was functionally associated "getting caught up in" experience, the deeper one was immersed the stronger the activation it became (Northoff et al., 2006). Studies of experienced meditators that the indicated posterior cingulate gyrus (PCC) was activated in "distraction" and deactivated in "concentration" (Brewer et al., 2013). Synchrony or connectivity between frontal and parietal lobes may also reflect the conscious awareness of the present moment (Taylor et al., 2013). Therefore, a certain neuronal basis was detected to underpin the brain functional change following the "react" to "respond" (Doran, 2014) transition.

Generally, mindfulness often begins with FA meditation (Hasenkamp and Barsalou, 2012), which is restricted to a specific object (normally the sensory experience of the breath). The calmness state was not so hard to achieve in mindfulness beginners. It would be of great value to evaluate the underlying mechanism that may provide new clues in relation to the psychosomatic intervention. Therefore, we postulate that the brain areas responsible for an interoceptive function would present with an intrinsic functional change after mindfulness training in novices, following the procedure of learning to pay more attention to internal processes (especially the body sensation), the brain areas responsible for an interoceptive function would present with an intrinsic functional change after mindfulness training. To test the prediction, resting-state functional MRI (rs-fMRI) was used to assess brain activation in mindfulness meditation beginners before and after 8-week of mindfulness practice as well as in matched controls. As a reliable index for the evaluation of neuronal activation, the regional amplitude of low-frequency fluctuations (ALFF) in the conventional frequency band (0.01–0.08 Hz) was adopted (Zang et al., 2007). It has been investigated in numerous neuropathological and physiological states since its proposition (Zang et al., 2007; Han et al., 2011; Wang et al., 2011; Liu et al., 2012; Pan et al., 2014; Xiao et al., 2015). Considering the current topic, it has been proven to be effective on analyzing the neural basis of both FA and mindfulness meditation (Miyoshi et al., 2019; Yang et al., 2019). In addition, to further explore the influence of mindfulness on the organization of the brain regions, FC was calculated in both voxel and the region of interest (ROI) level.

MATERIALS AND METHODS

Participants

In total, 32 healthy volunteers (16 men) without any mindfulness or meditation experiences were recruited in this study. They were randomly assigned to the mindfulness-based stress reduction group (MBSR) or control group (CON) (16:16). Those subjects in the MBSR group periodically attended MBSR practice for 8 weeks. While participants in the CON group merely accomplished relax practice during the same period.

All subjects were recruited through poster advertisements from the local community. They were interviewed by the two experienced psychiatrists using the SCID-I/NP (non-patient version) to exclude subjects with any history of neuropsychiatric illness. All participants were Han Chinese, right-handed, and assessed using the Annett Handedness Scale (Annett, 1970). For both groups, subjects with organic brain disorders, a history of alcohol or drug abuse, pregnancy, or severe physical illnesses were excluded. All participants provided written informed consent. The study was approved by the Ethical Committee of Kunming University of Science and Technology (ethical approval number: 2013JC003).

Mindfulness Meditation Training

Following the traditional setting (Kabatzinn, 2010), the 8-week MBSR program consisted of weekly group meetings and homework. Each weekly meeting lasted for 2 h each time, and was divided into 3 parts, a theoretical part (30 min), a practical part (60 min), and a debriefing part. In the theoretical part, MBSR and underlying neuroscience were introduced to participants. In the following practice part, sitting meditation exercises were conducted *via* simple physical and breathing exercises, focusing attention on thoughts and feelings that came in without dwelling on any of them. All classes were taught by a senior teacher having experience in mindfulness teaching over 5 years. The daily homework practice was composed of formal and informal practices. The former lasted for 30 min each day, took the form of a body scan, sitting meditation, floor yoga, the mountain/lake meditation, or the loving kindness meditation. Each week, participants were asked to fill a formal practice sheet that was tailored for that week and guided that week's practice. Aiming to integrate the learnings and practices into daily life, the informal practice was mainly simple awareness, i.e., bringing mindful awareness to routine activity, pleasant/unpleasant events, or communication situations. Additional techniques, such as 1-min breathing space (Ward, 2014) and recognize, accept, investigate, non-identification (RAIN) (Brewer et al., 2011) process were involved in informal practice help to notice automatic reaction and open awareness. At the end of each day, the participants took just 5 min or so to reflect on the day, using that week's informal practice sheet as a guide.

Process Measures

Mindfulness skills were assessed with the 39-item Chinese version of the Five Facet Mindfulness Questionnaire (FFMQ-C) (Hou et al., 2014). FFMQ, which is sensitive to a change in mindfulness-based interventions (Gu et al., 2015), consists of five subscales: observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience. In addition, to measure state and trait anxiety, the Chinese version of the State-Trait Anxiety Inventory (STAI) (Shek, 1988) was adopted. The STAI is a 40-item self-report questionnaire used to measure both current anxiety and state (20 items) anxiety. The Positive and Negative Affect Schedule (PANAS) was also applied both before and after the MBSR training to explore emotional states for all subjects. The PANAS is a 20-item self-report scale that measures positive and negative mood states in relation to the time frame of the previous week. Both negative and positive affect scales consist of 10 adjectives describing corresponding emotions, respectively. Participants rate the degree to which they feel each emotion on a scale from 1 (very slightly or not at all) to 5 (extremely).

MRI Data Acquisition

Functional MRI data were acquired using a Signa Excite 3.0 Tesla scanner (GE Healthcare, Waukesha, WI, United States) at the First People's Hospital of Yunnan Province with a spin echo-planar imaging (EPI) sequenced with an eight-channel phase array head coil. Data sets were aligned to the anterior–posterior commissure (AC-PC) line, using the following scan parameters: repetition time = 3,000 ms; echo time = 40 ms; image matrix = 64 × 64; field of view = 24 cm × 24 cm; 34 contiguous slices of 4 mm and without a gap; and restraining foam pads were used to minimize head motion. Subjects were instructed to simply relax, to keep their eyes closed, and to remain awake and perform no specific cognitive exercise.

fMRI Image Processing

Resting-state fMRI data preprocessing was carried out by using Data Processing Assistant for Resting-State fMRI (DPARSF, V2.2[1]), which was based on SPM8[2] and the Resting-State fMRI Data Analysis Toolkit plus (RESTplus, V1.1, see Text Footnote 1). The first 10 volumes were discarded to allow for steady-state magnetization. Further data preprocessing included slice timing correction, head motion correction, spatial normalization, and smoothing. Spatial normalization was performed by using the standard EPI template from the Montreal Neurological Institute (MNI). Then, linear detrending and temporal bandpass (0.01–0.08 Hz) filtering were performed to remove low-frequency drifts and physiological high-frequency noise. In addition, the effects of the global mean signal, white matter, and cerebrospinal fluid (CSF) were regressed out by using the default masks included in the package.

Amplitude of Low-Frequency Fluctuations Calculation

Amplitude of low-frequency fluctuations was calculated using the RESTplus software. Spatially normalized data were smoothed with a 6 mm full width at half maximum (FWHM) Gaussian kernel prior to ALFF calculation. The time series was first converted to the frequency domain using a Fast Fourier Transform for a given voxel. The square root of the power spectrum was computed and then averaged across the predefined frequency interval. This averaged square root was termed as the ALFF at the given voxel (Zang et al., 2007). ALFF measures the absolute strength or intensity of spontaneous low-frequency oscillations (typically 0.01–0.08 Hz). Under the studied frequency ranges, ALFF at each voxel was computed for each subject, and it was further applied with Fisher's r-to-z transformation to obtain a comparable z-value instead of the original.

[1]http://www.restfmri.net

[2]http://www.fil.ion.ucl.ac.uk/spm/software/spm8

Statistical Analyses

The independent sample t-tests and the chi-squared test were used to compare demographic data between MBSR and CON groups with SPSS 13.0 software (SPSS, Chicago, IL, United States).

Voxel-Wise Comparison of Amplitude of Low-Frequency Fluctuations Maps

Voxel-based comparisons of ALFF maps were performed to detect the intergroup and intragroup differences. The preprocessed data were analyzed as the two-sample/paired t-test by fitting the general linear model (GLM) in SPM8. The results at $p < 0.05$ at the voxel level, and $p < 0.05$ at the cluster level, with family-wise error (FWE) correction and cluster > 50 voxels for ALFF were considered to be statistically significant.

Network Analyses

Two levels of FC were conducted. Firstly, five spherical regions of interest (ROIs) were defined in the regions of ALFF alteration detected in the current study. The ROIs were defined as spheres of 6 mm radius centered on peak coordinates of regional differences in ALFF maps among practitioners. In the voxel-wise seed-based FC analysis, a whole-brain FC map for each seed was generated. In the ROI-wise analysis, a 5 × 5 correlation matrix was created for each subject. For the correlation coefficients, Fisher's r-to-z transformation was applied to obtain a comparable z-value instead of the original r, and then a difference of any paired z-value was calculated by using a paired t-test. For the voxel level analysis, $p < 0.05$ with FWE correction and cluster > 50 voxels were considered as the networks linked to the seeds. Bonferroni correction was applied in the ROI level FC analysis.

Correlation Analysis

Pearson correlation analysis was used for assessing associations between the coupling of ROIs (mean ALFF) and mindfulness (FFMQ) scores. The analyses were conducted using SPSS.

RESULTS

Demographic Description

In total, 16 subjects and demographically matched controls were recruited. There were no significant differences in demographic variables ($p > 0.05$) between the groups (**Table 1**).

TABLE 1 | Demographic data for all subjects.

	MBSR	CON
Age (years)	27.63 (1.25)	28.06 (1.60)
Gender (male: female)	8:8	8:8
Years of education	17.00 (0.57)	15.17 (0.67)

MBSR, mindfulness-based stress reduction training group; CON, control group; values are given as a number or mean (SE). No statistically significant differences between the groups (p > 0.05).

Change in Mindfulness Ability and Affective States

A paired t-test was conducted to analyze mindfulness ability and affective state change in the MBSR group. The total score and subscale scores except for the non-judgment of FFMQ indicated a significant raise of self-report mindfulness after MBSR training ($p < 0.05$). Both state and trait anxiety scores showed no difference between baseline and post-training evaluation ($p > 0.05$). The negative effect score of PANAS also significantly decreased after training ($p < 0.01$) (**Table 2**).

General Linear Modeling Results

An intergroup whole-brain contrast analysis between the MBSR and CON group in baseline was performed. Then, intragroup analyses were conducted between the baseline and 8-week assessments in both the groups separately. No significant difference was detected in the first contrast, neither in the intragroup comparison in the CON group ($p > 0.05$). In the contrast between baseline and post-training assessment in the MBSR group, decreased ALFF in the right anterior cingulate gyrus (ACC.R), left anterior and posterior insula (aIC.L, pIC.L), as well as the left superior medial frontal gyrus (SFGmed.L) was detected in case of practitioners. Increased ALFF was observed in the right postcentral gyrus (PostCG.R) (**Table 3** and **Figure 1**).

Pre- and Post- mindfulness-Based Stress Reduction Group Comparison of Functional Connectivity

As elaborated in the section "Materials and Methods," five spherical ROIs were chosen in the regions with ALFF alteration detected in the current study. Based on all 5 seed ROIs, voxel-wise functional analysis revealed strengthened FC between pIC.L and bilateral amygdala [cluster size: 90 voxels on the left (peak MNI coordinates $x = -18$, $y = 3$, $z = -12$; $p = 0.016$) and 185 on the right (MNI coordinates $x = 18$, $y = 3$, $z = -15$; $p = 0.017$), FWE corrected] (**Figure 2**). In the ROI-wise analysis, the dominance of coupling between the right ACC and left medial superior frontal gyrus (SFGmed) attenuated [$r_1 = 0.60 \pm 0.25$, $r_2 = 0.33 \pm 0.22$, $t_{(15)} = -3.215$, $p_{\text{corr}} = 0.003$], while the dominance of coupling between ACC.R and aIC.R enhanced after MBSR training ($r_1 = -0.03 \pm 0.16$, $r_2 = 0.15 \pm 0.27$, $t = -3.221$, $p_{\text{corr}} = 0.022$).

TABLE 2 | The Five Facet Mindfulness Questionnaire (FFMQ), the State-Trait Anxiety Inventory (STAI), and the Positive and Negative Affect Schedule (PANAS) scores before and after meditation training.

	Before training	After training	*T*-value
Mindfulness score (FFMQ)			
Observe	23.06 (1.54)	27.00 (1.27)	**−3.134**
Describe	22.37 (1.09)	28.44 (1.19)	**−6.235**
Awareness	20.31 (1.15)	27.81 (1.11)	**−3.890**
Non-judgment	23.63 (1.32)	26.63 (1.22)	−1.324
Non-reactivity	19.50 (1.09)	22.31 (1.31)	**−2.397**
Total	108.876 (4.21)	132.19 (3.84)	**−5.307**
Anxiety state (STAI)			
State Anxiety Inventory	45.56 (1.49)	41.87 (1.15)	2.112
Trait Anxiety Inventory	44.43 (1.57)	44.12 (1.43)	0.168
PANAS			
Positive affect	30.84 (0.86)	30.38 (0.95)	1.225
Negative affect	16.63 (0.89)	12.88 (0.62)	**5.616**

Values are given as group means (SE). Bold values indicate p < 0.05.

Association Between Coupling of Region of Interests and Mindfulness Scores

Within the MBSR group, the mean ALFF value of ROIs located in right anterior cingulate cortex and aIC.L cortex was negatively correlated with the total score ($r = -0.513$, $p = 0.042$) (**Figure 3A**) and observing score ($r = -0.520$, $p = 0.0392$) (**Figure 3B**) of FFMQ, respectively. The activation of the posterior insula (pIC) ROI was positively correlated with the non-judgment score ($r = 0.509$, $p = 0.044$) (**Figure 3C**). A coupling between pIC.L and aIC.L was positively correlated with the non-judgment score ($r = 0.574$, $p = 0.020$). The PANAS negative affect score was positively correlated with ACG.R ($r = 0.542$, $p = 0.030$).

DISCUSSION

In the present work, as a reliable data-driven approach, ALFF was adopted to map the resting-state functional topology based on the magnitude of spontaneous neural activity. There were two main findings in the current study. Firstly, decreased ALFF was detected in three clusters, including the ACC.R, aIC.L, and pIC.L accompanied by strengthened FC between pIC.L and bilateral amygdala. Both ACC and aIC belong to the SN. While postcentral gyrus belonging to the somatosensory network was observed with increased ALFF. Furthermore, the mean ALFF value of ROIs located in SN showed a correlation with mindfulness scores. Secondly, the core region of the default mode network (DMN), i.e., SFGmed.L, also showed decreased ALFF and a weakened correlation with SN. The postCG.R as another region related to attention control showed an adverse change in activation. Together with a decreased negative affect score, strengthened coupling within SN was also observed in an ROI level analysis. These findings may be of significance in explaining the underlying brain mechanisms for short-time mindfulness practice.

TABLE 3 | Brain areas with a change of amplitude of low-frequency fluctuations (ALFF) after MBSR training.

Region	BA	*t*-value	*P*-value	Cluster size	Peak MNI-coordinates		
					x	*y*	*z*
ACC.R	32	7.43	≤0.001	509	15	48	18
pIC.L	48	6.26	0.0089	119	−36	−27	24
SFGmed.L	10	5.32	0.0464	83	−6	54	21
aIC.L	48	5.25	0.0063	127	−30	27	12
PostCG.R	7	−5.65	0.0005	190	30	−45	72

Shown are results of paired t-tests of regional ALFFs in MBSR group after 8 weeks' training compared with baseline [cluster level, family-wise error (FWE) corrected, $p < 0.05$]. ACC.R, right anterior cingulate cortex; pIC.L, left posterior insula; SFGmed.L, left medial superior frontal gyrus; aIC.L, left anterior insula; PostCG.R, right postcentral gyrus; BA, Brodmann area; MNI, Montreal Neurological Institute.

First and foremost, the structural and functional brain changes induced by the 8-week MBSR were similar to traditional long-term meditation practice (Gotink et al., 2016). Among those regions, the cingulate cortex, insula, and dlPFC were major neural underpinnings of mindfulness-based intervention (Bilevicius et al., 2016). In our results, decreased ALFF was observed in the core regions of SN, i.e., ACC and the anterior insula in mindfulness beginners. SN was relevant to the experience and training of mindfulness, given its role in both interoception and redirecting attentional resources (Mooneyham et al., 2016). The first result gives an indication of the outcome of mindfulness practice in relation to attention control.

As mentioned earlier, mindfulness ability was cultivated when interoceptive information was elaborately processed (Paulus et al., 2013). Interoception included receiving, processing, and integrating body-relevant signals together with external stimuli and finally affect motivated behavior (Craig, 2002). It refers to the process of how the brain senses and integrates signals originating from inside the body, providing a moment-by-moment mapping of the body's internal landscape. This is closely related to one's state of well-being, energy, and stress levels, as well as mood and disposition (Craig, 2002). Individuals often habitually take the form of escape from the present moment to feel better or to avoid feeling worse. Sensory awareness is achieved to provide a way, which makes that the interoceptive information could be read and then translated into facilitating self-awareness and self-care (Cjp et al., 2019). In this procedure, active attention to the inner body is required. Besides, it has also been told that the integration of interoceptive signals constrains the scope through which cognitive appraisals of well-being occur (Zanna and Cooper, 1974; Farb et al., 2015). Thus, mindfulness and well-being may be bridged basically by interoception. In the framework of mindfulness, focusing on one's own feelings with acceptance may lead to well-being without expending effort to control negative experiences (Wenzel et al., 2020).

The underlying mechanism could be summarized as bottom-up processing of information. Accumulating evidence from neuroimaging studies mostly support this idea (Westbrook et al., 2013). It was reported that a functional change in insula was induced by MBSR (Sevinc et al., 2018) or MBSR tasks (Farb et al., 2013), as well as dispositional mindfulness (Laneri et al., 2017). Both anterior and posterior parts of the insula were normally discussed. The anterior insula could be activated both in interoceptive awareness (Cui et al., 2020) and emotion perception task (Lamm et al., 2010) including pain perception (Farb et al., 2013). It has been proposed that an emotional change is always accompanied by a physiological change. Being consciously aware of bodily signals could lead to an understanding and acceptance of the feeling states of one's own body (Kuehn et al., 2015). Therefore, emotional improvement could be a major effect of body-awareness enhancement. It has been reported in detail that mindfulness could promote the precision of afferent signals (Paulus et al., 2013; Duquette, 2017) as the result of increased sensory attention, then increase perceptual inference processing of prediction errors in support of learning that can lead to the adjustment of behaviors (Duquette, 2017). That being the case, it is reasonable to assume that mindfulness practice could increase the efficiency in processing of interoceptive information in practitioners. With the promotion of awareness, one may respond rather than react to an internal or external situation (Meppelink et al., 2016). It happens to be the goal of psychotherapy practice in any theoretical model, described of decreased reactive responses and increased moment-to-moment awareness (Duquette, 2017).

Interoceptive awareness probably originates from the anterior insula (Craig, 2009b). As a method to direct intervention/practice, mindfulness was observed to show a regulated effect on anterior insula activity directly Nevertheless, the processing of interoceptive information was dependent on the cooperation of the subregions of both pIC and aIC. Those two regions were assumed to supply objective and subjective representations of the physical conditions, respectively (Craig et al., 2000; Kuehn et al., 2015; Meppelink et al., 2016). The signal flows through the posterior-to-anterior axis making it possible for the integration of objective interoceptive information. However, the processing could be modified by focusing on bodily sensations. A previous study showed that in a state of bodily focusing, pIC inhibition could decrease the processing of other interoceptive (Kuehn et al., 2015; Meppelink et al., 2016). Moreover, low baseline activity coupled with a high response in the anterior insula was generally observed in experienced meditators (Lutz et al., 2013). Experienced mindfulness meditators are able to attenuate reward prediction signals in a passive conditioning task, which may be related to interoceptive processes encoded in the pIC (Kirk and Montague, 2015). In the current work, the decreased activity of both pIC and aIC in the resting state happens to repeat the results in experienced

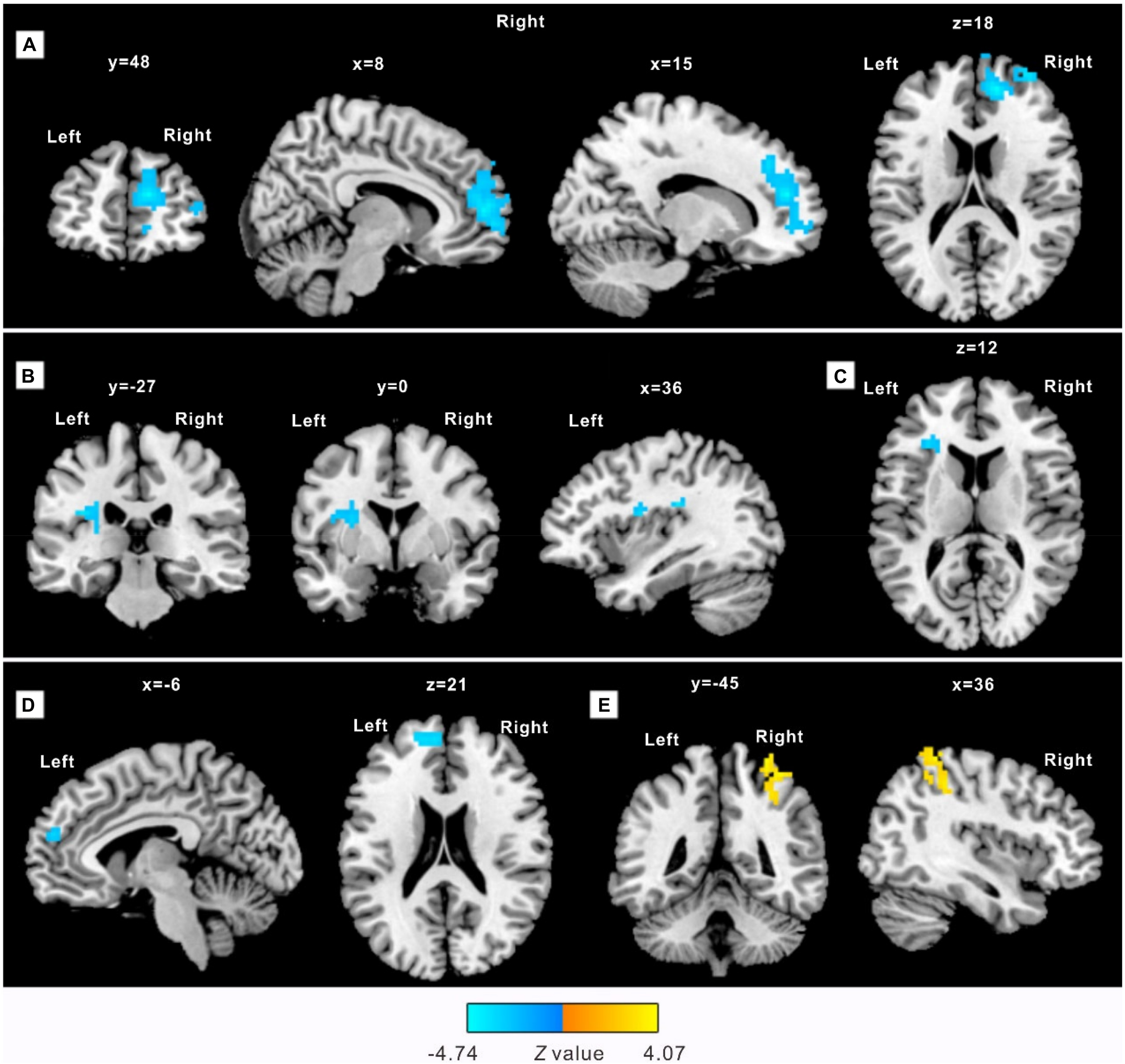

FIGURE 1 | Practitioners demonstrate a significantly different amplitude of low-frequency fluctuations (ALFF) after an 8-week practice. The clusters detected with decreased ALFF include: **(A)** right anterior cingulate gyrus (ACC.R), extending into the right middle frontal gyrus; **(B)** left posterior insula (pIC.L), extending into the left putamen; **(C)** left anterior insula (aIC.L), extending ventrolateral into the left middle frontal gyrus; **(D)** peak in the left superior medial frontal gyrus (SFGmed.L), extending into the left superior dorsolateral frontal gyrus. A cluster located in the right postcentral gyrus (PostCG.R) extending into the right superior parietal gyrus **(E)** showed increased ALFF. Sections are shown in sagittal, axial, and coronal planes with Montreal Neurological Institute (MNI) coordinates of the selected sections representing the peak in the *x*-, *y*-, and *z*- direction.

meditators. Moreover, to a certain extent, both regions showed a correlation with mindfulness ability (especially non-judgment and acceptance facet) to a certain extent. This may indicate that insula is involved in the processing of interoceptive information as a way of acceptance in mindfulness beginners.

Anterior cingulate cortex was related to the computation of prediction errors based on one's current state and the expected state (Paulus et al., 2013), which resulted in the motivation of individuals for approaching or avoiding stimuli (Holroyd and Yeung, 2012) to restore balance (Khalsa and Lapidus, 2016). Similarly, mindfulness-related structural and activation changes in ACC were also captured by MRI studies. Individuals who were more mindful of the present had greater gray matter volume in the ACC (Lu et al., 2014). The activation of ACC was observed in breath-focused mindfulness tasks (Lazar et al., 2000; Hölzel et al., 2007), deep meditation (Craigmyle, 2013), and decreased in experienced meditators when converting to a state of mindfulness (Ritskes et al., 2003). Mindfulness effects were detected with the decoupling of resting-state FC (rs-FC) between subgenual ACC and amygdala (Taren et al., 2015) or other craving-related regions (caudate, ventral striatum, premotor cortex, and insula) (Westbrook et al., 2013). Both insula (especially the anterior part)

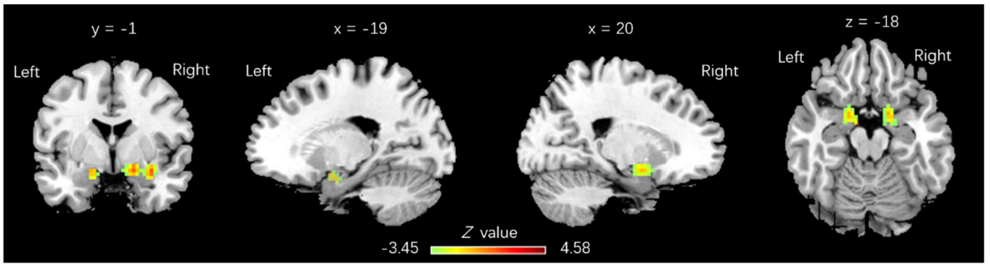

FIGURE 2 | Regions with functional connectivity (FC) increase linked to pIC.L. pIC.L-related FC with a significant increase was observed in bilateral amygdala, with 90 voxels on the **left** ($x = -18$, $y = 3$, $z = -12$; $p = 0.016$) and 185 voxels on the **right** ($x = 18$, $y = 3$, $z = -15$; $p = 0.017$), family wise error (FWE) corrected.

(Craig, 2009a) and ACC (Hakamata et al., 2013) were reported to be of great importance in mindful awareness. Attenuation of the right anterior insula and ACC was related to the loaded breathing task (Haase et al., 2014). As to the connection within SN, greater SN connectivity in pIC (but not aIC) and intrinsic connectivity of all insular functional subdivisions to SN regions (including the anterior insula, orbitofrontal cortex, ventral striatum, and midbrain) correlated with a greater interoceptive accuracy (Chong et al., 2017). In the current study, alleviated activation of ACC in the resting state also duplicated that decreased pattern in experienced meditators (Ritskes et al., 2003). Besides, the negative affect score was positively correlated with the activation of ACC, which may indicate the role of this region in mindfulness-related emotional improvement.

Except for the changes mentioned above, the activation of ACC and insula was detected by neuroimaging studies in several self-related processing, such as self-criticism and self-reassurance (Longe et al., 2010). Both ACC and insula were crucial structures in self-evaluation and satisfaction. In the current study, decreased spontaneous activity in the resting state was observed in the right ACC and left insula (including both anterior and posterior parts). This was quite similar to the increased activation observed in depression (Orenius et al., 2017) and decreased skilled practitioners. It has been proposed that the attenuated self-related process was related to emotional amelioration either (Verplanken et al., 2007). Furthermore, in the second part of the current results, SFGmed belongs to the midline structure that is also associated with the self-related process (Orenius et al., 2017; Terpou et al., 2019). The decrease of this region also makes it possible for individuals to achieve a state of mind for the reduction of negative thoughts. Similar to previous reports with the same sample, the regions of DMN were detected with a functional change after MBSR. In the current study, the direct investigation was used rather than an ROI analysis in a previous study (Xiao et al., 2019). However, except for the consideration of methodology, mindfulness under the scope of DMN still needs to be implemented in future. “The mediation effects of DMN on mindfulness and behavioral performance outcomes as well as DMN and its role in individual behavior performance” were nominated (Nien et al., 2020).

As to the divergence across studies, various impact factors can be distilled to the heterogeneity. For instance, the subregions of cingulate cortex have been reported with functional and structural changes related to mindfulness and meditation. Among these studies, long-term, short-term, and trait mindfulness (Lu et al., 2014) with different study designs, sample sizes, demographics, meditation styles, and cingulate subdivisions were used as a reference (Zsadanyi et al., 2021). As proof, the subgenual cingulate cortex was observed with lower rates of annual tissue loss in long-term meditators, suggesting a protective effect of meditation on the emotional and cognitive function (Kurth et al., 2021). The protective effects have also been indicated by short-term body-mind training (Tang et al., 2020). While, in the current study, right ACC was revealed to have alleviated spontaneous activity in post-MBSR assessment and negatively related to mindfulness ability. The divergent results may be attributed to demographic factors, meditation styles, and experience, as well as practice terms. In our previous research work, left medial cingulate cortex functional change was detected (Xiao et al., 2019). The neuroimaging index adopted may explain the variation of the results. For details, ALFF in the current study was considered to be a reflection of neuroactivities in focal regions (Zang et al., 2007), while ReHo adopted previously may characterize the cohesiveness in neighboring brain regions (i.e., focal connectivity) (Zang et al., 2004). Recent works on clinical population have also imposed the focusing on neural correlates of somatic and attention mechanisms underlying the emotional process (Hatchard et al., 2020). Future studies focusing on clinical phenotypes may provide more specific indicators for detecting the interactive process.

Though it may offer some profound and important conclusions, in this study, there are also some limitations that must be taken into consideration. First, there is a moderately small sample size in the current work, which limited the detection of small differences and inflated our chances of revealing positive findings. Secondly, the design of current study only reflects the mindfulness practice as a whole rather than the effects of its component. This could be further studied by using different interventions. Though all mindfulness practices could increase the positivity of effect, energy, and present focus and decreased thought distraction, each of them still presents distinct psychological fingerprints. Besides, a self-reported study also revealed that a positive effect and a reduction of a negative effect would be elicited by being attentive and accepting of unpleasant experiences, respectively (Blanke et al., 2017). In the current study, a typical MBSR procedure was adopted, which

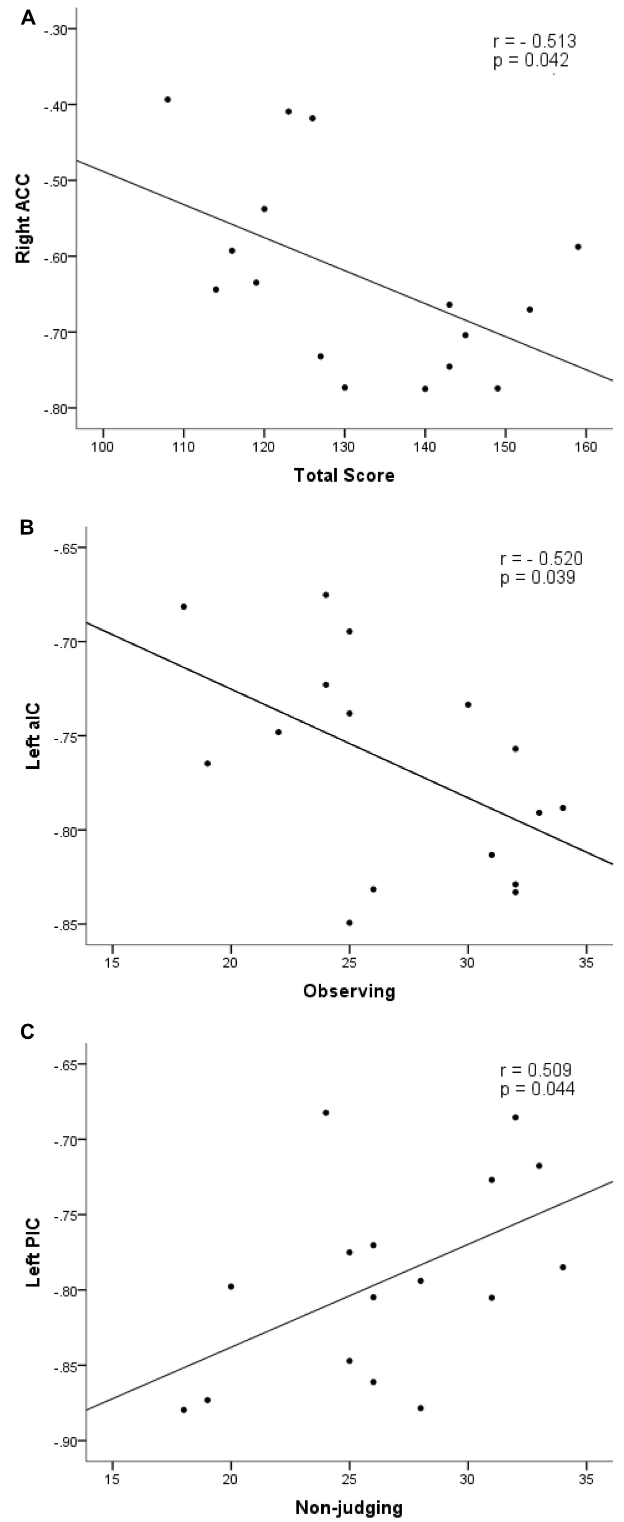

FIGURE 3 | Scatter plot diagrams. The plots and fitted lines indicate: inverse correlations between the ALFF values of ROIs in right anterior cingulate cortex and aIC.L cortex with the total score (r = –0.513, p = 0.042) **(A)** and observing score (r = –0.520, p = 0.0392) **(B)**; a positive correlation between the ALFF value of posterior insula (pIC) and non-judgment score (r = 0.509, p = 0.044) **(C)** of FFMQ.

seemed to be a compound of the abovementioned practices. It was absolutely necessary to verify which part is more critical in promoting well-being. By answering this, a future study may help to enhance the different aspects of effective well-being by addressing specific facets of mindfulness.

To sum up, after 8-week MBSR training, namely a decrease in the activity of the SN was detected. Besides, enhanced rs-FC was detected in the coupling with or within SN. The correlation of corresponding nodes was related to mindfulness ability and emotional assessment. Those results may shed light on the effect of mindfulness on the brain mechanisms of novice practitioners.

Though no direct relation was detected between emotion and mindfulness ability, our results still showed a decreased negative effect induced by short-term mindfulness practice. The brain regions related to attention and interoception can be involved in the underlying mechanism. Further exploration of the relationship between these brain regions and the corresponding body sensory after mindfulness training is needed. Both subjective and objective evaluations of the internal perceptual awareness or attention should be involved. In short, those results suggested that emotional regulation can be achieved after the beginning of an 8-week mindfulness exercise in healthy volunteers. The accompanying decrease of activity in the SN can provide new clues in elucidating the brain mechanisms of mindfulness novices.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee, Kunming University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QG and ND contributed to data collection, data processing, data analysis, statistical analysis, original manuscript drafting, and manuscript editing. GB, RL, and XZ contributed to data collection, data processing, and data analysis. JZ, SW, and YZ contributed to project conception and manuscript revision. YF and LC helped to perform the analysis with constructive discussions and revised the manuscript. ZC and KW contributed to project conception, research design, and manuscript revision. All authors contributed to the article and approved the submitted version.

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REVIEW
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Classification of Mindfulness Meditation and Its Impact on Neural Measures in the Clinical Population

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Different forms of mindfulness meditation are increasingly integrated in the clinical practice in the last three decades. Previous studies have identified changes in the neurophysiology and neurochemistry of the brain resulting from different mindfulness meditation practices in the general population. However, research on neural correlates of different types of meditation, particularly on the clinical outcomes, is still very sparse. Therefore, the aim of this article is to review the neural impact of mindfulness meditation interventions on different mental disorders via the classification of main components of mindfulness meditation. The clearer classification of mindfulness meditation may inform future clinical practice and research directions.

Keywords: mental illness, mindfulness meditation (MM), psychopathology, cognitive neuroscience, classification

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INTRODUCTION

What Is Mindfulness Meditation

The introduction of mindfulness meditation (MM)-based interventions is growing in popularity. This may be contributed by its versatility to reach clinical and non-clinical groups, the diversity that provides an alternative to treatment-resistant patients, and its adherence to familiar activities such as yoga and breathing exercises that enhance engagement and adoption of mindfulness meditation-based intervention in our daily lives. Interventions of MM have been shown to reduce stress and improve one's subjective wellbeing in different age groups and ethnic backgrounds (Turakitwanakan et al., 2013; Black et al., 2015; Ghane et al., 2018; Zollars et al., 2019; Liu et al., 2020; Chen et al., 2021). Due to its positive effect in enhancing individuals' wellbeing and resilience, the practice of MM attracts research on the underlying mechanism of its effects in the mental health setting.

Mindfulness is the foundational attentional stance implicated in different schools of Buddhist meditation tradition, such as Theravada tradition, Vajrayana tradition, Zen, and Vipassana mediation (Hart, 2011). The word "mindfulness" is translated from the Buddhism Pali's term "sati," which means to be mindful and aware of the experience by refining attention and action with a calm and untrained mind (Peacock, 2014). Mindfulness meditation is an umbrella term of the family of meditational practice that describes the action of focusing one's attention in the present, with the attitude of being non-judgmental, open, and curious of the experience (Bishop et al., 2004).

Types of Mindfulness Meditation

Various forms of meditation are found in different populations, religions, and cultures. Particularly, there are different types of MM developed specifically for the clinical population. Since the 1990s, Kabat-Zinn developed a secular intervention known as mindfulness-based stress reduction (MBSR) suited for the general population and for those suffering from chronic pain and stress symptoms (Kabat-Zinn, 2003). It was then brought to the clinical population where Segel later modified and developed mindfulness-based cognitive therapy (MBCT) to target specifically clinically depressed patients (Morgan, 2003). The idea of mindfulness is also integrated into other forms of behavioral interventions such as dialectical behavioral therapy developed for borderline personality disorder, and acceptance and commitment therapy (ACT) has been effective in patients with chronic pain, depression, obsessive-compulsive disorder, psychosis, and those under palliative care (Linehan, 1993; O'Hayer et al., 2018; Zhao et al., 2021). MM is adopted to broader mental health populations, such as substance use, anxiety disorder, and eating disorder (Evans et al., 2008; Kristeller and Wolever, 2011; Bowen et al., 2014).

Main Techniques of Mindfulness Meditation

The different types of MM interventions in practice and in clinical research make it difficult to bring consistent prediction of the effects of MM on psychopathology. However, there are consistencies in the aim of some MM interventions such as MBSR and MBCT, which are commonly found to relieve negative symptoms by enhancing ways to cope with negative thoughts and emotions. In theory, the primary basis of the mindfulness-based interventions consists of two main techniques, namely, focused attention (FA) and open monitoring (OM). During the MM interventions, the instructor will guide practitioners to attend to a specific object (FA) such as bringing awareness to their breathing (Kabat-Zinn, 2003). Meanwhile, practitioners are encouraged to notice if their mind wandered to a task-irrelevant object, i.e., thinking about the to-do grocery list. When noticing the distraction, it is warmly reminded to shift attention back to the self-related processing such as the sensation of breathing and to try and sustain the attention of the experience, i.e., air coming in and out from the nostril. FA enables the enhancement of top-down selective and maintenance of attention against distractors (Fujino et al., 2018). This strengthens the regulation of emotion by reducing sensitivity to emotional distractors, and hence, attending to the attentional focus may help to relieve the perceived intensity of physical and psychological symptoms (Zeidan et al., 2012; Guendelman et al., 2017). On the other hand, OM is the technique of being non-reactively aware of the moment-to-moment thoughts and feelings (Hölzel et al., 2011). It is suggested that FA and OM are gradual processes where FA sets the foundation for mental stability to further achieve OM (Zhang et al., 2019). Instead of avoiding and suppressing emotions, OM promotes the attitude of acceptance. This approach facilitates a more objective and accurate perception of experience and thus helps to further enhance mindfulness and maintain a good mood (Craig, 2002).

Components of Mindfulness Meditation

Aforementioned, the usual procedures of MM are integrated from a complex and interrelated range of ideas, attitudes, and cognitive processing that may explain the insufficient scientific consensus on the underlying mechanism of MM. Yet, there are core components that are related to improving coping and symptoms of patients (see **Table 1**). In this section, we described the core components of MM in the cognitive scope to facilitate the understanding of the neural effects of MM on mental illness which are discussed later.

Present-Centered Awareness

Present-centered awareness describes the regulation and temporal structure of attention to the here-and-now feeling, thoughts, and sensations. It is the "aware" and "focus" stage of MM. The practice of MM identifies the prioritization of selectively attending to present moment sensory and perceptual experience (i.e., breathing) (Lutz et al., 2008). The present-centered awareness also requires maintaining focus back at the present moment upon mind-wandering to distractors, which is the "focus" stage. Neuroimaging studies have suggested that the anterior cingulate cortex (ACC) requires top-down regulation that allocates attentional resources by being "aware" of the present moment in disregard of distractor to "focus" on the present (Bush et al., 2000). In relation to the anterior insula, the ACC works as a network to shift between different brain activities to facilitate cognitive control (Menon and Uddin, 2010). MM recruits the salience network where activations were observed in bilateral anterior insular and dorsal ACC implicated in the emotions, conscious perception of bodily response, and present moment awareness (Seeley et al., 2007; Craig and Craig, 2009; Singer et al., 2009). Supportive evidence emerges from functional magnetic resonance imaging (fMRI) studies that greater activation in ACC was found in meditators while practicing present-centered awareness as compared with controls (Hölzel et al., 2007; Gard et al., 2012). In the clinical population, greater awareness of the present moment is evident in improving mood disorders symptoms by enhancing attentional regulation (Brown et al., 2011). Through MM, the training on present-centered awareness may thus be targeted to improve mental illnesses that relate to attentional deficit such as attention deficit hyperactivity disorder (ADHD) and bipolar disorder (Maalouf et al., 2010; Passarotti et al., 2010).

Meta-Awareness

Meta-awareness refers to the cognitive capacity to monitor the process of consciousness that meta-awareness of the inevitable stage of mind-wandering during MM facilitates attentional shift back to the task (Smallwood et al., 2007; Mrazek et al., 2012). The practice of meta-awareness requires attention control to continuously adjust one's attentional focus, which needs response inhibition (Brefczynski-Lewis et al., 2007). The training of meta-awareness helps to reduce mind-wandering (Franklin et al., 2017). Robust activation was found in the default mode network (DMN) during mind-wandering, including the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), and inferior parietal cortices (Broyd et al., 2009). These regions are activated during the resting state, which is coherent to internal mental state processes such as self-referential processing, thinking about the past, or imagining the future (Buckner et al., 2008). Research has shown that DMN activities are

TABLE 1 | The description of mindfulness meditation (MM) components and neural mechanisms.

MM components	Description	Neural mechanism
Present-centered awareness	Selective attention to present moment sensory and perceptual experience	Salience network: bilateral anterior insular, dorsal ACC
Meta-awareness	Monitor the process of consciousness, mind-wandering, orientate attention back to present moment	Default mode network: posterior cingulate cortex, medial PFC, precuneus and inferior parietal cortices
Non-reactive self-related processing	Non-judgmental, accepting and curious attitude to view self-related perceptual and cognitive process	Narrative focus (cognitive interpretation of mental processes): ventral mPFC, dorsal mPFC, left lateral PFC, middle temporal and angular gyri Experiential focus (attend to present-moment sensory thoughts, feelings and sensations): ventral PFC, dorsolateral PFC, right insular, SII and inferior parietal lobule

ACC, anterior cingulate cortex; PFC, prefrontal cortex; mPFC, medial prefrontal cortex.

negatively related to mental health outcomes and attentional demanding task performance (Grimm et al., 2009; Brewer et al., 2011; Fernández-Corcuera et al., 2013; Hamilton et al., 2015). Correspondingly, the DMN is implicated in explaining the underlying mechanism of symptoms as ruminating on the past and worrying about the future are the negative thinking patterns commonly found in individuals with depression, anxiety, substance abuse, and eating disorders (Colvin et al., 2021). In other words, the enhanced meta-awareness via reducing mind-wandering may help to ameliorate the severity symptoms, hence improving wellbeing. In this study, we explored changes related to the process of mind-wandering to understand the impact of meta-awareness on mental illnesses.

Non-reactive Self-Related Processing

Non-reactive self-related processing refers to the non-judgmental, accepting, and curious attitude to view the perceptual and cognitive process during MM (Kabat-Zinn, 2003). Self-awareness is a core cognitive process interpreting the relationship between internal and external stimuli to self, and the dual-mode of self-reference suggests that distinct forms of self-focus have differentiated neural mechanisms (Farb et al., 2007). There is a tendency of default bias during resting state to narrative focus that describes the cognitive interpretation of mental processes, recruiting midline PFC (ventral and dorsal mPFC) and linguistic-semantic network (left lateral PFC, middle temporal, and angular gyri) (Mason et al., 2007). In contrast, experiential focus describes the inhibition of cognitive interpretation to attend to present-moment sensory thoughts, feelings, and sensations, recruiting right lateralized network (ventral and dorsolateral PFC) and right insular, SII, and inferior parietal lobule (Gusnard et al., 2001).

Non-reactive processing can be achieved through dereification and acceptance. Dereification describes the practitioner acts as a separate entity from their thoughts. It can also be understood as "psychological distancing" to reduce experiential fusion so that the practitioner can experience and interpret mental processes in a more objective and non-judgmental sense (Bernstein et al., 2015). Dereification can be viewed in the dual mode of self-reference as the shift from narrative focus to experiential focus (Farb et al., 2007). In addition, the acceptance stance is to enhance greater accuracy in perceiving mental contents instead of suppressing the content of mental experience (Dixon et al., 2020). As patients with mood disorders were found to be more active in the DMN than controls that are related to poor mental health, this non-reactive attitude targets to combat the automatic constraints to turn to negative valence during mind-wandering (Broyd et al., 2009). Both techniques of dereification and acceptance promote more mental flexibility which is lacking in patients with mood disorders (Gutierrez et al., 2015).

As different studies investigate the changes MM has to the brain with different measures and components, inconsistent findings were found. This study is going to explore how the different components mentioned above impact different mental illnesses neurologically. The understanding of the underlying neural effects of MM with greater clarity helps to provide a clearer prediction as to how components of MM impact on different mental illnesses and, hence, provide directions for future research and development of clinical practice.

METHODS

Search Strategy and Inclusion and Exclusion Criteria

A quantitative review search of PubMed, ScienceDirect, PsycInfo, and The Cochrane Library was performed for research articles. In the electronic databases, we searched for studies that included the terms "mindfulness meditation," "mental illness," "psychopathology," "patients," "meta-awareness," "mindful attention," "present-centered awareness," "acceptance," "non-reactive," "brain changes," "neural correlates," and "neural mechanism" up until February 2022. The selection criteria included research articles with clinical data and symptoms of mental illness. Studies of all sample sizes were analyzed. Studies were excluded if they were dissertations, reviews, or not published in English. The search resulted in 1,030 records. Excluding studies that did not include the mental health population, 12 studies were included in this review (see **Table 2**).

DISCUSSION

Despite the beneficial effects on wellbeing observed in previous literature, most studies investigate the underlying mechanism

TABLE 2 | Neurological changes in the brain associated with mindfulness meditation.

Article	Age	Clinical population	Sample size	Study design	Outcome
1. Present-centered awareness					
Zhao et al., 2019	32.6	Generalised anxiety disorder	37	Repeated measures pre-post 8-weeks MBCT Resting-state fMRI	MBCT: increased ACC and insula functional connectivity related to anxiety improvements
Goldin and Gross, 2010	35.2	Social anxiety disorder	14	Repeated measures Pre-post 8-weeks MBSR React to negative self-beliefs under fMRI Employ attention deployment techniques Breath-focused Distraction-focused (count backwards)	Breath-focused: reduced amygdala activation, increased cuneus and middle occipital related to improved self-esteem, anxiety and depression symptoms
Westbrook et al., 2013	45	Addiction (smoking)	47	Repeated measures React to smoking and neutral pictures fMRI Employ attention deployment techniques (a) Mindful attention (non- judgmental) Look at the picture with no techniques	Mindful attention: reduced functional connectivity between subgenual ACC and the bilateral insula, related to reduce cigarette craving
Schoenberg et al., 2014	36.7	Attention deficit/ hyperactivity disorder	44	Randomised controlled trial 12 weeks MBCT (*N* = 24) vs. wait-list control (*N* = 20) Completed Go/No-Go task with ERP	MBCT: increased P3 ERPs amplitudes, activities related to the inhibitory gating circuit
Sibalis et al., 2019	13	Attention deficit/ hyperactivity disorder	56	Randomised controlled trial 20 sessions mindfulness-based martial arts treatment: including FA and body scan (*N* = 34) vs. wait-list control (N-22) Completed Go/ No-Go task with EEG	MM: increased EEG beta with oscillation frequency of 12 to 30 Hz and reduced EEG theta with frequency of 4 to 7 Hz, reflecting more concentration and less unfocused thought, respectively
2. Meta-awareness					
Chou et al., 2022	37.5	Bipolar disorder	44	Two group repeated measures Bipolar disorder (*N* = 22) vs. healthy control (*N* = 22) 12 weeks MBCT vs. supportive psychotherapy Resting-state fMRI	MBCT: subjects with Bipolar disorder showed negatively correlated dlPFC- PCC activity, related to heightened self-report meta-awareness, rated on the Five Facet Mindfulness Questionnaire scale.
Tang et al., 2013	21.5	Addiction (Smoking)	50	Randomised controlled trial Smokers (*N* = 27) vs. non-smoker (*N* = 33) 2 weeks mindfulness meditation IBMT vs. relaxation training Resting-state fMRI	IBMT: increased activity ACC and PFC, linked to self-control. Reduced activity in PCC, related to reduce craving and cessation of smoking. Maintained reduced smoking after 4 weeks.
Cernasov et al., 2019	35.2	Depression (Anhedonia)	11	Repeated measures Pre-post 15 weeks MBCT fMRI Resting-state fMRI	MBCT: decreased in DMN connectivity between the mPFC and precuneus, correlated to reduced Beck's Depression Inventory scores
Wells et al., 2013	74	Mild cognitive impairment	14	Randomised controlled trial pilot 8 weeks MBSR (*N* = 9) vs. TAU (*N* = 5) Resting-state fMRI	MBSR: Increased functional connectivity between the PCC and bilateral mPFC and left hippocampus compared to controls. Showed trends of less bilateral hippocampal volume atrophy than control participants.
3. Non-reactive self-related processing					
Hölzel et al., 2013	37.9	Generalised anxiety disorder	26	Randomised controlled trial 8 weeks MBSR (*N* = 15) vs. stress management education (*N* = 11) Label angry and neutral face under fMRI	MBSR: increased functional connectivity between amygdala and PFC regions, negatively correlated to Beck Anxiety Inventory scores
King et al., 2016	31	Post-traumatic stress disorder	23	Randomised controlled trial 16 weeks mindfulness-based intervention (*N* = 14) vs. present-centered group (N=9) Resting-state fMRI	MM: increased DMN (PCC seed) connectivity to dlPFC regions within the CEN, correlated to improvement in avoidant and hyperarousal symptoms
Smallwood et al., 2016	46	Comorbid chronic pain and addiction	12	Pilot study Chronic-pain focused ACT (*N* = 6) vs. health education (*N* = 6) At rest and painful stimulation during Resting-state fMRI	ACT: reduced activation in middle frontal gyrus, inferior parietal lobule, insula, ACC, PCC, and superior temporal gyrus, areas related to pain responsiveness. Higher connectivity in amPFC – vmPFC and PCC and insular.

MBCT, mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction; IBMT, integrative body-mind training; ACT, acceptance commitment therapy; MM, mindfulness meditation; TAU, treatment as usual; ACC, anterior cingulate cortex; dlPFC, dorsal lateral prefrontal cortex; mPFC, medial prefrontal cortex; amPFC, anterior medial prefrontal cortex; vmPFC, ventral medial prefrontal cortex; PCC, posterior cingulate cortex; DMN, default-mode network; CEN, central executive network.

of MM by studying the general cognitive impact. There are existing studies targeting on the general neural mechanism on MM (Hölzel et al., 2011; Van Der Velden and Roepstorff, 2015). However, very limited studies provide data on the underlying neural mechanism of MM in the clinical population. To our knowledge, no existing studies learn about the neural impact of the specific components of MM in the mental health population. In this study, in the review of the studies on the specific effect of

MM components that induce brain changes, we have identified differentiated mechanisms that bring similar or different impacts on the clinical population.

Neural Effects of Present-Centered Awareness on Mental Illnesses

Neuroimaging research has proposed that present-centered awareness facilitates attentional regulation in different mental health populations. MBCT appeared to reduce anxiety symptoms significantly in a waiting-list control trial (Zhao et al., 2019). Adult patients with generalized anxiety disorder (GAD) had reduced activation in the bilateral insula with increased functional connectivity to ACC, which was associated with the reduced Hamilton Anxiety Rating Scale scores after 8 weeks of MBCT. The reduced activation in bilateral insula is implicated in the heightened awareness of present emotions and perceptions under the salience network that helps to relieve anxiety symptoms (Friedel et al., 2015; Mooneyham et al., 2017). The ameliorated anxiety scores may be explained by the attentional focus on present-moment experience where maladaptive patterns of thinking and behaviors can be regulated (Chambers et al., 2009). Consistent findings have shown that similar MM practice reduced social anxiety symptoms in patients with social anxiety disorder (SAD) by better visual attentional regulation of negative self-beliefs, reflected by greater MBSR-related activation in cuneus and middle occipital brain regions (Goldin and Gross, 2010). This provides evidence that the strengthened awareness of the present thoughts and emotions helps to regulate one's emotions, a crucial factor in the recovery process (Young et al., 2019).

The practice of present-centered awareness was also beneficial to enhance attentional regulation in treatment-seeking smokers. Adult subjects who were asked to react to smoking-related pictures had reduced craving to smoking cue upon deploying mindful attention training as compared with controls with no attentional deployment techniques used (Westbrook et al., 2013). A psychophysiological interaction was found in the representation of the effect of mindful attention in the decoupling between subgenual ACC and other craving-related processing such as insula and ventral striatum. The decoupling may suggest that mindful attention strengthens attentional control to present-moment and refrains from engaging in craving-related.

Similar neural effects in the salience network were identified in understanding the impact of MM on ADHD. Schoenberg et al. (2014) revealed that adults with ADHD improved bio-regulation skills and reduced impulsivity symptoms, coincided with enhanced P3 ERPs amplitudes, a component of the inhibitory gating circuit after 12 weeks of MCBT training in present-moment practice and body scan. Similar findings also extended to youths with ADHD that a significant increase in active attention engaging more concentration and less unfocused thought was found in youths performing Go/No-Go tasks. This was reflected by the lower theta/beta ratio after 20 weeks of mindfulness treatment programs where no difference was found in controls (Sibalis et al., 2019).

Studies exploring the neural correlates of present-centered awareness with different measuring modalities including resting-state fMRI, fMRI, and ERP have consistently suggested the significant role of the salience network in regulating attention and improving mood. The particular practice in the MM component of present-centered awareness has provided beneficial effects to patients with anxiety and attentional symptoms. However, studies in the review were mostly conducted with the adult populations, which can be difficult to be generalized to other age groups. The different measurement methods, i.e., evaluating the mind at the resting state as compared with the active processing when reacting to stimuli, can be hard to make comparisons in terms of the specific impact of present-centered awareness on patients.

Neural Effects of Meta-Awareness on Mental Illnesses

Aberrant DMN activities have been commonly found in different mental illnesses, with their negative impact on self-control, attention to task, and emotional regulation (Broyd et al., 2009). MM seems to have exerted an effect in modifying atypical DMN connectivity in patients with bipolar disorder (BD) that mirrors the healthy controls (Chou et al., 2022). At baseline, patients with BD showed hyperactivation in the dorsal lateral PFC (dlPFC), an area within the mind-wandering-related DMN network, as opposed to the anticorrelated activity between PCC and dlPFC in healthy controls while performing attentional tasks. Upon MBCT training, the atypical dlPFC connectivity was modified as akin to the healthy group which coincided with the heightened meta-awareness, and this change was not found in the control group. In other words, MM seems to enhance attentional regulation in BD.

Further neuroscience research along the same lines comes from Tang et al.'s (2013) study. It highlights the unconscious change of MM to reduced smoking. Reduced PCC activities and increased ACC–PFC connectivity were found to be correlated with reduced smoking in heavy smokers after integrative body-mind training that composes of MM elements, i.e., meta-awareness. The reduced PCC activities reflected reduced resting-state activities that were related to reduced craving and smoking intensity. Specifically, subjects were recruited with the aim of stress reduction, without the intention of quitting smoking. This study provides evidence of the unconscious role of MM in enhancing self-control in smokers.

A similar finding was observed in patients with significant anhedonia that the improved depression symptoms were correlated with reduced connectivity in the DMN, between the medial PFC (mPFC) and the precuneus after 15 weeks of MBCT training (Cernasov et al., 2019). Higher functional connectivity between mPFC and precuneus is implicated in the negative sense of self and self-esteem interpretation usually found in depressive patients (Rolls, 2016). Therefore, the reduced connectivity in this study may suggest that mood improvement may be due to less rumination and negative self-belief that help to explain the improved Beck Depression Inventory scores in patients.

Despite the DMN is marked as a biomarker of its detrimental effect on mental health, the resting-state DMN can be also used as a non-invasive biomarker to evaluate the effect of MM on the clinical population. In a pilot study, Wells et al. (2013) have shown that patients with mild cognitive impairment (MCI) had enhanced DMN connectivity in the hippocampus, mPFC, and PCC after MBSR training as compared with controls. Additionally, reduced hippocampal atrophy was identified more than controls. The altered brain changes suggested that MBSR helps with reserving cognitive resources from the development of MCI. However, factors such as more social engagement were not accounted for the effect; hence, the interpretation of the effect of MM should be of caution. It is further explained that the enhanced connectivity within the DMN stabilizes activities in the DMN, hence deactivating the DMN more adequately when the task demand increases (De Marco et al., 2018). In alignment with previous studies, modified activities in the DMN facilitate mood regulation and task concentration (Whitfield-Gabrieli and Ford, 2012).

Studies exploring the neural impacts of meta-awareness were more consistent in measuring the rest-state activity with the resting-state fMRI. The enhanced meta-awareness has been shown to be implicated in the altered DMN network in patients with BD, addiction, depression, and MCI. Different studies have reflected the role of meta-awareness with different depths and scopes in the DMN network, i.e., Chou and colleagues' study measured the changed connectivity between PCC and dlPFC, while Tang and colleagues' study compared the changes in the ACC and PFC connectivity and the activity level in the PCC. The differentiated identification of areas as a seed for neuroimaging may make a precise comparison of the neural changes hard, and thus, the interpretation of the precise changes in the DMN connectivity should be of caution.

Neural Effects of Non-reactive Self-Relating Processing on Mental Illnesses

A reversed PFC and amygdala connectivity was found in patients with GAD after MBSR. The post-treatment-enhanced connectivity between PFC and amygdala was negatively correlated with Beck Anxiety Inventory Scores (Hölzel et al., 2013). It is explained that the recruitment of more PFC activities is related to engaging in more active monitoring of affective states instead of downregulating or avoiding them, providing evidence for the role of acceptance in improving anxiety symptoms.

The training on the non-reactive self-related processing is also evident in the study of King et al. (2016). An enhanced DMN-central executive network connectivity was revealed in patients with posttraumatic stress disorder (PTSD) after 16 weeks of mindfulness-based exposure therapy but not psychoeducation controls. Particularly, the altered connectivity coincided with the improved avoidant and hyperarousal symptoms in the MM group. This finding provides evidence that the non-reactive and accepting stance to review internal processes promotes less avoidance to emotional experience and may be beneficial to patients with PTSD, enhancing treatment effectiveness. However, no significant difference was observed in the overall PTSD symptoms. The non-significant change in PTSD symptoms may be explained by the focus of acceptance value alone, which may not be targeted to the general PTSD symptoms but more focused on the cognitive and coping mechanism that requires further examination to exert effects on the overall symptoms of PTSD.

The application of ACT is suggested to enhance one's psychological flexibility by accepting the experience which aligns with the acceptance component of MM (Hayes et al., 2004). This is speculated in the study of patients with comorbid chronic pain and opioid addiction (Smallwood et al., 2016). Patients completed 8 sessions of ACT, and pain symptoms were alleviated reflected by lower activation in the regions related to pain processing, that is, insula, ACC, and PCC, but not in the health education controls. This study did not provide evidence regarding the impact of the core ACT elements, i.e., acceptance and mindfulness on pain processing. However, the increased connectivity pairing of anterior mPFC, ventral mPFC and PCC, right posterior insula during the resting state found in the ACT group may provide support to a stronger self-referential process and a greater awareness to own body's physiological state that parallels with the lowered perceived pain in patients.

Finally, the non-reactive attitude of self-relating processing was observed with differentiating connectivity in different regions of the brain but with a similar underlying mechanism. This component exerts effects more on the coping mechanism than the overall symptoms. The DMN is involved in the self-relating process, while the non-reactive element brings in interactive regions to impact on the clinical population. Under fMRI, heightened connectivity between PFC and amygdala was reflected in the GAD population during active tasks (Hölzel et al., 2013). In addition, at the resting state, an enhanced DMN-CEN connectivity resulted in patients with PTSD, while increased DMN-insular coupling was found in patients with comorbid chronic pain and opioid addiction (King et al., 2016; Smallwood et al., 2016). The positive connectivity highlights the enhanced role of processing the affective and emotional experience instead of suppressing it, a crucial representation of an accepting attitude of MM. The studies reviewed do not seem to provide evidence of dereification shown by the shift of narrative focus-related regions to experiential focus-related regions in the mental health population. Future studies may explore the dynamics of the aforementioned areas to understand the role and impact of dereification in MM.

Limitation of Existing Studies and Future Directions

The main limitation of the studies in MM in this review is the absence of a homogenous methodology. Despite resting-state fMRI being a common measure in studying the neural changes of MM, the variation in applying different regions as seeds for DMN can make neural correlates interpretation difficult. In addition, the study methodology to investigate the underlying mechanism of MM can be arbitrary, i.e., inference, instead of introducing measures targeting on different facets of MM, i.e., Five Facet Mindfulness Questionnaire scale to study the neural correlates. Also, the sample size of the studies is relatively small ($N < 30$) (Goldin and Gross, 2010; Hölzel et al., 2013; Wells et al., 2013; King et al., 2016; Smallwood et al., 2016; Cernasov et al., 2019), and the interpretation of the analysis is thus to be cautioned which may not be representative to the whole mental health population. As mentioned earlier, there are existing studies exploring the neural effects of MM, but less to none investigate the neural mechanism according to the components of MM. The challenge of measuring the neural effects of MM may then be contributed by the lack of consensus upon the constitutes of MM. Future studies are suggested to establish a framework of MM components so that studies on the neural effect of MM can dive into the specific impact of each component for in-depth analysis systematically. The clear identification of the neural correlates of each component can then help to provide more evidence-based alternatives and short-term acute support to the clinical population.

CONCLUSION

The brain changes identified based on the different MM components have helped to elucidate the specific neural mechanism of treatment effect under each component. Although it is not the focus of this review, the cognitive impact of each component is not distinctively different. However, through reviewing the related neural mechanism of each component, the differentiated functions are better understood. In summary of the review of previous studies, present-moment awareness concerns more on the external attentional regulation that recruits the salience network. The training of meta-awareness emphasizes on the interoceptive regulation of the whole consciousness process that involves the DMN. Finally, non-reactive self-related processing stresses on the attitude of viewing experience concerns of the DMN-central executive network connectivity. These findings have helped to deepen the understanding of the underlying neural mechanism of MM, hence highlighting the need for developing a common framework of MM components for future research in exploring the effects of MM with greater consensus and consistencies in the findings.

AUTHOR CONTRIBUTIONS

JN and CC prepared the full manuscript. Both authors contributed to the article and approved the submitted version.

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The neurophysiology of the intervention strategies of Awareness Training Program on emotion regulation

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Emotion regulation is essential for healthy living. Previous studies have found that mental training such as compassion meditation could help with emotion regulation. However, the underlying neural mechanism and possible intervention strategies of group-based Mahayana Buddhist intervention involved in emotion regulation are still unclear. This event-related potential (ERP) study investigated how compassion and wisdom meditations, two key components of the Awareness Training Program (ATP), may regulate emotion during different mental processing stages, namely attention deployment, cognitive change, and response modification. Eighty-five middle-aged working adults with moderate stress were voluntarily recruited for this study, using a 128-channel electroencephalogram system. After 7 weeks of training, participants (ATP attendance, $n=42$; waitlist control, $n=43$) were instructed to view negative pictures while practicing compassion or wisdom meditation, with corresponding priming words. Another normal priming condition and a neutral picture condition were set as control conditions. ERP results in the ATP group showed that negative pictures induced greater prefrontal activity (N400 component) in both compassion and wisdom meditation conditions compared with the normal condition, while the control group showed little difference between the conditions. Significantly higher heart rate variability was found in the compassion but not wisdom meditation when compared with the neutral priming condition. Correspondent changes in behavioural data were also found. Converging evidence showed that compassion meditation training could modulate negative emotion processing in stages of attention deployment, cognitive change, and behavioural responses. The prefrontal lobe could play an important role in the process of emotion regulation by compassion meditation, possibly due to the emphasis of the ATP on contemplative practices.

KEYWORDS

emotion regulation, event-related potential, Awareness Training Program, compassion and wisdom meditation, stress, heart rate variability

Introduction

Emotion regulation is an adaptive function essential for a healthy working and living. For evolutionary purposes, the human brain is more responsive to negative events than to neutral or pleasant events. However, this tendency could lead to negative bias, delusive rumination, and even affective disorders (Rozin and Royzman, 2001; Hilgard et al., 2014). Given the stressful environment associated with contemporary life, it is necessary to explore practical methods of emotion regulation and, more importantly, to understand the working mechanism and how these methods modulate emotion in different stages of affective information processing.

Affective information is sequentially processed by different brain regions. Correspondingly, emotion can be regulated in one or more stages to modulate/intercept affective information processing flow, resulting in various intervention strategies. According to the Gross process model, one can modulate emotion at different stages. Externally, the process of situation selection and modification can be employed. Internally, after having engaged with the situation, the individual can regulate their emotions *via* attention deployment, cognitive change, and modulation of response expression (Gross, 2002; Goldenberg et al., 2016).

Mindfulness training has become popular and has broad applications. Numerous studies have demonstrated that mindfulness meditation helps with emotion regulation in various populations, including patients with post-traumatic stress disorder, attention deficit hyperactivity disorder (ADHD), depression, or psychopathy (Freudenthaler et al., 2017; Mitchell et al., 2017; Tang, 2018; Reffi et al., 2019). A mindfulness-based stress reduction (MBSR) programme emphasizes being non-judgmental and stopping to pay attention to the ongoing emotional information (Catak and Ogel, 2010; Murakami et al., 2015). Thus, it may regulate the emotion in the stage of attention deployment, according to Gross's process model of emotion regulation (Gross, 2002; Goldenberg et al., 2016). Nevertheless, other intervention strategies can also be quite effective in emotion regulation. For example, cognitive reappraisal can be used in the cognitive change stage (Zilverstand et al., 2017; Dryman and Heimberg, 2018). Previous research has shown that cognitive change may be more effective for emotion regulation than other strategies like distraction and suppression (Thiruchselvam et al., 2011; Grezellschak et al., 2015). In addition, research has revealed that promoting awareness, understanding, and acceptance are adaptive strategies of emotion regulation, while avoidance and control of emotion are maladaptive strategies (Aldao, 2013; Tull et al., 2020).

Mindfulness meditation is currently the most popular means of mental training. Nevertheless, other mental training exists in meditation traditions and may also be effective in terms of helping people to regulate and cope with emotional disturbance and stress (Lopez and Pellegrini, 2011; Desbordes et al., 2015; Gao et al., 2017; Bayot et al., 2020). From a Buddhist point of view, meditation generally can promote concentration, mental clarity and awareness and, subsequently, tranquilize emotional turbulence. The practice of meditation has two parts: tranquillity (*śamatha*) and observation (*vipaśyanā*). When practiced in-depth concurrently, these two can lead to the attainment of ultimate enlightenment (John, 2000).

We thus designed the Awareness Training Program (ATP) to enhance negative emotion regulation by incorporating compassion and wisdom training. It is assumed that the development of compassion and wisdom of non-attachment as taught by Mahayana Buddhism could induce positive cognitive changes through better understanding and reappraisal of negative events. The ATP incorporated three pedagogical steps: learning, contemplation, and practice of developing wisdom as taught in the *Sandhinirmochana Sūtra*, the classic and most important text on meditation methods in the *Yogācāra* school of Mahayana Buddhism (John, 2000). The ATP is a group-based intervention that could efficiently enhance participants' emotion regulation and stress management. More details on the theoretical foundation, the experimental design, and the practice of the ATP can be found in a previous behavioural study (Wu et al., 2019).

In the current study, we examined the neural mechanism of emotion regulation induced by the ATP, especially its two key components: compassion and wisdom training. Usually, the affective process involves a responsive process induced by external or internal stimuli in a bottom-up manner (Anderson et al., 2003). In contrast, the ATP intervention may modulate emotional information processing in a top-down manner (Challis and Berton, 2015). Bottom-up generation of emotion is more related to amygdala and adjacent limbic structures, while top-down regulations come more from dorsolateral PFC and anterior cingulate cortex (ACC). The brain regions for bottom-up and top-down processing are dissociable (Stenson et al., 2021), while the connectivity between these neocortical and limbic areas increases during emotion regulation. Additionally, ventral medial PFC can release 5-HT in the forebrain and enhance dorsal raphe nucleus to release 5-HT and subsequently restore emotion balance (Veerakumar et al., 2014; Challis and Berton, 2015). The compassion and wisdom meditations taught in the ATP required cognitive contemplation to enhance emotion regulation, therefore we assumed that the prefrontal cortex (PFC) may play an essential role in the mental contemplation during the ATP practices.

A majority of neuroimaging studies have investigated the neural mechanism of mindfulness in stress reduction. A functional magnetic resonance imaging (fMRI) study has reported that when participants anticipated depressing pictures, a mindfulness intervention could increase prefrontal activity and downregulate the activity of the amygdala, which is involved in emotional processing (Lutz et al., 2014). Another event-related potential (ERP) study has indicated that dispositional mindfulness can attenuate the neural response to both highly unpleasant and erotic images (Brown et al., 2013). Other studies have also suggested that mindfulness helps to modulate emotion-related brain networks (Allen et al., 2012). A previous electroencephalographic (EEG) study on mindfulness training has revealed that this approach is effective in decreasing the irregularity of electrical brain activity, as indicated by entropy, possibly because of the sense of calm and peacefulness that is produced during mindfulness breathing (Gao et al., 2016).

Few studies, however, have explored the neural mechanism of compassion meditation training and its mechanism on emotion regulation (Kim et al., 2009; Engstrom and Soderfeldt, 2010). Compassion meditation engages specific patterns of neural activation, including the anterior cingulate cortex, insula, and PFC (Lutz et al., 2008, 2009). The results of an fMRI meta-analysis of compassion did not demonstrate consistent results, probably due to a small number of studies on compassion, empathy or loving-kindness meditation (Kim et al., 2020). There is also a lack of understanding on the strategies used for emotion regulation. The literature review likewise did not yield any neuroscientific research on the wisdom of non-attachment meditation. Given the excellent temporal resolution of ERPs, it could be used to investigate emotion regulation in different stages and the related temporal dynamics (Thiruchselvam et al., 2011; Koval et al., 2015). A previous ERP study on emotion regulation has found that manipulation of attention deployment takes place earlier than manipulation of cognitive change (Thiruchselvam et al., 2011). The location of the ERP component can also provide spatial information regarding the brain areas involved in various stages of emotion regulation. Furthermore, through the application of head models and the conversion of surface signals, ERP source analysis can further localize the related electrical activity in the brain (Heidlmayr et al., 2015; Gao et al., 2017). In a previous ERP study on religious chanting, brain responses to frightening images, in terms of late-positive potential, largely disappeared while chanting the name of Amitabha Buddha, a prevalent spiritual practice in East Asia (Gao et al., 2017). However, the change only happened in the late stage but not in the early stage of negative emotion information processing.

We hypothesized that the ATP intervention could improve an individual's emotion regulation ability, and the PFC would be involved in these modulations of affective information processing (Ochsner et al., 2004), probably during the cognitive change stage of emotion regulation. As a result of these modulations, we also hypothesized that as compared to the control group, the ATP group would show an improved resilience to stress and corresponding physiological and behavioural changes.

Materials and methods

Design of the intervention and data collection

In the current ERP study, 85 participants (ATP, $n = 42$; waitlist control, $n = 43$) were recruited from the previous randomized clinical trial (RCT) on the ATP; that is, these participants took part in the previous RCT study on the ATP and the current ERP study on the ATP (Wu et al., 2019). The mean age was 45.00 ± 8.00 and 46.67 ± 7.80 years old for the ATP and control groups, respectively. The two groups had no difference in mean age, gender, education level, marital status, and religious beliefs (see Supplementary Table S2). The experiment flow can be found in Supplementary Figure S1.

EEG data were collected from the ATP group after they completed the 7-week ATP course, and the data from the waitlist control group were obtained at a similar point in time. The experiment was conducted in a quiet room at an EEG laboratory. The EEG data were recorded using a 128-channel EGI™ machine (Electrical Geodesics, Inc. United States), with the impedance set below 30 kΩ. A LabChart™ system (PowerLab, ADInstrument Inc., Australia) was used to record other physiological data, including the ECG, pulse, and galvanic skin response (GSR), following the standard procedure.[1] The ECG electrodes were placed using a limb lead. Pulse was measured at the left thumb, and GSR was measured on the left middle and index fingers.

The ERP experiment was designed to examine the effect of compassion/wisdom meditation on negative emotion regulation, respectively. It had four conditions: (1) a compassion condition (COMP, watching negative pictures with priming of a compassion cue); (2) a wisdom condition (WISD, watching negative pictures with priming of a wisdom cue); (3) a neutral condition (NEUT, watching negative pictures with priming of a neutral cue); and (4) a normal control condition (NORM, watching neutral pictures with priming of a neutral cue). This design followed the design of a previous emotion regulation study (Thiruchselvam et al., 2011), which had three regulating conditions for negative pictures and one additional normal condition as a baseline. Because emotions usually arise and last for a relatively long time (Hilgard et al., 2014), a block design was used. Each condition had one block and lasted for approximately 4 min. The sequence of the four conditions was randomized for different participants to avoid sequential effects.

E-prime (Psychology Software Tools, Inc., United States) was used to display the pictures in the affective regulation task. The pictures were partly selected from the International Affective Picture System (IAPS), with additional valence-matched pictures from the Internet included. The negative pictures showed sad and miserable scenes of people, so as to easily induce negative emotion. At the beginning of the process for each condition, a brief passage regarding compassion, wisdom, or neutral instruction was presented for participants to contemplate. Thereafter, the participants were first shown a fixation (+), followed by a miserable picture that was displayed for 2,000 ms, followed by a phrase related to the earlier teaching

1 www.adinstruments.com/support/manuals

to serve as a priming reminder. The inter-stimulus interval (3,400 ms) was chosen based on a previous paper on emotion regulation (Gao et al., 2017). Sixty trials of the same type of pictures were displayed consecutively in each condition, followed by three questions on how the participants felt (see details below). These questions needed to be answered within 20 s (the average answer time was about 7 s). Each participant went through all four conditions in random order (see Figure 1). The entire ERP experiment lasted approximately 30 min.

The behavioural, EEG, and physiological data were analysed offline with SPSS, MATLAB, EEGLAB, heart rate variability (HRV) analysis software (HRVAS), and statistical parametric mapping (SPM). The data from the three types of measurements were analysed separately.

ERP data analysis

The ERP data were analysed by using EEGLAB, a toolbox based on MATLAB. The data were first pre-processed before final statistical comparisons were made to test our hypothesis. For pre-processing, EEG data were first resampled from 1,000 to 250 Hz; then, they were filtered by using a 30-Hz low-pass filter. EEG artefacts were removed by visually inspecting and deleting the EEG segment and channel data affected by apparently poor scalp-surface contact or excessive noise. Bad channels were reconstructed by using spherical interpolation. The independent component analysis method first generated the component data (IC), and around 10 to 20 ICs of eye blinks, bad channel, and muscle artefacts were discarded. Then, the event-related epochs were extracted and visually checked again for data quality. Finally, ERP data were generated by averaging the same types of epochs. The ERP map was re-referenced to a virtual reference with averaging of the potentials recorded at the left and right mastoids before statistical analysis.

The ERPs of the pictures were processed for each condition. The effect of compassion meditation and wisdom meditation was obtained by deducting the ERP of the neutral condition from the ERP of the compassion condition and wisdom meditation condition, respectively. These ERP data were then entered in the second-level analysis on group difference. ERP components within specific time windows were chosen for different stages of emotion regulation. P1/N170 and P2 components were assumed as early information processing in the attention deployment stage (Meaux et al., 2014), and N400 was identified as the later cognitive stage of emotion regulation, together with other time windows and components according to the ERP response and the literature (Herzmann et al., 2010; Kutas and Federmeier, 2011; Onitsuka et al., 2013; Nie and Yu, 2021). Independent *t*-tests were carried out to compare the differences between the groups in the compassion meditation condition and then in wisdom meditation condition, respectively.

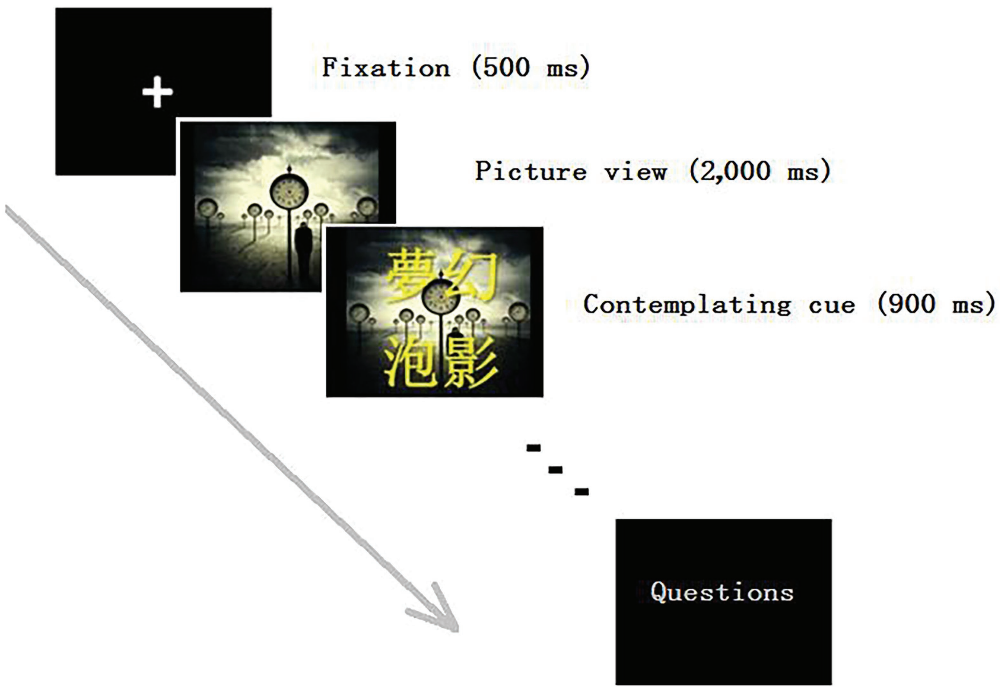

FIGURE 1
Design and timeline in the wisdom-compassion event-related potential experiment.

ERP source analysis

Source analysis was implemented with a toolbox named SPM12,[2] based on the MATLAB platform (MathWorks Inc., United States). The procedures were as follows: (1) EEGLAB data were converted to the SPM12-readable format; (2) the EEG sensor positions were linked to the coordinate system of MRI (MNI coordinates), which is a process known as *co-registration*; (3) using the Greedy search-based algorithm, an inverse reconstruction of the scalp electrode signals into the three-dimensional (3D) brain source signals was carried out; and (4) a factorial design was used to investigate the main effects and the group × condition interaction. Please refer to our previous work for more details (Gao et al., 2017).

Physiological data analysis

Data analysis of ECG, breath intervals, and GSR was performed for each participant and each condition using LABchart and MATLAB. Raw ECG data were cleaned *via* a Butterworth bandpass filter. The inter-beat interval was extracted following the replacement of outliers – three standard deviations away from the mean – *via* spline interpolation. Using the HRVAS toolbox,[3] we detrended the inter-beat interval data and computed the time domain features of the HRV. The derived HRV metrics, specifically the root mean square of the successive differences (RMSSD), were subjected to statistical testing using SPSS 24.0. Finally, mixed ANOVA and *post hoc* tests were utilized to assess differences between groups, conditions, and their interaction. The alpha level of significance was set at 0.05.

Behavioural data analysis

Demographic features (age, gender) of the participants and subjective behavioural responses after the picture viewing at the end of each block were analysed *via* analysis of variance (ANOVA) with SPSS. The subjective behavioural responses measured how the participants felt after viewing the pictures from the current block *via* three consecutive questions: (1) How stressed do you feel? (2) How miserable or sad do you think the people in the pictures feel? (3) To what degree do you feel you want to help the persons in the pictures? The responses were based on a 7-point Likert scale and recorded by E-prime software.

2 http://www.fil.ion.ucl.ac.uk/spm/software/spm12/

3 https://sourceforge.net/projects/hrvas

Results

Results of ERP picture viewing

The ERP results illustrated the temporal processing of negative pictures during different intervenal conditions, and further second-level analysis was performed between groups. Among the specified ERP components, the early P1/N170 components are involved in information processing in the perceptual stage, while N170 and P2 are correlated with an individual's emotional skills (Meaux et al., 2014). Therefore, the early components could be regarded as the attention deployment stage. The later stage contains more cognitive and affective processing of information in N400–600, and the component beyond 600 ms could be regarded as the cognitive change stage of emotion regulation. As the cognitive contemplation training of the ATP could influence frontal activity, we selected one channel in the frontal lobe (Fz) to observe and analyse the effects of the conditions in two groups when viewing the negative pictures (see Figure 2).

To further illustrate the effect of compassion and wisdom meditations, brain activity in these two meditation conditions was compared with that for the neutral priming condition. The effect of compassion meditation on a participant's responses to miserable pictures was calculated by subtracting the neutral instruction condition from the compassion meditation condition (compassion – neutral); second-level comparisons between groups are shown in the bottom row of Figure 3. The outcome demonstrated that compassion meditation elicited higher brain activity at the earlier stage of negative picture processing, and this activity lasted for a longer time in the ATP group than in the control group. When they viewed miserable pictures with compassion priming (COMP), the ATP group had higher brain activity in the frontal and occipital lobes (see Supplementary Figures S2a,b), whereas the control group only had higher occipital activity (see Supplementary Figures S3a,b). To further compare the overall effect of COMP, region of interest (ROI) analysis was performed for the N400 component of channels in the left frontal regions (Control: $M = -0.082\,\mu V$, $SD = 1.606\,\mu V$; ATP: $M = -0.822\,\mu V$, $SD = 1.739\,\mu V$; $t = 2.039$, $p = 0.045$; ROI of the left frontal region, see Supplementary Figure S4).

To further localize the brain region related to the compassion meditation (compassion-neutral condition) on miserable pictures, a source analysis was applied to illustrate the difference between the ATP and control groups. Source analysis suggested that the brain region involved in the compassion meditation condition is located in the medial prefrontal region (Figure 4).

Wisdom meditation had a similar effect as compassion meditation on the frontal lobe, although the significance was less marked. In addition, this frontal activity occurred slightly earlier than in the compassion condition (see Supplementary Figures S5a,b). At the same time, the control had only more occipital activity when compared to the neutral condition (see

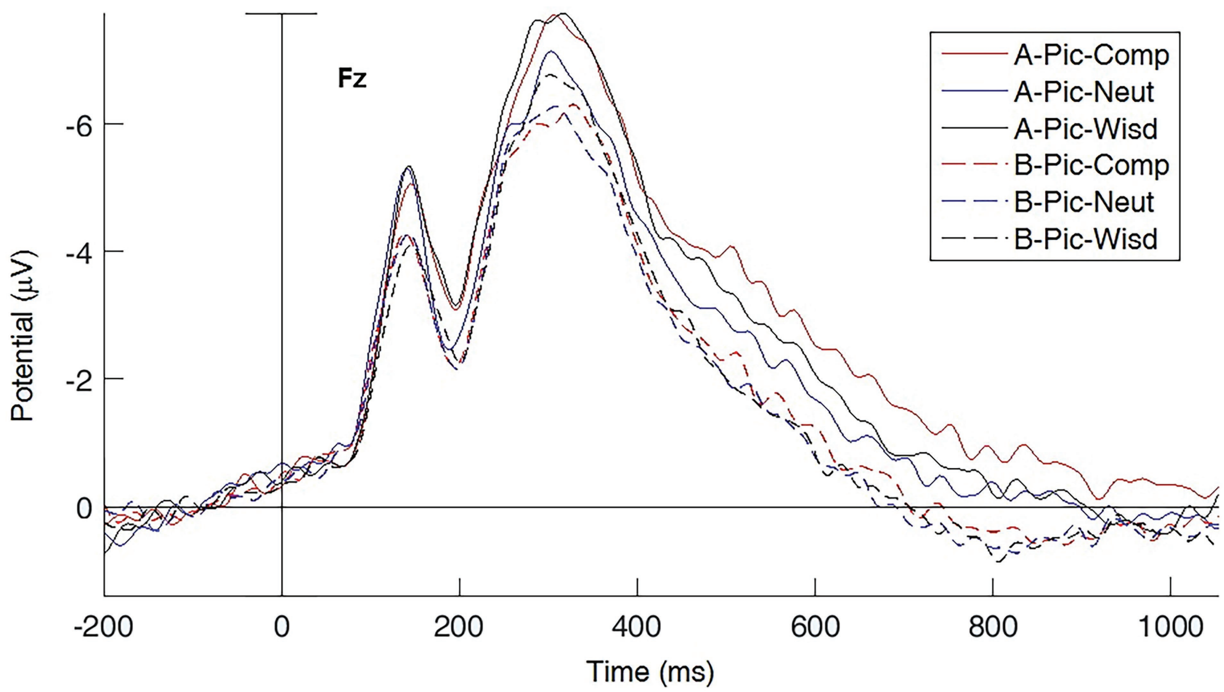

FIGURE 2
The event-related potentials of different priming conditions for negative pictures (Fz channel). The solid lines represent the ATP group and the dashed line is for the control group. ATP, Awareness Training Program; COMP, compassion meditation instruction; NEUT, neutral instruction; WISD, wisdom meditation instruction. A-, ATP group; B-, control group.

Supplementary Figures S6a,b). The pattern in Figure 5 illustrates that, with the wisdom meditation priming, the ATP group had more frontal activity than the control group during negative picture viewing.

Physiological results

The ECG results indicated that when viewing negative pictures, the ATP group had a higher HRV in terms of the RMSSD, $t(40) = -2.05$, $p = 0.047$ (see Figure 6), in the COMP condition ($M = 30.38$) than in the NEUT condition ($M = 28.97$). Nonetheless, no significant difference in the heart rate interval during picture viewing between groups or conditions, and no significant effects were found for the GSR and breathe data (see Supplementary Table S1).

Behavioural results

There was no difference in age or gender between the two groups (age of ATP group = 45.0 ± 8.0 years old; age of control group = 46.7 ± 7.8 years old). There was an apparent difference between the negative pictures (for the COMP, WISD, and NEUT conditions) and neutral pictures (NORM condition) when both groups answered the three subjective questions ($p < 0.001$). The significance of these results validated the separation between neutral and negative categories of pictures.

Further comparisons of subjective responses to the negative pictures indicated that the participants in the ATP group perceived the negative pictures as more miserable than the control group. However, the difference was significant only in the COMP condition ($p = 0.042$) and not in the WISD ($p = 0.754$) and NEUT ($p = 0.947$) conditions. The ATP group was less stressed than the control group, although the results were not statistically significant.

The participants perceived negative pictures as significantly more miserable in the COMP condition than in the WISD ($p < 0.001$) and NEUT ($p = 0.003$) conditions, but only in the ATP group. In addition, the results demonstrated that the ATP group was more willing to help, but only in the COMP condition, compared with the WISD condition ($p = 0.009$). Similarly, the ATP group tended to be less stressed in the WISD condition than in the COMP condition ($p = 0.094$). In contrast, these differences between conditions were not significant in the control group, as shown in Figure 7.

Discussion

Several behavioural studies, including ours, have shown the effectiveness of compassion or loving-kindness meditation on emotion regulation under challenging situations (Blevins, 2016; Newham, 2017; Inwood and Ferrari, 2018; Wu et al., 2019). However, these studies lack clarity with regard to the emotion

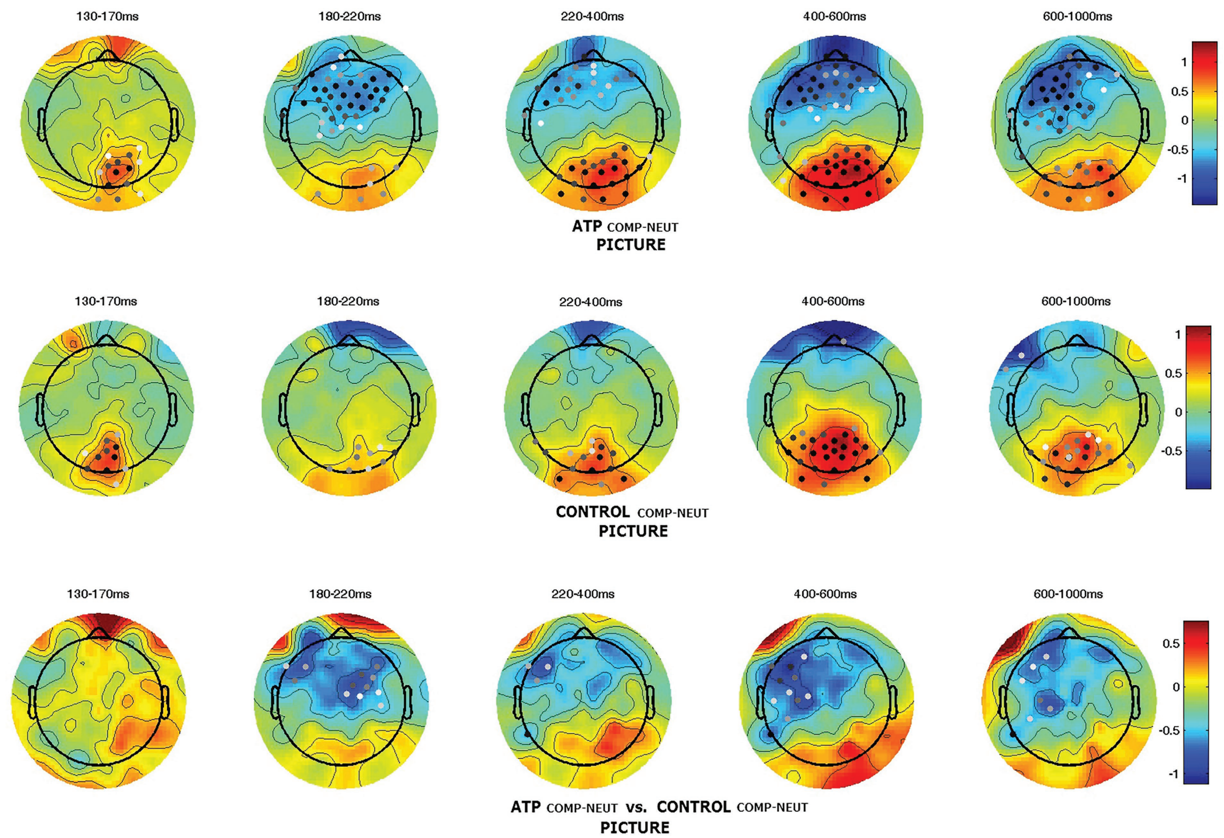

FIGURE 3
Group comparison of components in the compassion condition when viewing negative pictures. The patterns demonstrate that the Awareness Training Program (ATP) group had higher amplitudes (N400) in the left frontocentral region than the control group. Dots illustrate channels with significant differences ($p<0.05$), and darker dots indicate smaller p-values.

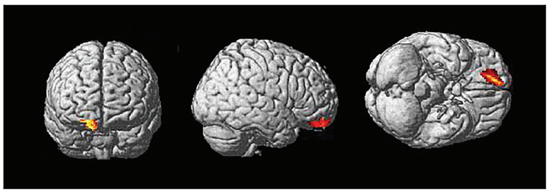

FIGURE 4
Source analysis on the comparison of compassion meditation effect between the Awareness Training Program (ATP) group and control group. Source analysis using statistical parametric mapping (SPM) indicated that the brain regions specifically activated by compassion meditation are located in the medial prefrontal region.

regulation strategies used and the underlying neural mechanism. The current ERP study demonstrated the neural correlates of emotion regulation by using different priming after the 7-week practice of awareness training. Based on the neurophysiological results, we discuss how the ATP intervention, especially compassion meditation, affects the three aspects of negative emotion processing: attention deployment, cognitive change, and response expression.

Effect of compassion/wisdom meditation on attention deployment

Attention deployment involves the early processing of perceptual information in the occipital lobe and the subsequent attentional neural activity in the frontal and parietal lobes (P1/N170 components). Compared with the NEUT condition, the ATP group showed greater P1/N170 component activity when viewing miserable pictures in both the COMP and WISD conditions. The control group did not show these early-stage neural activities in the COMP or WISD condition. Nevertheless, for these compassion-specific neural activities, the difference between the ATP group and the control group was not significant.

With primes of compassion/wisdom meditation, significantly more occipital activity was found in both the COMP and WISD conditions compared with the NEUT condition. This happened in the control and ATP groups. This finding indicates that participants in both groups tried to pay more attention when asked to show compassion or wisdom while viewing the negative and miserable pictures. Although participants of the control group were not explicitly taught how to meditate with compassion or wisdom, they did make efforts to contemplate following the primes of compassion

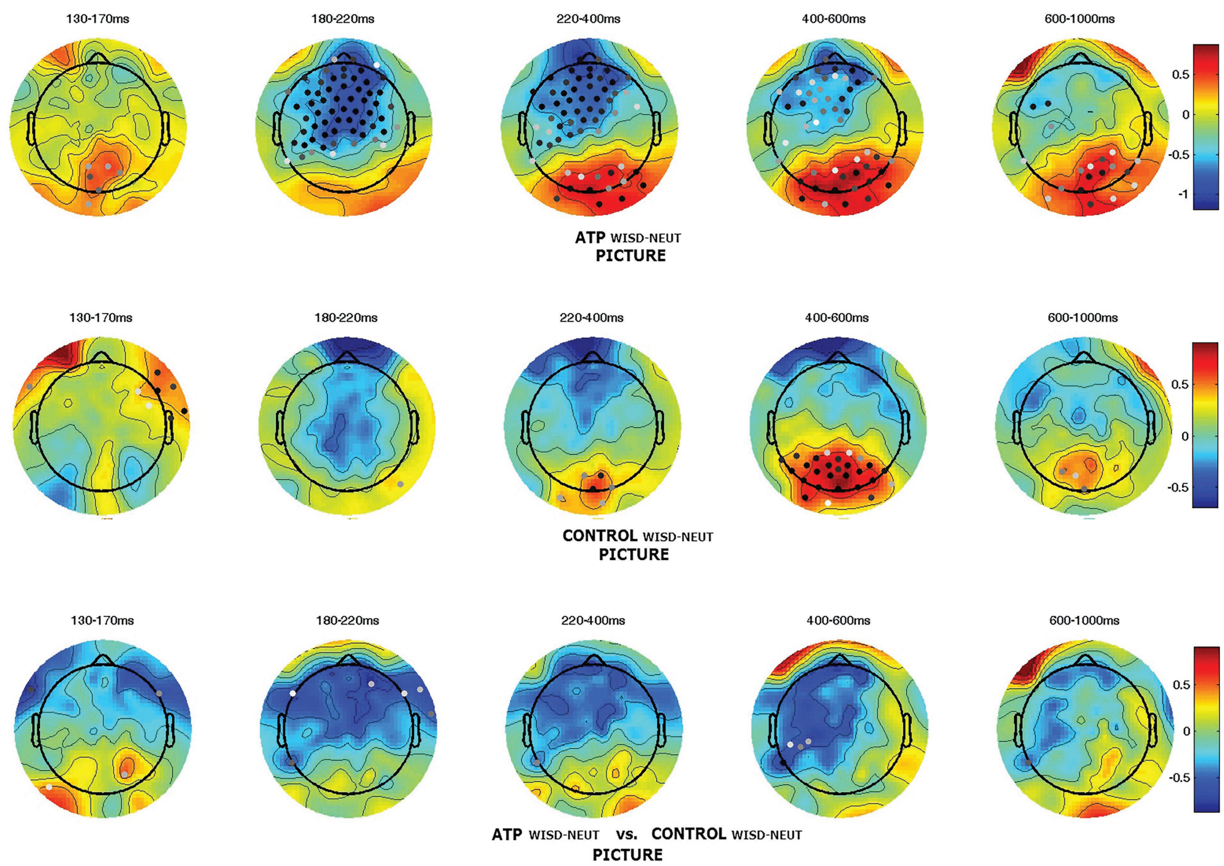

FIGURE 5
Group differences in the wisdom condition when viewing negative pictures. The Awareness Training Program (ATP) group had more neural activity (around N200–600 ms) in the frontal region than the control group. The dots illustrate channels with significant differences ($p<0.05$), and darker dots indicate smaller p-values.

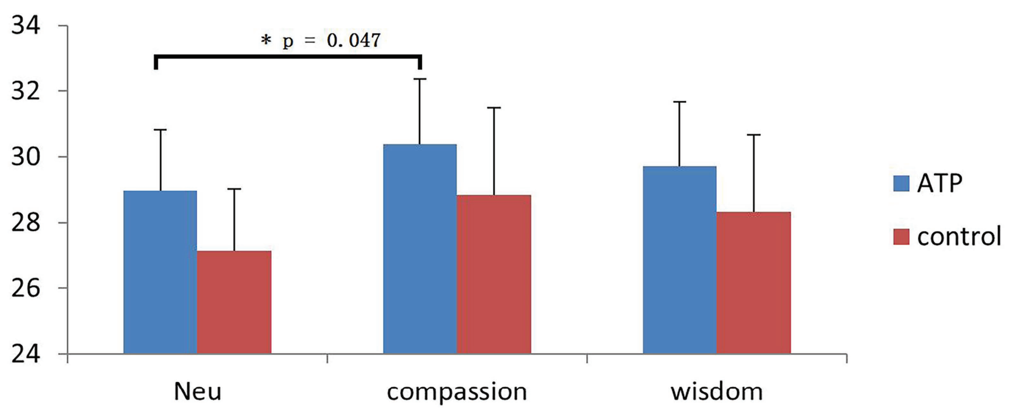

FIGURE 6
Group comparison of heartrate variability (HRV) under different conditions. The HRV is higher in the compassion condition than in the neutral condition in the Awareness Training Program (ATP) group. The error bar shows the standard error.

or wisdom meditation. Thus, the control group also demonstrated more occipital activity in the COMP and WISD conditions. The ATP group showed slightly greater occipital activity than the control group, but the difference between the groups was not significant. This results is in line with previous findings that visual areas such as occipital lobe is mainly stimulus driven as shown in retinotopy, while parietal and frontal areas are driven primarily by attention. Nonetheless, the attentional modulation does affect both early visual areas and attentional control areas in parietal and frontal cortex (Saygin and Sereno, 2008).

The ATP course teaches participants to cultivate awareness and attention. Furthermore, compassion training is obligatory in the ATP, as the mind of enlightenment (*bodhicitta*) has compassion as its foundation. This may help to explain that after the compassion training, participants tended to be more prepared and to display an earlier and stronger willingness to respond in the COMP condition. That said, the insignificant results revealed that there was a trend that the awareness of the ATP participants might enhance after the training on compassion and wisdom meditation. However, the difference between groups was not evident at the early stage of attention deployment. The effect of compassion mediation/wisdom meditation may be well beyond the attention deployment stage.

Effect of compassion/wisdom meditation on cognitive change

The cognitive change stage involved a period of later information processing at N400, and it could go beyond 600 ms to 1,000 ms, mainly in the frontal lobe. The most prominent finding in the ATP group was a significant amount of frontal activity after the priming of compassion meditation or wisdom meditation. In contrast, no such frontal activity was found in the control group. This outcome revealed that cognitive contemplation and the corresponding cognitive change were cultivated after practices of compassion and wisdom, and it played an important role in enhancing the ATP participants' ability of affective modulation.

The frontal negativity of the ATP group peaked at 400–600 ms, a period generally referred to as an N400 component. The period of this cognitive process could last from 200 to 1,000 ms in some situations (Curran et al., 1993; Kutas and Federmeier, 2011; Joyal et al., 2020; Junge et al., 2021). The N400 component is highly relevant to language and semantic processing. Nonetheless, a review paper has suggested that N400 indicates fundamental processing of meaningful/non-meaningful dimension more than the linguistic/non-linguistic dimension (Kutas and Federmeier, 2011). The change in N400 amplitude in the COMP and WISD conditions demonstrates that both the compassion and wisdom practices could help individuals to reconceptualize the meaning of events but in different ways.

During compassion meditation or loving-kindness meditation, practitioners need to send blessings to themselves, and to others, especially those in trouble (Salzberg, 1995; Ho and Mak, 2016; Condon and Makransky, 2020; Mantzios et al., 2021). This contemplation during the compassion training could prompt more linguistic processing and help the participants to reconceptualize the experience and meaning of the miserable pictures. The result demonstrated that the ATP group had a higher N400 amplitude in the COMP condition than the control group. With primes of compassion meditation, this greater activation of the left frontal lobe in the COMP condition might imply a motivation to help and possibly an approach tendency (Davidson et al., 2004; Harmon-Jones et al., 2006), as the left frontal activity is related to an approach tendency (Kelley et al., 2017). The results are consistent with a previous ERP study on compassion, which revealed the role of frontal lobe in compassion-focussed reappraisal (Baker et al., 2017).

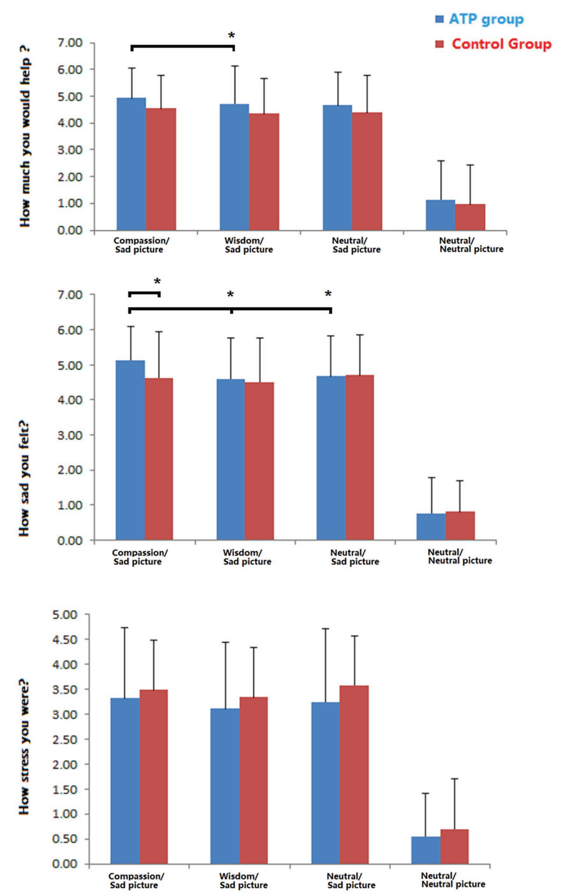

FIGURE 7
Behavioural measurements and comparison of how the participants felt when viewing the negative pictures. Note that all the scores are significantly different between negative and neutral pictures ($p<0.001$). ATP, Awareness Training Program. significant difference ($^*p<0.05$).

Further source analysis revealed that in the COMP condition, the ATP group demonstrated high neural activity in the medial PFC. There is evidence that the PFC can modify emotion according to socially acceptable norms by top-down processes (Morawetz et al., 2016). Damage to the frontal lobe or the pathways connecting the frontal lobe with the limbic system can disrupt the subject's emotion, volition, and personality (Riva et al., 2012). Our results are concordant with previous studies demonstrating that compassion meditation might induce activity in the medial PFC and anterior cingulate cortex in response to empathy and happy feelings (Engstrom and Soderfeldt, 2010). A meta-analysis of fMRI studies on compassion also revealed compassion related areas at frontal lobe including the anterior cingulate, the inferior frontal gyrus, anterior insular, as well as other brain regions of periaqueductal grey, left putamen, left thalamus (Kim et al., 2020). Interestingly, this study found more regions were induced by compassion in the left hemisphere than the right hemisphere. The practice of compassion meditation cultivates the feeling of compassion and generosity, and practitioners need to cultivate their relationships with others despite whether or not they originally liked it. This cognitive reappraisal process may engage the middle and ventral areas of the PFC (Gusnard et al., 2001).

A similar frontal N400 component was found in the WISD condition, although it peaked earlier (200–400 ms) and lasted from 200 to 600 ms. In contrast, frontal negativity peaked at 400–600 ms and lasted from 200 to 1,000 ms in the COMP condition. These ERP results revealed that the frontal activity induced by miserable pictures in the WISD condition emerged earlier but lasted for less time compared with that in the COMP condition. This may reflect different contemplation between the COMP and WISD conditions in the stage of cognitive change. Cognitive contemplation was applied in both the WISD and COMP conditions, but their contemplative focus and content may differ. The wisdom meditation taught in the ATP aims to cultivate non-attachment, a Buddhist concept based on the empty nature of the 'self' or 'other' (Shiah, 2016). This insight may help individuals to let go of mental fixation or attachment to specific concepts. Thus, the participants could avoid excessive emotional responses and demonstrate an earlier peak and a shorter duration of the frontal activity in the WISD condition. It is suggested that wisdom practice cultivates a detach tendency instead of an avoid tendency. While in the COMP condition, the ATP participants may learn to cultivate an approach tendency. They tended to be cognitively more considerate, as implied by their prolonged prefrontal activity in the COMP condition.

Effect of compassion/wisdom meditation on the ERP during the response modulation stage

The response modulation stage of participants could be observed in their behavioural response and physiological response of cardiac activity. The behavioural response showed that the ATP group displayed more empathy and willingness to help those in miserable situations than did the control group. However, this willingness to help seems only apparent in the COMP condition but not in other conditions. It is interesting to find that only in the ATP group, participants became more empathic to those in miserable situations in the COMP condition compared with the other two conditions, also they were more willing to help in the COMP condition than in the WISD condition. This finding shows that the priming cue could help the participants to retrieve their learning experience from the ATP training and enabled them to specifically reconceptualize the emotional pictures.

The ATP group had a higher HRV (in terms of the RMSSD) in the COMP condition than in the NEUT condition. As cardiac activity is modulated by the autonomic nervous system, which controls one's physiological response to stress, HRV reflects the balance between the sympathetic nervous system and the parasympathetic nervous system (Singh et al., 2018). For example, HRV has a significant correlation with highly negative emotions induced by the IAPS pictures (Choi et al., 2017). A higher HRV in the compassion condition implies a higher degree of emotional involvement when viewing the miserable pictures. Changes in the physiological data suggest the cultivation of empathy in the compassion meditation condition.

A previous study showed that cognitive reappraisal could induce cardiac-vagal flexibility and cultivate positive emotion. Nonetheless, this effect only appeared after habitual use – that is, a relatively long-term training. Otherwise, the effect on HRV would be less prominent, similarly to the effect of expressive suppression (Jentsch and Wolf, 2020). The physiological change may be accompanied by a possible change in neuroendocrine activity, as self-reported compassion towards sad faces induces greater activation in subcortical areas secreting dopamine, including the ventral tegmental area and substantia nigra, generating an intrinsic reward (Kim et al., 2009). Previous studies have demonstrated that the PFC could influence neuroendocrine activity when regulating extreme emotions *via* the cognitive reappraisal strategy (Sullivan, 2004; Zhan et al., 2017). This empathetic understanding of other's pain and the willingness to help may be related to the increased activation of the medial PFC (Immordino-Yang et al., 2009), as illustrated in our source analysis.

It is worth noting that to exercise fully the effectiveness of the cognitive reappraisal strategy of the ATP, both compassion and wisdom should be equally emphasized. Compassion training alone may entail an issue of compassion fatigue or secondary traumatic stress (van Mol et al., 2015). The simultaneous practice with the wisdom of nonattachement would allow the individual to step outside of their usual immediate response to an event and disentangle the habitual response of emotion from behaviour (Ayduk and Kross, 2010). In Buddhist teachings, compassion and wisdom meditations are inseparable, similarly to two wings of a bird. The current ERP study implies that compassion practice might endow a miserable event with more meaning and importance of life, thus cultivating an approach tendency. At the same time, wisdom practice might enable the participants to become acentric from a secular event and thus cultivate a detach tendency in the stage of cognitive reappraisal.

In sum, the current ERP study has demonstrated that both compassion meditation and wisdom meditation help affective modulation in middle-aged working adults with moderate stress. The behavioural results, physiological results, and ERP, especially the distinct frontal activity, provide converging evidence that the ATP could effectively regulate individuals' emotional responses to miserable events. These results align with previous studies that cognitive reappraisal is an especially promising strategy of emotion regulation. That said, it has been suggested that the combination of compassion and wisdom may maximise the efficacy of ATP intervention in emotion regulation, and the combination could help sustain cognitive transformation towards compassion together with the wisdom of non-attachment (Salzberg, 2011).

Several limitations are worth noting in the current study. Traditional awareness training usually takes much longer than 7 weeks. Longer programme duration may result in a more effective outcome, especially for wisdom meditation, which is more difficult to learn and practice. Second, subcortical regions such as the amygdala play a vital role in emotion generation, and subsequent regulation, and neuroimaging tools such as fMRI could clarify this processing better than EEG source localisation in terms of spatial resolution. A third limitation is that we did not collect the ERP data before the ATP course, a two-arm longitudinal randomized clinical trial would be more convincing. The present study has demonstrated the role of frontal activity in compassion meditation. Future fMRI studies could reveal the subcortical regions involved in the bottom-up process of emotion regulation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research Ethics Committee The University of Hong Kong. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JG designed and executed the study, analysed and interpreted the data, and wrote the manuscript. HL analysed and interpreted the ERP and physiological data, and collaborated in manuscript writing. JF collected and analysed the ERP data. BW developed the ATP intervention, recruited the participants, assisted in the study design, interpretation of the data and manuscript writing. HS developed the ATP intervention, collaborated on the direction of the study, and assisted in the study design, interpretation of the data and manuscript writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.891656/full#supplementary-material

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Enhancing Chinese preschoolers' executive function *via* mindfulness training: An fNIRS study

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Mindfulness training has been found to enable cognitive and emotional awareness and diminish emotional distraction and cognitive rigidity. However, the existing intervention studies have largely focused on school children, adolescents, and adults, leaving young children unexplored. This study examined the influence of mindfulness training on young children using the one-group pretest-posttest design. Altogether 31 Chinese preschoolers (M_{age} = 67.03 months, SD = 4.25) enrolled in a 5-week, twice-per-week mindfulness training. Their cognitive shifting, inhibitory control, and working memory were examined using a battery of executive function tasks. And their brain activations in the region of interest during the tasks were measured using fNIRS before and after the intervention. Results showed that their cognitive shifting and working memory tasks performance significantly improved, and their activation in the DLPFC significantly changed. Implications for this study were also included.

KEYWORDS

executive function, mindfulness training, fNIRS, preschooler, cognitive shifting, inhibitory control, working memory

Introduction

Executive function (EF) refers to the ability to control one's actions and thoughts consciously, which is considered a higher mental process (Zelazo and Müller, 2010; Griffin et al., 2016) and conducive to children's school readiness (Blair, 2002; Guedes et al., 2022). EF is developed in the early years to support children's ability to regulate their behavior (Moriguchi and Hiraki, 2011) and, in turn, develop their later social, emotional, and cognitive competence (Griffin et al., 2016). Preliminary evidence has shown that mindfulness training considerably improves young children's executive function and alleviates problem behaviors (Flook et al., 2015; Razza et al., 2015). However, most studies lack a comprehensive examination of EF's three components, and very few have provided neuroimaging evidence to support the training effect. Thus, this study is dedicated to filling this research gap.

Executive function and its three components

Miyake et al.'s (2000) influential work fractionate EF into three sub-domains that provide a foundation to regulate thoughts, behaviors, and emotions: (1) working memory, the ability to hold in mind information; (2) inhibitory control, the ability to inhibit fast and unthinking responses to stimulation; and (3) cognitive shifting, the ability to flexibly shift the focus of one's mental frame (Blair, 2016; Moriguchi, 2017). It develops during infancy, shows important developmental changes in preschool years (Zelazo and Müller, 2010), and varies by task (Huizinga et al., 2006). The existing studies have provided evidence to support the relationship between emerging executive functions and maturation of the prefrontal cortex (Moriguchi, 2017; Smith et al., 2017), yet less is known about the relation between brain development and specific executive functions. A series of structural equation models indicated that each sub-domain of EF plays a differential role in performance on a range of executive outcome measures, highlighting the need to recognize the diversity of these sub-processes. Recently, fNIRS has been used to measure task-related changes in cerebral hemodynamics, measurable and doable for very young children. Accordingly, a range of executive function tasks has been explored in preschoolers using fNIRS, including working memory (Tsujii et al., 2009; Buss et al., 2014), inhibitory control (Inoue et al., 2012; Mehnert et al., 2013), and cognitive shifting (Moriguchi and Lertladaluck, 2019; Li et al., 2021b).

Advances in studying executive function's three components

First, the fNIRS studies on cognitive shifting, the ability to flexibly shift between tasks or mental states, have made noticeable progress. In particular, the Dimensional Change Card Sort (DCCS) task is widely used to measure 3 to 6-year-olds' development of cognitive shifting (Zelazo, 2006). The existing fNIRS studies have found that 5-year-olds and adults could perfectly complete the task and show significant activation in the bilateral inferior prefrontal areas; only those 3-year-olds would perseverate to the previous rules (Moriguchi and Hiraki, 2011, 2014). Furthermore, 5-year-olds who are heavy users of tablets performed worse in the DCCS tasks and showed significantly different activations from non-users (Li et al., 2021a). The unexpected synchronous increase in HbO and HbR was similar to those during epileptic seizures (Pouliot et al., 2012). These findings jointly suggest that prefrontal cortex activations play an important role in successful shifting during the DCCS task and that individual differences might be associated with activation patterns.

Second, the fNIRS studies on inhibitory control, the ability to consciously inhibit a pre-potent response, have also attained some achievements. The go/no-go paradigm measures the response inhibition by requiring the subject to respond to a frequent target stimulus and suppressing the repress of the occurrence of a rare non-target stimulus (Mehnert et al., 2013). The existing fNIRS studies with the go/no-go task have revealed significant activation in both go and no-go trials in the right frontal and parietal regions. Furthermore, the functional connectivity analysis revealed that children ages 4–6 years showed stronger partial coherence in short-range connectivity in the right frontal and right parietal cortices than adults (Mehnert et al., 2013). These findings jointly suggest that right frontal and parietal activations might play an important role in performing the go/no-go task.

Third, the fNIRS studies on working memory, the ability to save, manipulate, and remember information, have also advanced in recent years. Several tasks have been designed to measure young children's working memory and its neural basis using fNIRS. In general, significant activation in the frontal and parietal cortex has been found during the working memory task (Tsujimoto et al., 2004; Buss et al., 2014), and child age was positively related to the increase in lateral prefrontal cortex (LPFC) activation, accuracy, and response speed (Perlman et al., 2016). These findings indicated the age-related changes in the prefrontal function, providing empirical evidence to support the effective development of EF during early childhood. However, the above-mentioned studies only focused on one aspect of children's EF and have seldomly examined all three components simultaneously, limiting our understanding of the development of the neural correlates of EF during early childhood, the critical period for the maturation of executive function.

Advances in early intervention studies

Various approaches and interventions have been introduced to enhance young children's EF, among which mindfulness practices have been widely implemented in early childhood classrooms (Razza et al., 2015; Li et al., 2019; Ren et al., 2019). The Intention-Attention-Attitude (IAA) model provides a mechanism of actions underlying mindfulness-based interventions (Shapiro et al., 2006). In this model, the potential mechanism of mindfulness is suggested as "intentionally (I) attending (A) with openness and non-judgmentalness (A) that leads to a significant shift in perspective, termed as reperceiving." Shapiro et al. (2006) also highlighted four additional mechanisms: (1) self-regulation, (2) value clarification, (3) cognitive, emotional, and behavioral flexibility, and (4) exposure. Later, Tang and colleagues (Hözel et al., 2011; Tang et al., 2015; Tang, 2017) proposed that mindfulness practice includes at least three components that interact closely to enhanced self-regulation: enhanced attentional control, improved emotion regulation, and altered self-awareness. Different from other cognitive training, mindfulness-based training has pervasive effects: they not only promote young children's social-emotional competence by reducing behavioral problems and increasing impulse control but also effectively enhance children's cognitive abilities such as attention and inhibition (e.g., Crooks et al., 2020; Razza et al., 2020; Li-Grining et al., 2021).

A recent review on mindfulness-based intervention with young children suggested that over time, with practice and integration, mindfulness programs could support EF development in the early years (Bockmann and Yu, 2022). In addition, this review study also found noticeable variations in the structure, design, skills taught, frequency of practice, and duration of mindfulness-based interventions globally. These interventions all included breathwork and increasing awareness of sensations, feelings, and thoughts as their focus. Another review study has suggested a relatively specific rather than the general benefit of EF from mindfulness, with consistent improvement in inhibitory control and more variable advantages to working memory and cognitive shifting (Gallant, 2016). However, the above-mentioned interventions only employed parent or teacher reports and behavioral tasks to examine the effects of the mindfulness programs.

Neuroimaging techniques have been applied to identify the neural correlates and cognitive processes associated with mindful practices. Changes in cortical thickness (Lazar et al., 2005; Grant et al., 2010), gray-matter volume and/or density (Vestergaard-Poulsen et al., 2009; Hölzel et al., 2011), fractional anisotropy and axial and radial diffusivity (Tang et al., 2010, 2012) have been captured after mindfulness practices. Furthermore, research using fMRI has demonstrated that mindfulness practices increase performances on attentional control tasks (Tang et al., 2007), inhibitory control tasks (Jack et al., 2013), and working memory tasks (Mrazek et al., 2013). Despite the pervasive evidence from fMRI, this technique is limited in measuring vulnerable populations, such as those with trauma or young children under stress. The non-invasive fNIRS device can measure and monitor hemodynamic concentration changes in oxygenated (HbO) and deoxygenated (HbR) hemoglobin as an indicator of brain region activation. A recent study with a group of female participants impaired by stress or traumatic stress found that engagement in a 6-week mindfulness intervention was related to significant changes in performances in attentional control, emotional regulation, and working memory tasks and changes in activation in the frontopolar area, orbitofrontal cortex, and premotor cortex (Bergen-Cico et al., 2021). However, no neuroimaging evidence has been reported to prove the effectiveness of mindfulness-based interventions in preschoolers. To fill this gap, this study endeavors to explore the neural mechanisms of change by taking pre- and post-intervention fNIRS measurements of a group of 5- to 6-year-old children attending mindfulness-based interventions during their pre-school education. In addition, we aimed to explore whether fNIRS is an effective non-invasive means of measuring EF changes associated with mindfulness-based interventions. Specifically, the following hypotheses guided the current study:

> H1: There is a significant change in young children's cognitive shifting after participation in the mindfulness-based intervention.

> H2: There is a significant change in young children's inhibitory control after participation in the mindfulness-based intervention.

> H3: There is a significant change in young children's working memory after participation in the mindfulness-based intervention.

> H4: The behavioral change in cognitive shifting is evidenced by fNIRS data.

> H5: The behavioral change in inhibitory control is evidenced by fNIRS data.

> H6: The behavioral change in working memory is evidenced by fNIRS data.

Materials and methods

Participants

Thirty-three preschoolers who attended the same upper class of the target preschool participated in this one-group pretest-posttest study, but two of the children failed to participate in the post examination and were excluded from the analysis. Shenzhen University's Institutional Review Board approved all study procedures, and all participants' parents gave consent for their children to participate in the study. The 31 participating children were right-handed and their months of age ranging from 62 to 73 months (*M* = 67.03, SD = 4.25).

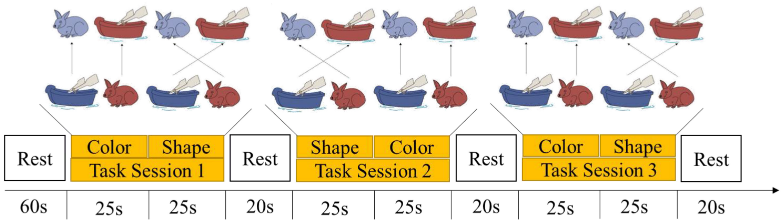

FIGURE 1
Experiment paradigm of the DCCS task.

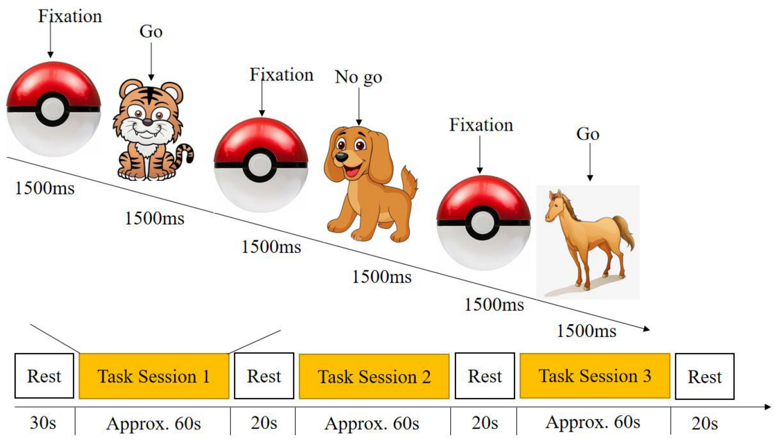

FIGURE 2
Experiment paradigm of the go/no-go task.

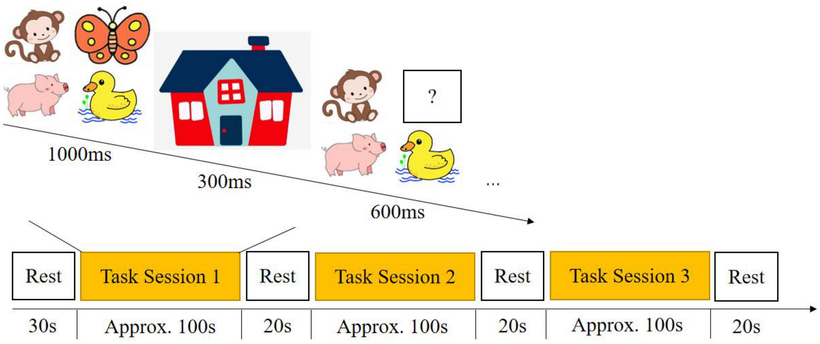

FIGURE 3
Test paradigm for the missing scan task.

Among them, 19 were boys (M = 67.58, SD = 3.99, range 62–73 months) and 12 were girls (M = 66.17, SD = 4.28, range 62–73 months). There were no significant differences in age between the two groups ($t = 0.91, p = 0.37$). The intervention and data collection were conducted from October 2021 to January 2022. *Post hoc* power analysis using G*Power 3.1.9.7 showed that with a sample size of 31, α error probability, and power of 0.95, the effect size was 0.59, which is acceptably large.

Measures

Three cognitive tasks were used to measure children's executive function. The first task, DCCS, measures children's cognitive shifting; the second task, missing scan, measures children's working memory; and the third task, go/no-go, measures children's inhibitory control. The three tasks were programmed using PsychToolBox (PTB) toolkit in Matlab.

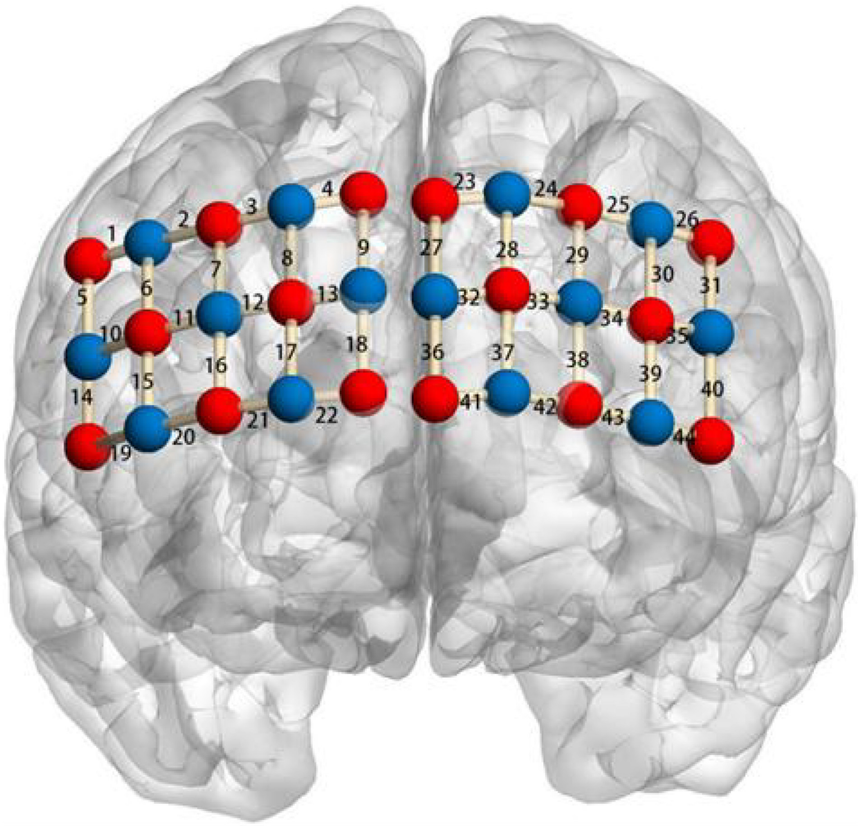

FIGURE 4
Localization of regions of interest. Right Ventrolateral prefrontal cortex (VLPFC): channel 16, 17, 21, 22; left VLPFC: channel 38, 39, 42, 43; right dorsolateral prefrontal cortex (DLPFC): channel 3, 4, 7, 8, 9, 12, 13; left DLPFC: channel 24, 25, 28, 29, 30, 33, 34; right posterior superior frontal cortex (PSFC): channel 1, 2, 5, 6; left PSFC: channel 26, 31; right temporal cortex (TC): channel 10, 11, 14, 15, 19, 20; left TC: channel 35, 40, 44; and Medial prefrontal cortex (MPFC): channel 18, 23, 27, 32, 36, 37, 41.

Stimuli were displayed on the computer screen, and responses were recorded by operating the keyboard. Before each task, participants were trained to make sure that they understood the rules of the tasks. During the test phases, the experimenter recorded each participant's reaction time and responses, who clicked corresponding reactions on the keyboard. Children were instructed to look at the "+" on the screen during the rest phases and sit still.

Dimensional change card sort task

The DCCS task has been used in the previous fNIRS studies to measure children's cognitive shifting (Li et al., 2021b; Xie et al., 2021). A set of stimuli cards were displayed in the center of the screen. The stimuli card had two dimensions: shape and color. The target cards (a red boat and a blue rabbit) and test cards (e.g., a blue boat and a red rabbit) were matched in one dimension but did not match the other dimensions. There were three consecutive test sessions and four rest sessions in between. Each test session consisted of a pre and post-switch phase, with each phase lasting 25 s. The rules for matching were changed according to the experimenter's instruction, and the rule order of the task was changed to avoid the learning effect (**Figure 1**): color→shape, shape→color, color→shape.

Go/no-go task

The go/no-go task was modified from Lahat et al.'s (2010) paradigm to measure children's inhibitory control, as it has good validity and well-mapped neural bases (Wiebe et al., 2012). Children were asked to respond to the go stimulus (e.g., a cow, horse, or tiger) by pressing the space bar and not to respond to the no-go stimulus (e.g., dog). There were 4 go trials and 4 no-go trials in the training session, where children will be reminded of the rules should they respond incorrectly. Altogether, there were three task sessions, with 10 go trials and 10 no-go trials randomly distributed within each session (**Figure 2**).

Missing scan task

The missing scan task was modified from Roman's task to make it suitable for the fNIRS experiment paradigm, as it is suitable for measuring working memory capacity for 3- to 6-year-olds (Roman et al., 2014). A total of 30 animal figures were

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TABLE 1 Results for paired sample *t*-test of behavioral tasks before and after the intervention.

Tasks		Correct rate			Reaction time		
		M (*SD*)	*t*-value	*P*-value	*M* (*SD*)	*t*-value	*P*-value
Total sample (*N* = 31)							
DCCS	Pre	0.93(0.07)	−0.42	0.67	5.6(0.88)	**2.48**	**0.02***
	Post	0.94(0.06)			5.3(0.66)		
Go/No-Go	Pre	0.94(0.06)	1.19	0.24	1.14(0.09)	0.62	0.54
	Post	0.92(0.06)			1.13(0.10)		
Missing Scan	Pre	0.44(0.18)	**−2.96**	**0.01****	5.06(0.51)	**2.73**	**0.01****
	Post	0.51(0.19)			4.82(0.51)		
Girls (*N* = 12)							
DCCS	Pre	0.94(0.05)	−0.62	0.55	5.88(1.01)	1.52	0.16
	Post	0.95(0.04)			5.48(0.72)		
Go/No-Go	Pre	0.94(0.06)	0.28	0.78	1.18(0.06)	−0.33	0.75
	Post	0.93(0.07)			1.18(0.07)		
Missing Scan	Pre	0.38(0.18)	−2.05	0.07	5.14(0.46)	1.58	0.14
	Post	0.49(0.17)			4.93(0.42)		
Boys (*N* = 19)							
DCCS	Pre	0.92(0.08)	−0.17	0.87	5.40(0.75)	**2.27**	**0.04***
	Post	0.92(0.07)			5.19(0.61)		
Go/No-Go	Pre	0.94(0.05)	1.59	0.13	1.12(0.09)	0.87	0.40
	Post	0.92(0.06)			1.10(0.10)		
Missing Scan	Pre	0.47(0.18)	**−2.16**	**0.04***	5.00(0.54)	**2.17**	**0.04***
	Post	0.53(0.20)			4.76(0.56)		

**$p < 0.01$; *$p < 0.05$. Bold values indicate significant values.

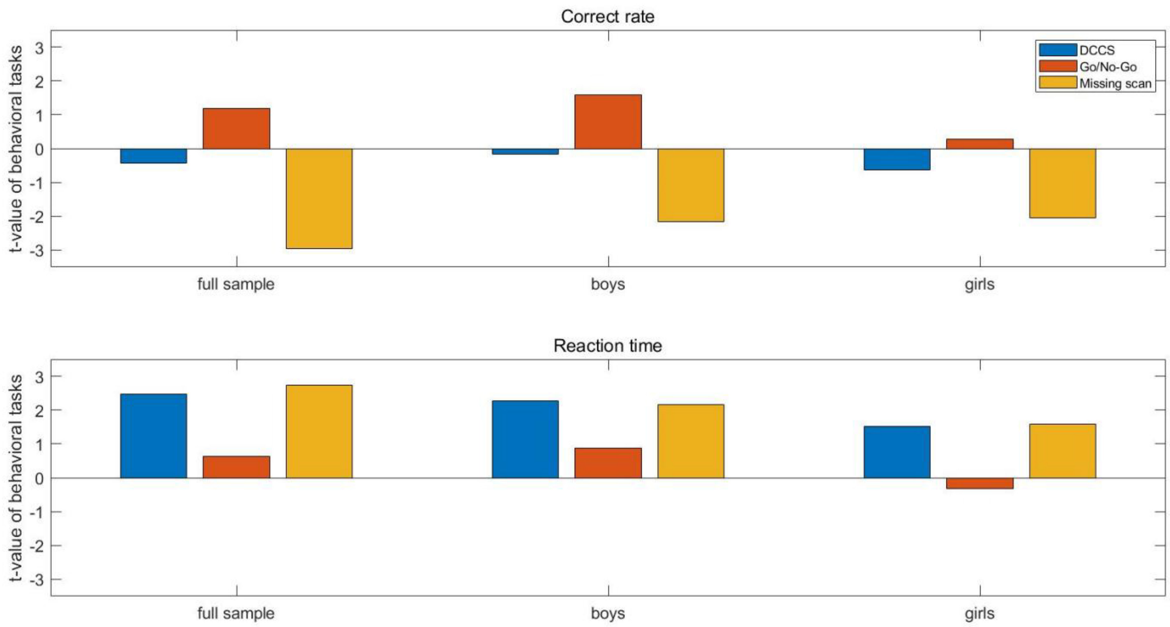

FIGURE 5
Bar chart for the behavioral results of the three tasks before and after intervention for the full sample, boys' group, and girls' group, respectively.

used as test stimuli. Examples of animals in the test set include monkey, pig, butterfly, and duck. Children were instructed to name pictures of each animal before carrying out the test to prevent the need to learn new vocabulary. The child used this label consistently and did not refer to another animal in the same set by the same name. Each time four animals appeared on the screen for 10 s, then disappeared into a "house" for 3 s, and then three animals re-appeared on the screen. Children were then instructed to call the name of the missing animal in 6 s before the next set of animals appeared on the screen. Each test session

TABLE 2 Comparison of increases in HbO before and after the intervention (full sample).

Task	ROI	Pre-intervention *M* (SD)	Post-intervention *M* (SD)	*t*-value	*P*-value
DCCS	Left VLPFC	−0.98(1.79)	−0.25(1.81)	−1.69	0.45
	Right VLPFC	−0.61(1.62)	−0.19(1.43)	−1.06	0.54
	Left DLPFC	−0.50(1.20)	−0.21(1.70)	−0.88	0.56
	Right DLPFC	−0.84(1.77)	0.38(1.40)	**−3.13**	**0.03***
	Left PSFC	−0.40(1.13)	−0.81(1.98)	0.73	0.56
	Right PSFC	−0.36(1.25)	0.13(1.19)	−1.30	0.51
	Right TC	−0.23(1.09)	−0.34(2.31)	0.25	0.80
	Left TC	0.00(1.46)	0.37(2.23)	−0.68	0.56
	MFPC	−1.21(1.55)	−0.67(1.78)	−1.35	0.51
Go/No-Go	Left VLPFC	−0.15(1.12)	−0.41(1.50)	0.63	0.80
	Right VLPFC	0.06(1.27)	0.22(1.41)	−0.39	0.90
	Left DLPFC	0.14(1.14)	−0.20(1.99)	0.81	0.80
	Right DLPFC	−0.20(1.24)	0.02(1.36)	−0.85	0.80
	Left PSFC	−0.09(0.62)	0.02(2.86)	−0.12	0.91
	Right PSFC	0.28(1.25)	−0.24(1.90)	0.67	0.80
	Right TC	0.02(0.97)	−0.48(1.74)	1.28	0.80
	Left TC	−0.14(1.51)	−0.56(1.54)	1.15	0.80
	MFPC	0.17(1.16)	0.09(1.63)	0.21	0.91
Missing Scan	Left VLPFC	−0.32(1.04)	−0.03(1.48)	−0.91	0.56
	Right VLPFC	−0.49(1.36)	0.08(1.06)	−1.81	0.36
	Left DLPFC	0.12(1.46)	0.04(1.12)	0.24	0.81
	Right DLPFC	−0.12(1.67)	0.48(1.49)	−1.83	0.36
	Left PSFC	0.12(1.31)	−1.04(1.84)	1.58	0.43
	Right PSFC	0.60(1.17)	0.10(0.90)	1.33	0.43
	Right TC	0.11(1.02)	0.30(1.62)	−0.58	0.66
	Left TC	−0.11(0.86)	0.18(1.17)	−1.19	0.43
	MFPC	−0.41(0.79)	−0.25(1.32)	−0.56	0.66

*$p < 0.05$. Bold values indicate significant values.

consisted of five trials, resulting in three test sessions and four rests (**Figure 3**).

The fNIRS examination

A multi-channel fNIRS system (Oxymon Mk III, Artinis, Netherlands) was used to collect the changes in oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HbR), and total hemoglobin (HbT) when children performed the three executive function tasks. The optical intensity density values were corrected by the Beer–Lambert law and then converted into changes in the concentration of HbO and HbR. Following the study design of previous studies on young children's EF(Schecklmann et al., 2010; Gu et al., 2017), a number of 30 optodes using a 3 × 10 light level stencil were located in the forehead, forming 44 fNIRS channels to cover the frontal area (see **Figure 4**). To ensure consistent light-level array positions for all participants, the lower middle of the array was positioned at the Fpz position, which is consistent with the 10–20 measurement system. Previous studies have shown that the frontal area was actively involved in executive function (Li et al., 2021a,b; Moriguchi, 2022). The sampling rate was set at 50Hz for data acquisition. A subject-specific differential pathlength factor (DPF) constant was calculated based on the age of each subject (Duncan et al., 1996): ($DPF = 4.99 + 0.067 \times Age^{0.814}$).

Procedure

The 5-week mindfulness-based intervention design is conducted as follows. First, in the baseline pre-session, all participants completed the three executive functions, and their parents filled out questionnaires concerning their children's demographic information. Print questionnaires and consent forms were enveloped and carried home by children to their parents, who gave consent and filled the questionnaires. Children then bring them back to the preschool, and class teachers collected these forms and passed them to the research team. Next, the participants were invited to complete the three executive function tasks in a quiet classroom at the preschool. Before the tasks, an experienced NIRS technician put

TABLE 3 Comparison of increases in HbR before and after the intervention (full sample).

Task	ROI	Pre-intervention *M* (SD)	Post-intervention *M* (SD)	*t*-value	*P*-value
DCCS	Left VLPFC	−0.05(1.49)	−0.35(1.65)	0.69	0.60
	Right VLPFC	−0.03(1.41)	−0.63(1.80)	1.54	0.37
	Left DLPFC	−0.16(1.02)	−0.62(1.32)	1.42	0.37
	Right DLPFC	0.34(1.44)	−0.42(1.35)	**3.05**	**0.04***
	Left PSFC	−0.51(0.74)	−0.72(2.12)	0.30	0.77
	Right PSFC	−1.85(2.51)	−0.41(1.45)	−1.86	0.37
	Right TC	−0.38(1.58)	−0.64(1.88)	0.63	0.60
	Left TC	−0.08(1.54)	−0.35(1.37)	0.80	0.60
	MFPC	−0.01(1.46)	−0.26(1.48)	0.78	0.60
Go/No-Go	Left VLPFC	0.06(1.51)	−0.33(1.30)	1.10	0.58
	Right VLPFC	−0.28(1.29)	−0.51(1.61)	0.62	0.58
	Left DLPFC	−0.18(0.86)	0.16(1.27)	−1.13	0.58
	Right DLPFC	−0.18(1.04)	0.03(1.39)	−0.65	0.58
	Left PSFC	−0.22(1.28)	0.25(1.12)	−0.99	0.58
	Right PSFC	−0.11(1.98)	−1.75(2.45)	1.32	0.58
	Right TC	−0.22(1.19)	−0.03(1.76)	−0.56	0.58
	Left TC	−0.65(1.49)	−0.21(1.18)	−1.17	0.58
	MFPC	−0.25(1.08)	0.00(1.32)	−0.79	0.58
Missing Scan	Left VLPFC	0.11(1.01)	0.20(0.94)	−0.36	0.86
	Right VLPFC	0.05(1.18)	0.01(0.98)	0.13	0.90
	Left DLPFC	0.09(0.97)	−0.27(1.00)	1.27	0.64
	Right DLPFC	0.06(1.22)	−0.39(0.97)	1.78	0.43
	Left PSFC	0.11(0.90)	−0.30(1.02)	0.92	0.69
	Right PSFC	−0.27(0.93)	0.10(1.06)	−0.77	0.69
	Right TC	−0.15(0.98)	0.09(1.27)	−0.86	0.69
	Left TC	0.29(1.05)	−0.22(1.42)	1.72	0.43
	MFPC	0.08(0.94)	0.00(0.88)	0.30	0.86

*$p < 0.05$. Bold values indicate significant values.

the child-sized NIRS cap and installed optodes. At the same time, a student who majored in early childhood education or psychology engaged in story-book reading with the child. All three tasks were computerized using Psychophysics Toolbox extensions and displayed on a 55.35 cm × 31.13 cm Dell monitor. Children were trained to perform the tasks before each experiment began. For the DCCS and missing scan task, the experimenter recorded participants' responses using the keyboard, and for the go/no-go task, children pressed on the space bar instead. Both responses and response time were recorded. After the baseline assessment, all the participants were engaged in a 5-week mindfulness training session per week. After the 5-week intervention, the participants were invited to complete the same executive function tasks (DCCS, missing scan, and go/no-go) while wearing fNIRS equipment.

The mindfulness training was adapted from Lv's (2017) mindfulness training and Stewart and Braun's (2017) mindfulness activities to make it both playful and mindful. The training package consisted of three parts that spanned ten sessions, two sessions a week, and 20 min per session. The first phase focused on breathwork and attention, which included activities such as introduction to mindful breathing, breathing like a frog, mountain raising, and rooted like a tree; the second phase focused on emotional awareness and regulation, which included activities such as mindful bubbles, fist squeeze, peaceful place, the power of blue, and joyful jellyfish; and the third phase focused on gratitude, which included activities such as loving-kindness, heart garden, animal dance, and floating smiles. A certified preschool mindfulness teacher and researcher in early childhood education and a researcher in mental health psychology adapted the training course. The class teacher of the participants received training from the certified teacher and delivered the mindfulness training during the school day.

Data analysis

The participants' behavioral results were exported from Matlab and calculated for the three experiment tasks. First, paired sample *t*-tests were conducted to examine whether there were significant differences in groups' response time and correct rate before and after the mindfulness training. Furthermore, we grouped the participants by gender and explored whether the changes differed for boys and girls.

Next, for the blood oxygen concentration and deoxygenation concentration data of the 44 channels were first visually inspected to assess the quality of the signal. If the optical coupling between the optode and the scalp is not good, it will cause the whole channel to have high frequency signal interference coming from head movement, so such channels are

TABLE 4 Comparison of increases in HbO before and after the intervention for girls (N = 12).

Task	ROI	Pre-intervention *M* (*SD*)	Post-intervention *M* (*SD*)	*t*-value	*P*-value
DCCS	Left VLPFC	−1.26(1.78)	−0.52(2.01)	−0.98	0.79
	Right VLPFC	−1.20(2.11)	−0.19(1.43)	−1.35	0.79
	Left DLPFC	−0.55(1.75)	−0.91(1.56)	0.62	0.99
	Right DLPFC	−1.09(2.12)	0.22(1.45)	−1.65	0.79
	Left PSFC	−0.74(1.71)	−0.66(1.90)	−0.14	0.99
	Right PSFC	0.00(2.75)	−0.52(2.31)	1.65	0.79
	Right TC	−0.79(1.07)	−0.53(3.22)	−0.28	0.99
	Left TC	0.11(2.13)	0.38(3.31)	−0.21	0.99
	MFPC	−1.55(1.73)	−1.55(1.68)	0.01	0.99
Go/No-Go	Left VLPFC	−0.20(0.87)	0.14(0.98)	−0.74	0.89
	Right VLPFC	−0.23(1.33)	0.34(1.70)	−0.71	0.89
	Left DLPFC	0.30(0.87)	0.34(1.93)	−0.06	0.98
	Right DLPFC	−0.12(1.16)	−0.10(1.40)	−0.03	0.98
	Left PSFC	0.22(0.64)	−0.16(0.35)	1.60	0.82
	Right PSFC	−0.43(0.78)	0.83(1.60)	−2.18	0.82
	Right TC	−0.24(1.09)	−0.54(1.09)	0.52	0.92
	Left TC	0.00(1.36)	−0.66(1.04)	1.23	0.82
	MFPC	0.14(1.04)	0.32(1.63)	−0.32	0.97
Missing Scan	Left VLPFC	−0.44(0.94)	−0.11(1.90)	−0.50	0.81
	Right VLPFC	−0.32(1.51)	0.07(0.65)	−0.70	0.81
	Left DLPFC	−0.29(1.25)	0.37(0.72)	−2.05	0.29
	Right DLPFC	−0.42(1.13)	0.41(0.77)	−2.16	0.29
	Left PSFC	−0.40(1.44)	−0.22(1.10)	−0.27	0.87
	Right PSFC	0.84(1.41)	0.23(0.38)	0.84	0.81
	Right TC	0.24(1.14)	0.17(0.99)	0.17	0.87
	Left TC	−0.21(0.99)	0.05(1.08)	−0.63	0.81
	MFPC	−0.43(0.74)	−0.04(1.50)	−0.71	0.81

removed before formal analysis (Brigadoi et al., 2014). Then, the NIRS-KIT software (Hou et al., 2021) was used to perform first-order baseline correction on the blood oxygen concentration and deoxygenation concentration data. Motion artifacts were removed using the DTTR algorithm (Fishburn et al., 2019). A bandpass filter (third-order Butterworth filter) with cut-off frequencies of 0.01–0.08 Hz (Pinti et al., 2019) was then applied to the data to reduce slow drifts and high-frequency noise.

After the fNIRS data were prepossessed, the HbO and HbR concentration were converted into *z*-scores using the mean value and *SD* of the HbO and HbR concentration changes during the rest phase, respectively. Next, a two-level mixed effect model Region of Interest (ROI) analysis was performed. At the first level analysis, GLM was performed for each channel and each subject by comparing the task to the rest phase. To increase the signal-to-noise ratio, the 44 channels were averaged into nine ROIs, where the time-series data were averaged within each ROI (Gu et al., 2017): the left ventrolateral prefrontal cortex (VLPFC), right VLPFC, left dorsolateral prefrontal cortex (DLPFC), right DLPFC, left posterior superior frontal cortex (PSFC), right PSFC, left temporal cortex (TC), right TC, and medial prefrontal cortex (MPFC). At the second level group analysis, the pre- and post-intervention betas for each ROI were compared using paired sample *t*-test by group level of the total sample, and the *p* values were FDR adjusted. We also explored whether boys showed different patterns from girls by grouping the total sample by gender.

Results

Behavioral results

Paired sample *t*-test revealed that two out of the three tasks showed significant improvement after mindfulness-based intervention (**Table 1** and **Figure 5**). First, for the DCCS task, children's response time shortened, showing improved cognitive shifting abilities and supporting H1. Second, children's correct rate improved, and response time shortened for the missing scan task, showing improved working memory abilities and supporting H3. Finally, for the go/no-go task, there was no significant change in children's correct rate or response

TABLE 5 Comparison of increases in HbR before and after the intervention for girls (N = 12).

Task	ROI	Pre-intervention *M* (*SD*)	Post-intervention *M* (*SD*)	*t*-value	*P*-value
DCCS	Left VLPFC	0.19(1.58)	−0.19(1.17)	0.60	0.72
	Right VLPFC	0.10(1.78)	−0.26(1.04)	0.69	0.72
	Left DLPFC	−0.06(0.73)	−0.88(1.32)	1.68	0.72
	Right DLPFC	0.41(1.81)	−0.04(1.53)	0.93	0.72
	Left PSFC	−0.02(0.49)	−0.30(0.36)	0.57	0.72
	Right PSFC	−4.41(3.75)	−1.04(1.56)	−2.18	0.72
	Right TC	−0.16(1.45)	−0.49(2.34)	0.46	0.72
	Left TC	0.42(1.80)	0.18(1.40)	0.42	0.72
	MFPC	−0.18(1.75)	0.01(0.83)	−0.37	0.72
Go/No-Go	Left VLPFC	−0.11(1.24)	0.21(1.05)	−0.85	0.46
	Right VLPFC	−0.71(1.06)	0.21(1.25)	−2.09	0.15
	Left DLPFC	−0.20(0.85)	0.27(1.24)	−0.96	0.46
	Right DLPFC	−0.60(1.01)	0.49(1.45)	−2.05	0.15
	Left PSFC	−1.00(1.44)	−0.46(0.69)	−1.22	0.46
	Right PSFC	−0.65(2.11)	−1.43(3.85)	0.19	0.88
	Right TC	−0.43(1.46)	0.68(2.16)	−2.17	0.15
	Left TC	−1.02(2.15)	0.00(1.01)	−1.29	0.40
	MFPC	−0.54(0.59)	0.45(1.10)	**−3.95**	**0.02***
Missing Scan	Left VLPFC	0.57(1.12)	−0.19(1.02)	1.96	0.14
	Right VLPFC	0.44(0.74)	−0.40(0.61)	**3.99**	**0.01***
	Left DLPFC	0.25(1.10)	−0.60(0.78)	2.14	0.13
	Right DLPFC	0.54(1.00)	−0.65(0.73)	**4.48**	**0.01***
	Left PSFC	0.24(1.02)	−0.34(1.16)	0.54	0.72
	Right PSFC	−0.85(1.99)	−0.49(0.12)	−0.24	0.85
	Right TC	−0.53(1.12)	−0.17(0.70)	−1.15	0.36
	Left TC	0.57(1.22)	−0.17(0.89)	1.50	0.24
	MFPC	0.34(0.79)	−0.25(0.68)	2.14	0.13

*$p < 0.05$. Bold values indicate significant values.

time, failing to support H2. We further explored whether boys and girls were different in the behavioral changes before and after the mindfulness-based intervention by doing paired sample t-tests for boys' and girls' groups separately. The results show no significant differences in girls' behavioral results before and after the intervention. Still, there were significant differences in boys' behavioral results: reaction time for the DCCS and missing scan task shortened, and the correct rate for the missing scan task improved. When comparing the performances between boys and girls, there were no significant differences in pre- and post-interventions for the three tasks ($ps > 0.05$), except for the reaction time in the go/no-go task in post-intervention ($t = -2.56$, $p < 0.05$).

fNIRS results

First, a set of two-sample (independent groups) t-tests was conducted to determine any significant difference in the mean HbO and HbR increase before and after the mindfulness-based intervention. As multiple channels were involved, all the results were corrected for multiple comparisons using the false discovery rate (FDR), and the adjusted significance level of the p-value was set at 0.05. The results indicated a significant between-group difference in the right DLPFC. As shown in Tables 2, 3, a significant increase in HbO ($t = -3.13$, $p < 0.05$) and a significant decrease in HbR ($t = 3.05$, $p < 0.05$) was observed in the right DLPFC after the intervention, supporting H6. However, H4 and H5 were not supported.

We also explored whether the changes in neural activation before and after the mindful-based intervention differed for boys and girls. Therefore, paired sample t-tests of the pre- and post-intervention brain activations were conducted for girls and boys separately. Table 4 showed that for girls, there were no significant changes in HbO before and after the mindful based intervention ($ps > 0$), but Table 5 showed significant increase in HbR in MPFC ($t = -3.95$, $p < 0.05$) and decrease in right VLPFC ($t = 3.99$, $p < 0.05$) and right DLPFC ($t = 4.48$, $p < 0.05$). Table 6 showed that for boys, there were no significant changes in HbO

TABLE 6 Comparison of increases in HbO before and after the intervention for boys ($N = 19$).

Task	ROI	Pre-intervention *M* (SD)	Post-intervention *M* (SD)	*t*-value	*P*-value
DCCS	Left VLPFC	−0.79(1.82)	−0.08(1.71)	−1.36	0.34
	Right VLPFC	−0.24(1.13)	−0.18(1.46)	−0.12	0.90
	Left DLPFC	−0.46(0.72)	0.24(1.67)	−1.88	0.23
	Right DLPFC	−0.67(1.55)	0.48(1.40)	−2.84	0.10
	Left PSFC	−0.27(0.97)	−0.86(2.13)	0.79	0.54
	Right PSFC	−0.45(0.94)	0.29(0.96)	−1.76	0.28
	Right TC	0.09(0.98)	−0.23(1.68)	0.72	0.54
	Left TC	−0.06(0.89)	0.36(1.27)	−1.16	0.39
	MFPC	−1.00(1.44)	−0.11(1.64)	−1.97	0.23
Go/No-Go	Left VLPFC	−0.12(1.28)	−0.76(1.68)	1.07	0.59
	Right VLPFC	0.24(1.24)	0.15(1.24)	0.20	0.84
	Left DLPFC	0.03(1.29)	−0.54(2.01)	1.13	0.59
	Right DLPFC	−0.25(1.32)	0.09(1.37)	−1.11	0.59
	Left PSFC	−0.20(0.62)	0.09(3.41)	−0.23	0.84
	Right PSFC	0.46(1.32)	−0.51(1.96)	1.05	0.59
	Right TC	0.17(0.89)	−0.45(2.05)	1.16	0.59
	Left TC	−0.22(1.63)	−0.50(1.82)	0.54	0.82
	MFPC	0.18(1.25)	−0.05(1.66)	0.48	0.82
Missing Scan	Left VLPFC	−0.25(1.12)	0.02(1.21)	−0.79	0.53
	Right VLPFC	−0.59(1.28)	0.08(1.28)	−1.80	0.53
	Left DLPFC	0.38(1.56)	−0.17(1.29)	1.19	0.53
	Right DLPFC	0.07(1.94)	0.53(1.82)	−0.95	0.53
	Left PSFC	0.32(1.31)	−1.35(2.03)	1.76	0.53
	Right PSFC	0.54(1.20)	0.07(1.01)	1.03	0.53
	Right TC	0.04(0.97)	0.37(1.92)	−0.74	0.53
	Left TC	−0.05(0.79)	0.26(1.25)	−1.01	0.53
	MFPC	−0.40(0.84)	−0.39(1.22)	−0.03	0.97

before and after the mindful-based intervention ($ps > 0$), but **Table 7** showed a significant decrease in HbR in the right DLPFC ($t = 3.56$, $p < 0.05$).

The observed changes in the HbO and HbR concertation in the nine ROIs during the three tasks for the full sample, girls' group, and boys' group are averaged within group for each ROI and are shown in **Supplementary Figures 1–6**, respectively.

Discussion

First, this study found that after the mindfulness-based intervention, children's behavioral performance significantly improved in the DCCS task, indicating that the mindfulness-based intervention effectively enhanced children's behavioral scores in the cognitive shifting. This finding is consistent with previous studies, confirming a positive effect of mindfulness training on children's cognitive shifting (Flook et al., 2015; Bockmann and Yu, 2022). Second, this study found that children improved their behavioral performance in the Missing Scan task after the intervention, indicating that the mindfulness training was also effective in increasing children's working memory span, which is consistent with previous studies (Janz et al., 2019; Razza et al., 2020). Third, this study did not find improvements in children's behavioral performance in the Go-No-Go task (even lower scores in post-intervention), indicating no significant changes in children's inhibition control after the mindfulness training, which failed to provide supplementary evidence to the existing literature (Flook et al., 2015). The reasons for this non-significant change may be that the current Go-No-Go task was designed as having the average number of the go and no-go trials, which limited the opportunities of the children to perform in the no-go trials, as the no-go trials were generally related to higher mindfulness (Logemann-Molnár et al., 2022). Therefore, future studies may enlarge the number of no-go trails to increase the opportunities for mindfulness-related sessions/events for the children to react. Generally speaking, mindfulness training is effective in enhancing young children's EF, which corroborates with the findings of a recent literature review. However, the longer duration and higher training frequency tend to improve (Bockmann and Yu, 2022). It was also interesting

TABLE 7 Comparison of increases in HbR before and after the intervention for boys ($N = 19$).

Task	ROI	Pre-intervention *M* (SD)	Post-intervention *M* (SD)	*t*-value	*P*-value
DCCS	Left VLPFC	−0.21(1.45)	−0.45(1.92)	0.41	0.77
	Right VLPFC	−0.11(1.17)	−0.86(2.14)	1.36	0.66
	Left DLPFC	−0.22(1.17)	−0.45(1.33)	0.54	0.77
	Right DLPFC	0.30(1.21)	−0.66(1.20)	**3.56**	**0.02***
	Left PSFC	−0.69(0.76)	−0.89(2.50)	0.20	0.85
	Right PSFC	−1.21(1.93)	−0.25(1.49)	−1.14	0.66
	Right TC	−0.51(1.68)	−0.72(1.62)	0.42	0.77
	Left TC	−0.39(1.30)	−0.68(1.29)	0.68	0.77
	MFPC	0.10(1.29)	−0.43(1.78)	1.25	0.66
Go/No-Go	Left VLPFC	0.17(1.68)	−0.66(1.36)	1.67	0.51
	Right VLPFC	0.00(1.38)	−0.96(1.68)	2.03	0.51
	Left DLPFC	−0.17(0.89)	0.09(1.31)	−0.66	0.66
	Right DLPFC	0.09(0.99)	−0.26(1.31)	0.96	0.66
	Left PSFC	0.07(1.18)	0.51(1.17)	−0.69	0.66
	Right PSFC	0.03(2.08)	−1.83(2.36)	1.38	0.63
	Right TC	−0.09(1.02)	−0.44(1.39)	0.89	0.66
	Left TC	−0.41(0.86)	−0.35(1.28)	−0.18	0.86
	MFPC	−0.07(1.28)	−0.28(1.39)	0.46	0.73
Missing Scan	Left VLPFC	−0.18(0.85)	0.45(0.81)	−2.29	0.31
	Right VLPFC	−0.20(1.35)	0.27(1.09)	−1.13	0.79
	Left DLPFC	−0.02(0.89)	−0.06(1.09)	0.11	0.93
	Right DLPFC	−0.25(1.27)	−0.22(1.08)	−0.09	0.93
	Left PSFC	0.06(0.93)	−0.29(1.06)	0.68	0.79
	Right PSFC	−0.12(0.65)	0.24(1.14)	−0.69	0.79
	Right TC	0.08(0.84)	0.24(1.51)	−0.40	0.89
	Left TC	0.12(0.92)	−0.24(1.70)	0.97	0.79
	MFPC	−0.08(1.00)	0.16(0.96)	−0.65	0.79

*$p < 0.05$. Bold values indicate significant values.

to find that when separating the boys and girls, changes in the behavioral tasks (DCCS and missing scan) were significant only in the boys' group, indicating that the mindfulness-based intervention benefited boys more than girls. This finding corroborates with the existing literature in which boys initially showed more somatic complaints than girls did and this difference disappeared by the end of the mindfulness-based intervention (Semple et al., 2010). Furthermore, the ages differences (despite non-significant) might explain for the different results for gender groups, which deserves further investigation.

Second, this study found a significant increase in HbO activation and a significant decrease in HbR activation in the right DLPFC after the mindfulness-based intervention in the total sample and the boy's group, which indicated that fNIRS data also evidenced the behavioral changes in cognitive shifting. This finding is congruent with previous studies, which suggest mindfulness practices stabilize attention and improve cognitive flexibility (Bulzacka et al., 2017; Vieth and von Stockhausen, 2022). An individual engaging in the early stage of mindfulness practice often utilizes the DLPFC and parietal cortex (Posner et al., 2015; Tang et al., 2015) to try to get into the mediative state, which supports the findings of the current study with a group of preschoolers who were new to the mindfulness practice. Using the IAA model (Shapiro et al., 2006) and the attention regulation as components of the mindfulness mechanism (Tang et al., 2015), they both consider mindfulness practice to improve attentional processes by improving sustained attention and better monitoring as well as effective shifting between task set (i.e., cognitive shifting; Vieth and von Stockhausen, 2022).

Third, this study found a significant decrease in HbR activation in the MPFC after mindfulness-based intervention in the girl's group, despite non-significant changes in go/no-go behavioral results. This indicated that changes in girls' brain activation during inhibitory control tasks were not reflected in the behavioral performance. This is somewhat incongruent with a review study that found all but one of the studies reported mindfulness practice-related improvements to the inhibition outcomes (Gallant, 2016). Using the above-mentioned frameworks (Shapiro et al., 2006; Tang et al., 2015), mindfulness practices contribute to inhibitory control by maintaining attentional focus on a task (Vieth and von Stockhausen, 2022).

Finally, the study found a significant decrease in HbR activation in the right VLPFC and right DLPFC after mindfulness-based intervention in the girl's group during the working memory task, but not for the boy's group or the total sample. Despite incongruence between behavioral performance and neural activations, the findings jointly highlight that mindfulness-based intervention was beneficial for preschoolers' working memory, which is congruent with previous studies (Jha et al., 2010; Mrazek et al., 2013). Jha et al. (2010) revealed that mindfulness training helped people reduce their stress levels, facilitating them to perform better in working memory tasks. This finding implied that mindfulness training might reduce the brain burden caused by stress during the working memory task to reduce brain activations. Coincidently, Mrazek et al. (2013) found that mindfulness training reduced mind wandering during the working memory task. This may be one reason for the decreased brain activation during the working memory task after mindfulness training, as there would be less burden caused by distracting thoughts. Furthermore, the neural efficiency model also postulates that in medium- to low-difficulty cognitive tasks, high performers tend to show lower brain activation than low performers due to higher efficiency in allocating neural resources (Dunst et al., 2014), which is also found in bilingual young children with advanced bilinguals showing less brain activation than less-advanced bilinguals (Xie et al., 2021). However, some sleep studies also found that decreased brain activation during a working memory task was associated with sleep-deprivation vulnerability (Mu et al., 2005). Therefore, the mechanism of this activation decreased during the working memory after mindfulness training deserves further investigation. Nonetheless, the current study suggests a relatively specific rather than general benefit of a mindfulness-based intervention to the three components of preschoolers' EF, highlighting the advantages of examining all three components of EF simultaneously.

Limitations and future research

The limitations of the current study are worth mentioning. First, given the wide variations of mindfulness-based interventions in the current literature, the existing study used two sessions per week, 5 weeks in total, which might not be enough duration and frequency for enhancing young children's EF. This might lead to different patterns of change between behavioral performance and brain activations and between boys and girls. Second, all the participants were in the intervention group. Without a control group, the intervention effect is not convincing enough. Taking the limitations mentioned above, future research shall consider mindfulness training with a longer duration and a higher frequency. If possible, groups with different frequencies, duration, and gender might provide more evidence of the benefit of duration and frequency of the training. Furthermore, future studies shall consider intervention versus control group design to substantiate the benefits of mindfulness training.

Conclusion and implications

The current study found that a 5-week, twice-per-week mindfulness training can enhance young children's cognitive shifting and working memory, especially for boys. These changes in behavioral tasks were evidenced by significant changes in brain activation during cognitive shifting and working memory tasks. Furthermore, girls' brain activation was significantly different during the missing scan task despite not being revealed in the behavioral results. The current study provided preliminary evidence that preschoolers can benefit from mindfulness training and implies that integrating it into the preschool curriculum might have some training effects. Furthermore, it implies that fNIRS is an effective tool in detecting neural activations changes brought by mindfulness training in young children.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Research Ethics committee of Shenzhen University (PN-2021-038, approval date October 14, 2021). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SX contributed to project conceptualization, data collection, and original manuscript drafting. CG and JL contributed to data collection, processing, analysis, and statistical analysis. HL constructive discussions and manuscript revision. DW contributed to constructive discussions and manuscript drafting. XC contributed to project conceptualization and research design. CC contributed to data processing, analysis, manuscript revision, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Loving-kindness meditation (LKM) modulates brain-heart connection: An EEG case study

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Loving-Kindness Meditation (LKM) is an efficient mental practice with a long history that has recently attracted interest in the fields of neuroscience, medicine and education. However, the neural characters and underlying mechanisms have not yet been fully illustrated, which has hindered its practical usefulness. This study aimed to investigate LKM from varied aspects and interactions between the brain, the heart, and psychological measurements. A Buddhist monk practitioner was recruited to complete one 10-min LKM practice, in between two 10-min resting tasks (pre- and post-resting) per experimental run. Two sets of single-channel wearable EEG devices were used to collect EEG data (placed at Fz and Pz) and heart rate simultaneously. A self-report evaluation was conducted to repeatedly record the comprehensive performance of mind and body in each session. EEG data were preprossessed and analyzed by EEGlab. Further statistics were made by SPSS. Spectrum analysis showed a significant increase of theta power (Fz: $t = -3.356$; $p = 0.002$; Pz: $t = -5.199$; $p < 0.001$) and decrease of heart rate between pre- and post-resting tasks ($t = 4.092$, $p < 0.001$). The analysis showed a negative correlation between theta power and heart rate (Fz: $r = -0.681$, $p < 0.001$; Pz: $r = -0.384$, $p = 0.008$), and a positive correlation between theta power and the self-designed report score (Fz: $r = 0.601$, $p < 0.001$). These findings suggest that LKM is accompanied by significant neurophysiological changes, mainly an increase in slower frequencies, such as theta, and a decrease in heart rate. More importantly, subjective psychological assessments were also correlated with objective neurophysiological measurements in a long-term meditator participant. During LKM meditation, this connection was stronger. The results of this case report have promising implications for LKM practice in daily life.

KEYWORDS

electroencephalogram (EEG), loving-kindness meditation (LKM), single-channel EEG, theta power, brain-heart connectivity, LKM self-report

Introduction

Psychological wellbeing plays a critically important role in contemporary society, and researchers keep exploring more feasible therapeutic ways to improve mental health (Al-Ghabban, 2018; Allen et al., 2021; Don et al., 2022). After decades of clinical and neuroscientific studies, meditation and mindfulness became popular and gained traction in both scientific and general communities (Boellinghaus et al., 2013, 2014; Le Nguyen et al., 2019; Agrawal and Sahota, 2022; Don et al., 2022). Solid evidence has shown that mindfulness can relieve stress and improve psychological health. Mindfulness is one of the various meditation traditions. Since different meditation techniques may focus on training different mental characters (Lumma et al., 2015; Colzato and Kibele, 2017; Bhanushali et al., 2020; Roca et al., 2021). Different methods of EEG data analysis may result in further conclusions on meditation effectiveness. Moreover, there could be a non-linear trajectory between brain activity and behavioral assessment (Shaw and Routray, 2016, 2018; Gupta et al., 2018; Britton, 2019). Future research is needed to characterize the nature of the many types of meditation (Dahl et al., 2015; Lindahl et al., 2017).

Loving-Kindness Meditation (LKM) is one of the most established Buddhist practices, aiming to generate positive emotions toward oneself and others (Fredrickson et al., 2008; Hutcherson et al., 2008; Cohn and Fredrickson, 2010). LKM training enables individuals to better control their minds and enhance their focus and concentration (Kabat-Zinn and Hanh, 2009). When practicing LKM, individuals need to train the mind to flow smoothly and naturally while enhancing the quality of awareness (Anālayo, 2019). LKM is a cultivation of the sentiments of love, benevolence, kindness, affection, friendship, and goodwill (Fredrickson et al., 2008). LKM emphasizes empathy more than vipassana, i.e., mindfulness, which emphasizes focused attention on specific objects such as breathing. Previous studies may have this difference (Liu et al., 2020).

Several studies and review papers have demonstrated the effectiveness of LKM on symptom improvement for psychiatry disorders, including relieving pain, increasing social connection, reducing anger, hostility, depression, and anxiety (Hutcherson et al., 2008; Galante et al., 2014; Seppala et al., 2014; Zeng et al., 2015; Amutio-Kareaga et al., 2017). A previous study framed out a model to contain a wider range of traditional and contemporary meditation practices, categorized into attention, constructive, and deconstructive groups. It worked on the mechanisms of attention regulation and meta-awareness; perspective taking and reappraisal; and self-inquiry. Also, constructive groups aimed to develop healthy interpersonal relationships and positive ethical values that lead to wellbeing. These good and positive relationships with people could expand to loving-kindness and compassion which is associated with wellbeing and emotion (Dahl et al., 2015).

It is assumed that LKM meditators can concentrate on generating loving-kindness and create a sentimental feeling of goodwill with unconditional love. It has been reported that experienced meditators can significantly change their brain activities, especially during compassion meditation (Lutz et al., 2004). The LKM practice follows a Buddhist meditation guidebook, Ven. Buddhaghosa's Visuddhimagga, which provides systematic instructions for LKM (Ñāṇamoli, 1991). A few other studies investigated more modern forms of LKM or compassion meditation (Salzberg, 2002; Hofmann et al., 2011; Galante et al., 2014). Long-term LKM meditators are reported to have a lifelong change of positive psychological characteristics such as empathy, motivation, and honesty. This may partially explain why LKM is known to increase a sense of well-being (Chen et al., 2021).

Neuroimaging studies have found that long-term practitioners of LKM have increased activation in the amygdala, right temporoparietal junction, and right posterior superior temporal sulcus during LKM. In response to emotional stimuli, long-term practitioners of LKM can alter the activation of neural circuitries linked to empathy and the theory of mind (Lutz et al., 2004).

Neuroscientific research can provide more objective evidence on brain reactions to a particular task including meditation (Lutz et al., 2009; Valk et al., 2017). Neurophysiology thus helps to establish a framework model to examine human emotions and mindfulness after meditation (Valk et al., 2017; Don et al., 2022). This model is also comprised of social-affective skills and socio-cognitive skills (Valk et al., 2017). For example, loving-kindness compassion can help individuals tackle difficult and prosocial motivation, while improving their social-affective skills, and this is accompanied by plasticity in frontoinsular regions (Valk et al., 2017). Socio-cognitive skills are related to metacognition of self and others. It might also have influence on inferior frontal and lateral temporal cortices (Valk et al., 2017). This research contributed to the present study by helping to explain the mechanisms at work in meditation.

In the LKM meditation tradition, the practice is mainly related to the heart, which is frequently referred to as the cardiac and body functions, instead of the brain or mind. This is less studied as a majority of the neuroscientific studies are on brain function, although several studies have investigated the potential correlation between meditation practice and cardiac activities. A previous ECG study found that deep Zen meditation can alter heart activity and heart rate variability (Lo and Tian, 2016). An increased correlation between brain and heart is also found during autogenic meditation (Kim et al., 2013, 2014). A more recent neuroimaging study found that meditation is accompanied by specific brain processing and corresponding cardiac rhythms. The interaction between brain networks and cardiac activity may contribute to the fundamental understanding of the neural mechanisms of meditation (Jiang et al., 2020). Concerning compassion meditation, one functional magnetic resonance imaging (fMRI) study revealed that compassion meditation induces a differential correlation between the insula activity and cardiac function between novices and experts LKM meditators (Lutz et al., 2009). This literature, although insufficient, indicates a potential correlation between the brain and heart during LKM meditation.

In this study, by simultaneously measuring brain activity and heart rate, we aimed to better understand the neurophysiological mechanisms and psychological effects of LKM. The purpose of this study was to investigate the effect of LKM on neural activity, body physiology, and their interaction. It is hypothesized that the practice of LKM can induce significant neurophysiological changes, specifically the coherence between heart rate and EEG data.

Methodology

Data collection

A 43-year old long-term meditator from the Theravada Buddhist tradition participated in this study. Using two sets of UMindSleep (EEGsmart) with electrodes placed at Fz and Pz, two EEG Channels were recorded along with heart rate. The sites were selected following preliminary data from a previously unpublished high-density EEG (128 channel) study on LKM, which showed that the frontal and parietal lobes had significant changes in brain activity during LKM practice. The EEG sampling rate was 250 Hz. All EEG signals were referenced to the right mastoid. Data from the device was uploaded to a smartphone *via* Bluetooth. The EEG and pulse rate data were transferred to a computer and then analyzed using EEGLab as a MATLAB toolbox (Delorme and Makeig, 2004) (see Figure 1A).

Loving-kindness meditation

The participant performed 30 sessions of LKM meditation. Each meditation session started with the participant sitting comfortably with a naturally straight back, with 3∼4 deep breaths taken. Then, the forehead was allowed to relax, along with the rest of the body. The sitting posture was Burmese-style posture (easy sitting posture) and sitting on a chair (see Figure 1B).

There were three separate conditions the participant performed (see Figure 2): pre-resting task, meditation (LKM), and post-resting task. Each session lasted for 10 min. In the resting tasks, the participant simply rested with his eyes closed while not engaging in any specific mental activity.

During the LKM task, the participant visualized himself with eyes closed and repeatedly radiated loving-kindness toward himself. Simultaneously, the participant silently recited the following set of phrases: "*May I be free from danger and hostility; May I be free from mental suffering; May I be free from physical suffering; May I be happy and well.,*" following the Theravada tradition. LKM practice is in line with the tradition in the book of *Visuddhimagga* (Ñāṇamoli, 1991; Buddhaghosa, 2020).

Post-LKM self-report

The post-LKM self-report assessment was a specially designed instrument to reflect the outcome of practicing loving-kindness meditation in the Theravada Buddhist tradition (Ñāṇamoli, 1991; Sraman, 2004; Bhaddanta Ācinna, 2012; Nyanatusita, 2021). Effectively measuring the progress of LKM practice. Overall progress during meditation was measured with scales which were in line with the awareness concepts of LKM.

With regard to psychological measures, it was important to record the participant's subjective experience with questions composed of psychological measurables. This post-LKM self-report questionnaire consisted of 7 items, including: Body-comfort; Mind-comfort; Body-movement; Radiating-LKM; Visualized-image (envision participant's self-image); Wandering-mind, and Fall-asleep (Thiradhammo, 2014; Anālayo, 2021) (see Supplementary material).

The participant recorded the quality level of each aspect during each task. These measures were used because they described common subjective experiences and obstacles that many LKM meditators experienced. The rating on each item used the Likert scale of 1–9, with 1–3 being "Not Good;" 4–6 being "Neutral;" 7–9 being "Good." The self-report score was the sum of the 7-item mentioned above in each trial.

PSS and LCS questionnaires

The effects of LKM were evaluated by comparing the stress level and loving-kindness compassion level. Data were collected at the beginning and the end of the whole experiment (see Figure 1C). The participant's stress level was estimated by the Perceived Stress Scale (PSS), which measured the perception of stress (Cohen et al., 1983). The Loving-kindness Compassion Scale (LCS) was used to evaluate three factors. They were self-compassion, loving-kindness and self-centeredness (Cho et al., 2018).

EEG processing

EEGLab was used to preprocess EEG and heart rate data during offline analysis. For the EEG analysis, the data was first

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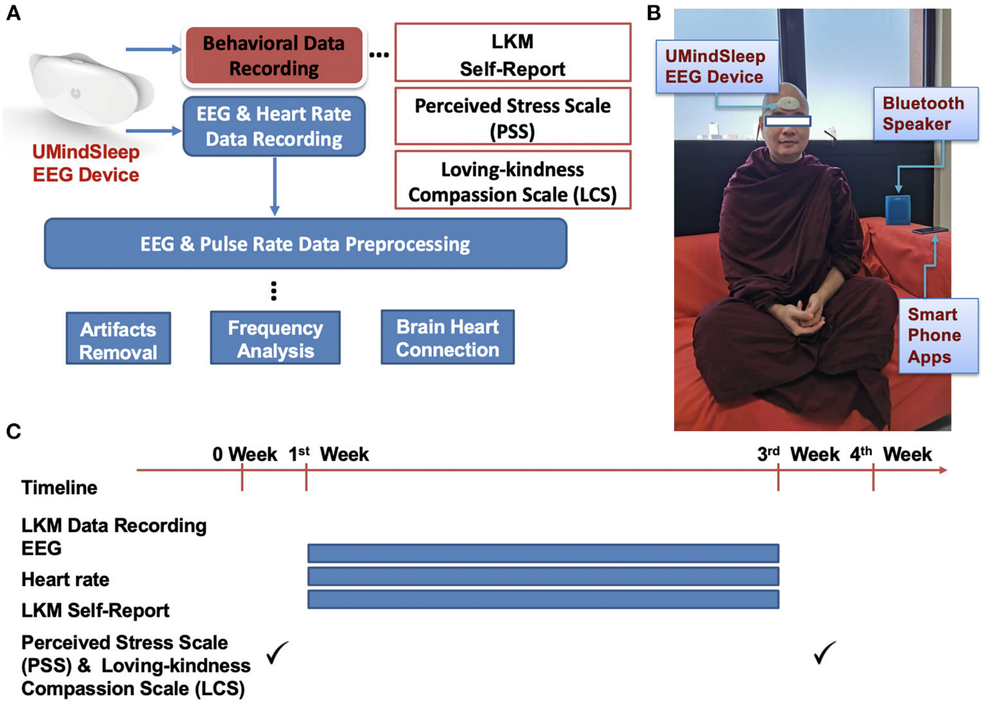

FIGURE 1
Illustration of data collection and analysis. **(A)** Experimental structure of data collecting. **(B)** A real experimental demonstration. **(C)** The experimental timeline lasted for 3 weeks. Self-report was collected in each session. Perceived Stress Scale (PSS) and Loving-kindness Compassion Scale (LCS) were collected before the first session and after the last session.

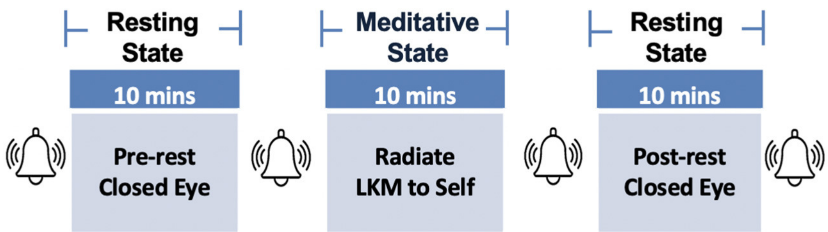

FIGURE 2
Experimental paradigm constructed of pre-resting, LKM, and post-resting state.

cleaned of artifacts. Major artifacts including head movement and ocular movement were removed manually. Generally, there were few artifacts as the meditation, pre- and post-LKM resting state were very stable. A notch filter of 50 Hz was used to reduce the contamination of power line interference. The sampling rate was kept at 250 Hz. No segmentation was performed during spectrum EEG analysis, and the whole session of EEG data was analyzed using a Fast Fourier Transform (FFT). The frequency powers were defined as delta (1–4 Hz), theta (4–7 Hz), alpha (8–10 Hz), beta (13–18 Hz), and gamma (25–32 Hz).

Statistical analysis

The self-assessment recorded the participants' performance quality in each conditional task. Data analysis for this self-report was interpreted by comparing responses in dyads. This included comparing Body-comfort with Body-movement; Mind-relaxation with Wandering-mind; Mind-relaxation with Radiating-LKM; Radiating LKM with Wandering-mind; and Radiating-LKM with Visualized-image. By looking at the data with multiple measures, we were able to get a better idea of the participant's inner experience.

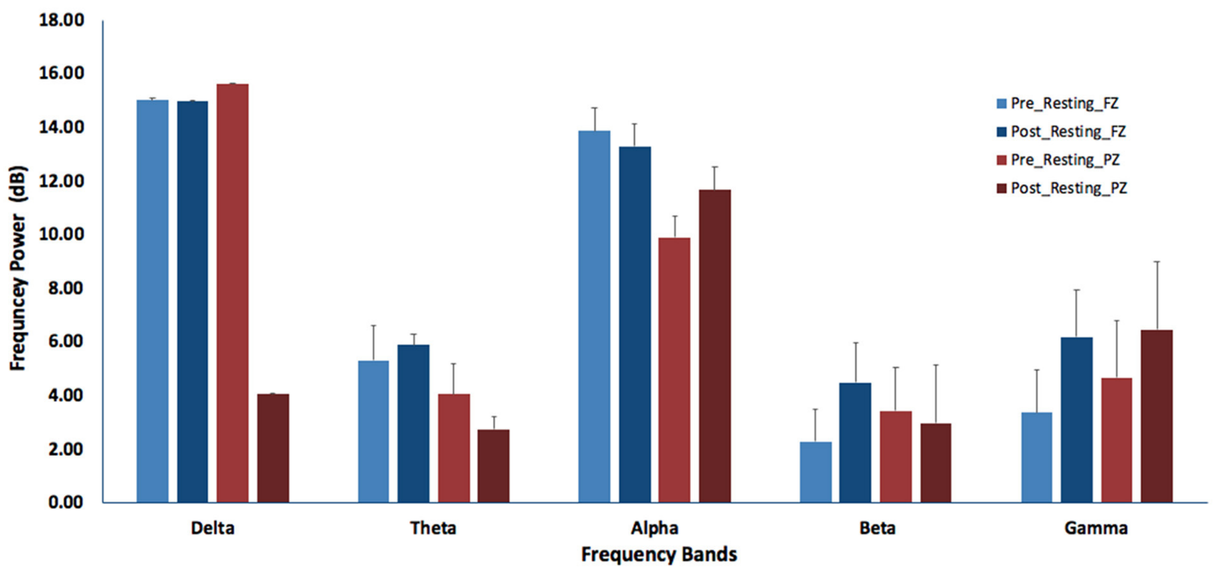

FIGURE 3
The band-powers of different EEG spectra before and after Loving-Kindness Meditation at Fz and Pz electrode placements.

Statistical analysis was performed using the IBM SPSS software (SPSS Inc., Chicago, Illinois, USA). For the EEG frequency power (delta, theta, alpha, beta, and gamma) component, repeated-measure analysis of variance, with time and component as within-subject factors, was used to assess the effects of LKM. Pearson's correlation analysis was used to calculate potential associations between EEG indexes (frequency power), pulse rate, and subjective assessment. The significance level for all statistical analyses was set at $p < 0.01$, adjusted by Bonferroni correction for five EEG spectrum bands.

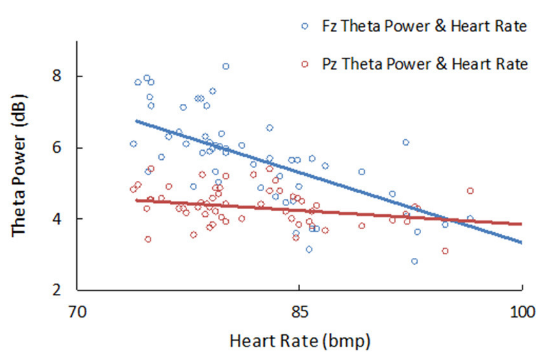

FIGURE 4
The significant correlation between heart rate and theta power at Fz ($r = -0.681$, $p < 0.001$) and Pz ($r = -0.349$, $p = 0.008$) during LKM task.

Results

The results showed that the difference of EEG power between the pre- and post-LKM resting-states were quite significant, with decreased power of Delta band ($t = 2.387$; $p = 0.024$), Alpha band ($t = 3.261$; $p = 0.003$), and increased power of Theta band ($t = -3.356$; $p = 0.002$), Beta band ($t = -6.311$; $p < 0.001$), and Gamma band ($t = -7.04$; $p < 0.001$) at Fz. For the parietal activity, the result at Pz showed decreased power in Delta band ($t = 3.682$; $p = 0.001$), Alpha band ($t = 4.478$; $p < 0.001$), and increased power in Theta band ($t = -5.199$; $p < 0.001$), Beta band ($t = -6.389$; $p < 0.001$), and Gamma band ($t = -5.8$; $p < 0.001$). Heart rate was significantly decreased from pre-resting to post-resting ($t = 4.092$, $p < 0.001$). The self-report score was significantly increased ($t = -5.215$, $t < 0.001$) (see Figure 3).

Pearson's correlational analysis showed that the heart rate was negatively correlated with theta power at both the frontal placement of Fz and the parietal lobe placement of Pz during pre- and post-resting states, with r = -0.681, $p < 0.001$, and $r = -0.384$, $p = 0.008$, respectively (see Figure 4). At the same time, heart rate was also negatively correlated with alpha power at Fz, $r = -0.363$, $p = 0.004$; and positively correlated with delta power at Fz, $r = 0.461$, $p < 0.001$. Spearman correlation analysis showed a positive correlation between theta power at Fz and the self-designed report score ($r = 0.580$, $p < 0.01$).

There were also significant correlations between Fz theta power and the overall quality of the behavioral assessment of LKM ($r = 0.601$, $p < 0.001$). The overall quality of the behavioral assessment was negatively correlated with heart rate

($r = -0.401$, $p < 0.001$). Interestingly, the alpha band near the frontal lobe at Fz was also correlated with the overall quality of LKM as measured by behavioral assessment ($r = 0.277$, $p = 0.008$).

Perceived Stress Scale (PSS) and Loving-kindness Compassion Scale (LCS) were collected before the first session and after the last session. The results showed that the participant's stress level had slightly decreased (PSS decreased by 3 points), and the Loving-kindness Compassion level increased (LCS increased by 7 points). The PSS score decreased from 25 to 22 indicating stress reduction for the participant. LCS total score increased from 53 to 60 for the participant. All three factors in LCS increased slightly (LCS-Lovingkindness: from 15 to 19; LCS-compassion: from 15 to 20; LCS-Self-centeredness: from 13 to 21).

Discussion

This pilot study explored the effect of LKM on brain activities and potential brain-heart coherence using wearable devices. In line with the previous study (Jiang et al., 2020), our results revealed that LKM practice has a widespread effect on both the brain and the body.

Among a variety of significant findings in this experienced meditator, theta power was the most sensitive index for LKM training. LKM practice can cultivate a positive attitude which can improve emotion regulation and self-motivation, as revealed by an fMRI study (Kyeong et al., 2017). This fMRI study also demonstrated that LKM can modulate resting-state functional connectivity between the amygdala with the right dorsomedial prefrontal cortex and the left dorsal anterior cingulate cortex. These functional connectivities are correlated with anxiety and depression scales (Kyeong et al., 2017). We suggest that an increased theta power contributes to the cognitive rehearsal of radiating love-kindness to oneself, as theta is synchronized across multiple brain areas during complex cognitive tasks (Ekstrom et al., 2005). These results are in line with other studies on LKM that have found increased theta oscillations during meditation and a positive correlation of theta power with the amount of experience in meditation training (Harne and Hiwale, 2018; Nyhus et al., 2019).

Secondly, we explored the potential body-mind connection, as is much emphasized in traditional Buddhism meditation. We found theta power to be significantly correlated with heart rate. The connection between cerebral and cardiac activities during LKM was also found in a previous fMRI study (Lutz et al., 2009). In that study, a positive coupling of dorsal ACC activity and heart rate was higher during LKM than during the neutral state. This state effect of LKM on brain-heart coupling was stronger for experts than beginners, especially in the right inferior parietal lobe and somatosensory area. This study further suggested that LKM practice can enhance awareness and somatosensory representation of emotion (Lutz et al., 2009).

Thirdly, we found theta power to be significantly correlated with behavioral assessments, which record the quality of mind and body situation during LKM practice. This indicates that the post-LKM self-report could be served as criterion validity of LKM training. A credible subjective report is important in monitoring the progress of LKM practice, because different LKM teachers may have various understandings of LKM techniques, which leads to students having various understandings. Thus, it is difficult to set common standards to assess effectiveness and progress during LKM practice. In the current study, we simplify the behavioral assessment through objective estimations of the quality of both body and mind conditions with two opposing questions: (i.e., comfort and uneasiness). For the body part, an experienced meditator could sit comfortably without much body movement. Moreover, a good LKM meditator can concentrate on LKM by visualizing and radiating love-kindness toward a specific target, without much mind wandering. The mind and body are both comfortable in LKM practice for the experienced meditator. This comfort of mind and body is also referred to as passaddhi in Pali and sometimes translated as calmness or tranquility. It is a key indicator for deeper meditation, according to traditional Buddhism meditation documents (Ñāṇamoli, 1991).

The significant correlation between frontal theta and behavioral scores gives some credit to this simplified behavioral assessment tool as a good estimate of LKM practice. The correlation between frontal brain activity with behavioral scales, is also found in previous studies (Lee et al., 2013; Kyeong et al., 2017), indicating frontal activity plays a key role in relevant behavioral assessments (Hoy et al., 2022; Sriranjan et al., 2022). Interestingly, a recent EEG study also found the religious coping scale to be positively correlated with theta in the right inferior frontal and temporal gyri (Imperatori et al., 2020).

Theta plays an important role in dynamic interactions between different lobes, and this interaction can be modulated by experience and mental training. For example, theta amplitude in frontal-temporal network connectivity is negatively correlated with the duration of meditation experience in a previous study (Jiang et al., 2020). It is further suggested that meditation can alter cortical plasticity in terms of intrinsic reorganization and activity of brain networks. Among the neural plasticity after meditation training, neural representations of visceral activity, especially cardiac activity can be integrated into higher cortical regions associated with cognition and emotion (Jiang et al., 2020).

This study's uniqueness is due to the involvement of subjective assessments on the quality of LKM. This is usually omitted by other research on meditation or mindfulness, as the participants may not know how to assess the quality of meditation. Interestingly, these subjective assessments were strongly correlated with the objective assessments, specifically the theta power. This approach of understanding the subjective data along with the objective data is important for studying LKM, as this meditation in particular, includes the mind and body (mind and heart). This unique finding on EEG, heart rate, and subjective assessments may also help explore neural biomarkers for LKM.

From the Theravada Buddhist perspective, loving-kindness (mettā) tends to proactively follow a positive aspect. It is a positive feeling of kindness and warmth for oneself and sharing with others (Sayadaw et al., 2003; Sayadaw, 2019). On the contrary, compassion (karunā) is more on the passive side. That is, the practitioners tend to perceive people's suffering and want to help them to deal with their adversity (Ñāṇamoli, 1991; Sraman, 2004; Buddhaghosa, 2020). To be more precise, compassion can be defined as perceiving the sufferings of people and being motivated to help (Dahl et al., 2016). Compassion consists of two components which are affective and motivational aspects. In the affective aspect, it involves emotional contagion that induces empathy such as empathic distress and compassion (Singer and Klimecki, 2014; Dahl et al., 2016).

Neff pointed out that self-compassion is related to personal experiences of suffering (Neff, 2003a,b). These sufferings were, for example, encountering failures, inadequacies and pains of life. Self-compassion involves three reactions when painful thoughts and emotions arise. They were a sense of common humanity vs. isolation; mindfulness vs. over-identification; and self-kindness vs. self-judgment. Self-kindness tended to be caring and understanding with oneself (Neff, 2003a,b). When facing unhappiness or dislike, they responded positively with good and supportive words (Neff, 2003a,b). Nevertheless, there is an overlap between LKM and compassion, and compassion arises when one practices loving-kindness meditation (Ñāṇamoli, 1991; Buddhaghosa, 2020). Indeed, the development of these mental states are to reach boundless and further research into the neural mechanisms are open to be explored (Cho et al., 2018; Sirotina and Shchebetenko, 2020; Somaratne, 2022).

This study also demonstrated that a wearable EEG device could be a convenient way to collect neurophysiological data, especially during meditation. The feasibility of EEG devices is vital for meditation data collection, given the nature of meditation. This is in contrast to the time-consuming set-up process and less-comfortable electrical caps of multi-channel EEG, which may affect the comfortability and, subsequently, the quality of meditation training. The advances in neurophysiological technology may finally allow researchers to start exploring more feasible biomarkers associated with ancient meditation techniques due to accumulating data. EEG research with high-density EEG can more accurately illustrate brain activities during meditation, and we have also collected a set of high-density EEG data of LKM. Nonetheless, due to the large variation of meditation methods and different features of neuroimaging technologies, it is important to have a more convenient way to collect bigger datasets, together with subjective assessments of both body and mind, in order to better monitor the neural dynamics of meditation. Our results may imply that the theta frequency and its correlation with cardiac activity could potentially be a neural biomarker during LKM practice.

There are several limitations worth noting in the current study. First, since there was only one experienced LKM meditator, the results lack duplicate detection and therefore further implications of the study are limited. Another limitation is that the wearable EEG device is susceptible to artifacts of body movement, ocular activity and potentially other environmental influences. These artifacts are not easily removed with single-channel EEG data, as traditional algorithms such as independent component analysis (ICA) cannot be applied to single-channel EEG data. Independent component analysis (ICA) together with singular spectrum analysis (SSA) may help with artifact suppression in one-channel EEG data.

Conclusion

In summary, this study found that LKM can significantly modulate brain activities before and after meditation for a long-term practitioner. More importantly, EEG changes after LKM, in theta power were found to be significantly correlated with the physiological change of heart rate, along with the subjective assessments. These results indicate that the theta band and its correlation with heart rate are sensitive to the effect of LKM meditation. In the future, groups of long-term meditators, as well as laymen with high-density EEG could be recruited to validate the current findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Human Research Ethics Committee (HREC) of the University of Hong Kong (No. EA210145). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

GW was involved in collecting data and methodology design and writing. RS provided software program and data analysis. JA helped writing and proofreading. KY helped proofreading. SY helped on device technique support and data analysis. JG methodology helped on design and writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author SY was employed by Shenzhen EEGSmart Technology Co., Ltd. KY studied at The Buddha Dharma Centre of HK.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2022.891377/full#supplementary-material

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Interoceptive awareness: MBSR training alters information processing of salience network

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Mindfulness refers to a mental state of awareness of internal experience without judgment. Studies have suggested that each mindfulness practice may involve a unique mental state, but the underlying neurophysiological mechanisms remain unknown. Here we examined how distinct mindfulness practices after mindfulness-based intervention alter brain functionality. Specifically, we investigated the functional alterations of the salience network (SN) using functional magnetic resonance imaging (fMRI) among the two interoceptive mindfulness practices—breathing and body scan—associated with interoceptive awareness in fixed attention and shifted attention, respectively. Long-distance functional connectivity (FC) and regional homogeneity (ReHo) approaches were applied to measure distant and local neural information processing across various mental states. We hypothesized that mindful breathing and body scan would yield a unique information processing pattern in terms of long-range and local functional connectivity (FC). A total of 18 meditation-naïve participants were enrolled in an 8-week mindfulness-based stress reduction (MBSR) program alongside a waitlist control group (n = 14), with both groups undergoing multiple fMRI sessions during breathing, body scan and resting state for comparison. We demonstrated that two mindfulness practices affect both the long-distance FC_{SN} and the local ReHo, only apparent after the MBSR program. Three functional distinctions between the mindfulness practices and the resting state are noted: (1) distant SN connectivity to occipital regions increased during the breathing practice (fixed attention), whereas the SN increased connection with the frontal/central gyri during the body scan (shifting attention); (2) local ReHo increased only in the parietal lobe during the body scan (shifting attention); (3) distant and local connections turned into a positive correlation only during the mindfulness practices after the MBSR training, indicating a global enhancement of the SN information processing during mindfulness practices. Though with limited sample size, the functional specificity of mindfulness practices offers a potential research direction on neuroimaging of mindfulness, awaiting further studies for verification.

KEYWORDS

mindfulness, mindfulness-based stress reduction (MBSR), functional magnetic resonance imaging (fMRI), functional connectivity, regional homogeneity, interoceptive awareness, salience network

1. Introduction

Mindfulness refers to a mental state of awareness of internal and external experiences without judgment (Kabat-Zinn, 1994). Mindfulness-based stress reduction (MBSR) is the most widely studied form of mindfulness-based intervention. MBSR was designed to enhance a mindfulness practitioner's abilities to retain awareness in the present, interpret intra- and interpersonal situations with clarity, and respond appropriately to adversity (Santorelli et al., 2017). Numerous studies have reported the benefits of MBSR, such as reduced anxiety and depression, enhanced emotional regulation, alleviation of sleep disturbances, improved quality of life, and even postponed dementia onset among mindfulness practitioners (Davidson et al., 2003; Goldin and Gross, 2010; Larouche et al., 2015; Huang et al., 2019).

Using functional magnetic resonance imaging (fMRI), recent meta-analysis disclosed that mindfulness trainings alter the brain connectivity of multiple brain networks, associated with the cognitive performances of attention control, pain relief and emotion regulation (Sezer et al., 2022). These beneficial outcomes and brain-network changes after the mindfulness training may originate from the "being mode" mindset (i.e., non-attachment, non-striving, and an accepting attitude) and the persistent practice of core techniques during the 8-week MBSR program, including breathing, body scan, yoga, loving-kindness, sitting meditation, and open monitoring (Kabat-Zinn, 1990, 2003). Although these elementary mindfulness practices are not usually differentiated from the entirety of MBSR package, studies have demonstrated that mindfulness practices may involve a certain level of cognition and underlying peripheral nervous system. For example, Lumma et al. demonstrated that both the increase in heart rate and the reduction in high-frequency heart rate variability (HRV) reported after meditation training are more prominent after loving-kindness than after breathing practice (Lumma et al., 2015). Kok et al. compared the state changes recorded through self-assessed psychological measures after presence (breathing and body scan), loving-kindness, and observing-thoughts meditation, concluding that each technique is characterized by its own distinct short-term psychological fingerprint (Kok and Singer, 2017). From the viewpoint of brain functions, Brewer et al. demonstrated the elevated connectivity between dorsal anterior cingulate cortex (dACC) and posterior cingulate cortex (PCC) only occurred in the choiceless awareness, rather than concentration or loving-kindness meditations, among long-term meditators (Brewer et al., 2011), implying the distinction of goal-directed attention levels among different mindfulness practices. Moreover, Fujino et al. reported reduced ventral-striatum connectivity during the open monitoring meditation but increased connectivity in the same regions during the focused attention meditation (Fujino et al., 2018), inferring the reduced habitual behavior and enhanced memory function during the open-monitoring meditation. At the current stage, the neurophysiological specificity of distinctive mindfulness practices remains largely unknown. Therefore, identifying the discrepancies in the brain-network organizations yielded by distinct mindfulness practices can provide further insights into how mindfulness-based intervention shapes brain functionality and alters behaviors.

To achieve this goal, we determined to investigate the two fundamental mindfulness practices—the mindful breathing and the body scan. These two practices typically require the use of interoceptive awareness with increased vagal tone (Gerritsen and Band, 2018). By placing attention on bodily sensations, these practices help to anchor the mind in the present moment, thereby facilitating relaxation without entanglement in affective ruminations (Gibson, 2019). Although these two practices are classified within the same broad category, each has its own unique features. Breathing meditation entails fixed attention on the bodily sensations associated with breathing (e.g., the passage of airflow through the nostrils, contraction of the abdomen), whereas during the body scan practice, participants are instructed to shift their attention toward certain body parts sequentially (Malinowski, 2013; Gibson, 2019). In subjective reports, some meditation participants prefer the body scan practice to breathing because it is less monotonous and thus relaxing, whereas others express a preference for breathing precisely because of its emphasis on a single target for interoceptive awareness without the need to constantly shift attention to other objects. The distinct features and subjective evaluations of adaptive interoceptive attentional styles observed between breathing mediation and body scan lead to the speculation that these two mindfulness practices would involve in distributed but dissociable neurocognitive mechanisms (Tomasino and Fabbro, 2016; Gibson, 2019). In our previous work with objective measures, we conducted electroencephalography (EEG) recordings in both practices (breathing and body scan) before and after the MBSR program, and the results indicated reduced EEG Delta power during the breathing but not the body scan (Ng et al., 2021), suggesting a higher vigilance level in the breathing practice among novice practitioners. Accordingly, we speculate that even in individuals with similar levels of attention and introspection, different mindfulness strategies (breathing and body scan) can lead to distinctive brain-connectivity patterns.

The resting-state functional connectivity (FC) is the neuroimaging technique to extract the spatiotemporal features of spontaneous synchronizations without external stimuli (Biswal et al., 1995), and the long-distance FC elucidate neural information processing across various mental states (Haase et al., 2015; Jao et al., 2016). To understand the neural circuitry underlying mindfulness, the FC approach has been widely applied to topics ranging from the mindfulness trait (Parkinson et al., 2019) and mindfulness intervention (Doll et al., 2015; Huang et al., 2020) to clinical pathologies (Zhao et al., 2019; Fam et al., 2020). For example, Kral et al. demonstrated that FC between the PCC and the dorsolateral prefrontal cortex (DLPFC) continually increased, even after the 8 weeks of MBSR program (Kral et al., 2019), which implies a plausible neuroimaging indication of altered thought processes in a wandering mind. However, most of the FC studies examined temporal correlations among brain regions distant away from each other, but the local information processing in brain (i.e., neural communications within a 2–10 mm radius), in which interneurons are clustered and exhibit a common resonance mode (Gray, 1999), has often been overlooked. To this viewpoint, we further hypothesize that the two mindfulness practices, breathing and body scan, may display different information processing patterns in terms of long-range and local connectivity. To account for the FC in both distant and local spatial scales, this study adopted an additional functional index of regional homogeneity (ReHo). ReHo is a measurement of intraregional communication within a set of nearest-neighbor voxels, reflecting local synchronizations or local connectivity of brain spontaneous activities (Zang et al., 2004). Previous studies found the positive correlation between ReHo and glucose metabolism (Nugent et al., 2014; Aiello et al., 2015), and investigators commonly used ReHo to evaluate brain functions in clinical cases, such as depression or migraine (Iwabuchi et al., 2015; Cui et al., 2022; Lin et al., 2022). Recently, we analyzed the local and distant connectivity (ReHo and FC, respectively) simultaneously across different sleep stages, and the observations of increased ReHo and declined FC during the sleep stage 2 indicated the altered brain functionality toward local processing, rather than long-distance communications in wakefulness (Kung et al., 2021). Therefore, we hypothesized that the information processing pattern, regarding both local and distant connectivity at the same time, changes during mindfulness practices and/or after training. To date, only four studies have utilized the ReHo index to evaluate the brain functional changes in mindfulness programs (Kong et al., 2015; Yang et al., 2016; Xiao et al., 2019; Zhao et al., 2019). Two out of the four studies based on mindfulness interventions indicated the declined ReHo in the dorsal anterior cingulate cortex (dACC) and the increased ReHo in the right superior parietal lobule after the 8-week MBSR program (Xiao et al., 2019; Zhao et al., 2019), demonstrating the possibility of changed local connectivity after the mindfulness training. Additionally, Yang et al. reported non-significant ReHo changes after a 40-day mindfulness program (Yang et al., 2016). Because of the inconsistency in the results of these ReHo studies, it is unclear whether mindfulness practices modulate the local connectivity, along with the distant connectivity at the same time (the underlying information processing). To test the brain-network reorganization in mindfulness, we postulated three possible scenarios: (1) both FC and ReHo increase, indicating an overall enhancement of information processing irrelevant of spatial scales; (2) FC increases, but ReHo remains the same, implying an enhancement of long-distance communication alone (between-network connectivity); and (3) FC increase, but ReHo decreases, signifying a shift in resource allocation from local to distant information processing. By examining FC at both the local and distant levels, the differences in brain information processing can be identified between the normal resting state and the mindfulness practices.

We examined the distinct functional characteristics of different mindfulness practices, and the longitudinal training effect (before and after the MBSR program). Hence, a pre- and post-MBSR-intervention design was implemented to investigate the brain functionality post mindfulness training, and to account for the possibility that meditation-naïve participants may be unable to differentiate between breathing and body scan practices. Regarding the network specificity of FC, studies have indicated that interoceptive awareness (breathing and body scan) is associated with the salience network (SN), especially on dACC and insula (Singer et al., 2004; Sevinc et al., 2018; Gibson, 2019).

2. Materials and methods

2.1. Participants

A total of 33 healthy Taiwanese adults, aged 28–68 years, participated in this study. Candidates with prior meditation experiences, or with a history of cardiovascular diseases, terminal illness, or surgery involving metallic implants, were excluded from the cohort. The cohort was randomly divided into an MBSR group (MBSR; n = 18) and a waitlist control group (CTRL). One CTRL group participant was unable to attend the second data collection session and was thus excluded from the final analysis (n = 14). Prior to the experiment, written informed consents was obtained from each participant, and the study protocol was approved by the Joint Internal Review Board of Taipei Medical University (N201905049).

2.2. Intervention: MBSR and CTRL

Each participant completed questionnaires and MRI experiments twice. The first data collection session was regarded as the baseline (PRE), and the second data collection session was held 8 weeks later (POST). The MBSR group was enrolled in an 8-week MBSR training program (Kabat-Zinn, 1994; Santorelli et al., 2017). The MBSR course was taught by a licensed MBSR instructor. The classes schedule consisted of eight 2.5-h weekly classes in addition to a single day-long mindfulness workshop. These weekly classes involved the development of several mindfulness-related skills, dialogue, reflection on the home-based mindfulness practice, and formal practice sessions. The participants were assigned daily home-based mindfulness practices, which comprised both formal and informal meditation activities. The formal activities included body scan, mindful breathing, sitting meditation, mindful yoga, walking meditation, mountain or lake meditation, and loving kindness, required 45 min to complete each day. The participants were required to complete a practice and information sheet. The CTRL group was instructed to continue their usual life activities but not engaged in any mindfulness-related activities (including religious activities) during the 8 weeks. After the POST experiment, the CTRL group received an additional MBSR program as compensation.

2.3. Experimental procedure

The participants completed three questionnaires: (1) the Five Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2006); (2) the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004); (3) the Pittsburg Sleep Quality Index (PSQI) (Buysse et al., 1989). An fMRI protocol was performed using a 3-T PRISMA scanner (Siemens, Erlangen, Germany) at National Taiwan University. Structural images were obtained using a high-resolution magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (repetition time [TR] = 2,000 ms; echo time [TE] = 2.28 ms; flip angle [FA] = 8°; image dimensions: 192 × 256 × 256; voxel resolution: 1 × 1 × 1 mm^3). Functional images were obtained using a gradient-echo echo-planer imaging (GE-EPI) sequence (TR: 2,000 ms; TE: 32 ms; FA: 77°; image dimensions: 64 × 64 × 33; voxel dimensions: 3.4 × 3.4 × 3.4 mm^3). The scanning session consisted of one T_1-weighted anatomical scan, followed by three functional scans. During the resting-state (*Resting*) scan (5 min, 150 measurements), the participants were instructed to lie still with their eyes closed, not to fall into sleep, not dwell on one singular train of thoughts, and not to perform any mindfulness practices. Then, another 5-min (150 measurements) mindful breathing (*Breath*) was conducted, during which the participants were asked to lay still with their eyes closed, and to focus on the sensation of the breath passing through the nostrils and the philtrum areas. Finally, a 5-min (150 measurements) body scan practice (*BodyScan*), was performed, during which the participants were instructed to lie still with eyes closed but to this time focus on bodily sensations they were felt and remained aware of these sensations without analysis or judgements to them. The data of this study will be available on request from the corresponding author.

2.4. fMRI analysis

Functional imaging data pre-processing was performed using IClinfMRI (Hsu et al., 2018) in MATLAB R2014b (Mathworks Inc., Natick, MA) and analysis of functional neuroimaging (AFNI) (Cox, 1996). The procedure involved slice-timing correction, alignment with the anatomical T_1-weighted image, head motion correction (censoring criteria: maximum displacement of > 3 mm or delta displacement > 0.5 mm, and the maximum volume number above the criteria was 21), de-spiking, linear detrending, nuisance regression (the used regressors included motion parameters, white matter and cerebrospinal fluid), bandpass filtering with a range of 0.01–0.08 Hz, spatial smoothing (Gaussian kernel: FWHM = 4 mm), and spatial normalization to the standard Montreal Neurological Institute (MNI)-152 template (voxel size: 2 mm^3 × 2 mm^3 × 2 mm^3). The fMRI data of two participants (both in MBSR:PRE) in the *Breath* session were neglected from further analysis, one because of equipment malfunctioning on the day of scanning, and the other because of excessive head motion. Voxel-wise seed-based correlation analysis (seeding with 4-mm radius) was employed to quantify the FC strengths of the SN. In the SN, the seed locations were prescribed from the bilateral dorsal anterior cingulate cortex (dACC, MNI: ± 6, 18, 28) (van der Werff et al., 2013), and the bilateral anterior insula (MNI: ± 38, 26, −5) (Goveas et al., 2013). The voxel-wise correlation between the seeds and the whole brain were calculated using Fisher's Z transformation to standardize them for further statistical analysis. Regarding the local connectivity of ReHo, Kendall's coefficient of concordance (KCC), a measurement of the correlation between each voxel and its 93 neighboring voxels (radius = 2.9 mm) over the time course, was calculated with 3dReHo in AFNI (Taylor and Saad, 2013). Finally, an MNI template was applied as the regional mask to generate a standardized image of the entire brain for statistical analysis.

2.5. Statistical analysis

Statistical analysis was performed using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, CA, United States), and the significance level was set as $p < 0.05$ with multiple comparison of the false-discovery-rate (FDR) method. Questionnaire scores (FFMQ, DERS and PSQI) were analyzed with a 2-way mixed Analysis of Variance (group × time), followed by *post hoc* tests with FDR correction. For the fMRI indices, POST–PRE paired comparisons of FC and ReHo were performed based on Threshold Free Cluster Enhancement (TFCE: 5000 permutations) (Smith and Nichols, 2009) for both MBSR and CTRL groups using the FSL randomise (Winkler et al., 2014). From TFCE results, we prescribed multiple regions of interest (ROIs) from the nearest Yeo brain template (400 parcellations, noted as Yeo_{400}) to extract FC and ReHo values for ROI analysis (Yeo et al., 2011; Schaefer et al., 2017). Subsequently, we performed the same 2-way mixed ANOVA (group × time) and *post hoc* tests with FDR correction. To unveil the time/training effect in the MBSR group, an additional one-way repeated-measure ANOVA (rm-ANOVA) with FDR correction was also applied to the POST-PRE differences of connectivity indices (ΔFC and ΔReHo) across the 3 conditions. At last, Pearson correlation analysis was used for two evaluations: (1) [time effect] to calculate the correlation between the POST–PRE changes of questionnaire scores (ΔFFMQ and its five sub-scales, ΔDERS, and ΔPSQI) and the those of functional indices (ΔFC and ΔReHo); and (2): [practice effect] to estimate whether the correlations between FC and ReHo (the hypothetical information processing) would change across the three conditions (*Resting, Breath* and *BodyScan*), before and after the training in the MBSR group.

3. Results

No significant differences in age, sex, or educational level were noted between the MBSR and CTRL groups (**Table 1**). Regarding a potential MBSR training effect, **Table 2** presents that significant group × time interactions were found in FFMQ ($F_{1,30}$ = 13.28, p = 0.001) and DERS ($F_{1,30}$ = 4.12, p = 0.05), but PSQI only exhibited significant time effect ($F_{1,30}$ = 4.88, p = 0.035) without interaction. The *post hoc* tests exhibited that significance POST-PRE differences in the MBSR group, but not in the CTRL group. In the MBSR group, all participants exhibited significantly higher FFMQ scores (t_{17} = 5.32, $p < 0.001$), in each of the five dimensions (i.e., observing, describing, acting with awareness, non-judgment, and non-reaction) in the post-MBSR assessments (compared with PRE). The MBSR group members exhibited significant decreases in

DERS (t_{17} = 2.48, p = 0.047), indicating improvements in emotional regulation. By contrast, in the CTRL group, no such changes in questionnaire scores between the PRE and POST data collection sessions were noted.

Figure 1 shows the SN-related FC maps exhibiting significant POST–PRE differences across the *Breath* and *BodyScan* conditions (TFCE, *FDR-corrected* $p < 0.05$), and the significant FC changes were only observed in the MBSR group, not in the CTRL group. During the *Breath* practice, the seed dACC yielded increased FC in the bilateral occipital regions, including the bilateral fusiform, lingual gyri, and the ROI findings were presented in Figure 2A (Yeo_{400} 2/3/4/202/203/204, group × time interaction: $F_{1,30}$ = 0.08, p = 0.776; rm-ANOVA across POST-PRE changes of ΔFC_{Rest}, ΔFC_{Breath}, $\Delta FC_{BodyScan}$: $F_{2,30}$ = 2.53, p = 0.096). During the *BodyScan* practice, the left middle frontal gyrus (lMFG) exhibited increased FC with the bilateral dACC (Figure 2B: Yeo_{400} 181, group × time interaction: $F_{1,30}$ = 4.30, p = 0.012; rm-ANOVA: $F_{2,30}$ = 4.91, p = 0.014). With seeding at bilateral anterior insula, the SN exhibited increased FC with the sensorimotor network (SMN) during *BodyScan* after training (Figure 2C: Yeo_{400} 33/34/35/230/231/232/233, group × time interaction: $F_{1,30}$ = 3.21, p = 0.08; rm-ANOVA: $F_{2,30}$ = 3.41, p = 0.046). An increased FC of the SN-related regions was noted during the mindfulness practices (the third column of Figure 2), and such FC increase was not apparent when participants were in the resting state. Regards with ReHo, the right angular gyrus and superior parietal lobe (Yeo_{400} 268/269/270) exhibited POST-PRE difference in the MBSR group during the *BodyScan* (Figures 3A, B), but it did not show significant group × time interaction (Figure 3C, $F_{1,30}$ = 2.14, p = 0.15, with rm-ANOVA: $F_{2,30}$ = 0.33, p = 0.72, Figure 3D). In general, the results for both FC and ReHo suggest increased long-distance connectivity and mostly unchanged local connectivity after the MBSR training.

To demonstrate the time effect, we estimate the association between questionnaire score changes and connectivity changes (ΔFC and ΔReHo). In the *Breath* condition, $\Delta FC_{dACC-occipital}$ (Figure 2A) and $\Delta ReHo_{angular}$ (Figure 3B) both exhibited positive correlation with ΔObserve (r = 0.49, p = 0.005; and r = 0.50, p = 0.005, respectively). In the *BodyScan* condition, $\Delta FC_{Insula-SMN}$ (Figure 2C) exhibited positive correlation with ΔObserve (r = 0.40, p = 0.025), and $\Delta ReHo_{lMFG}$ exhibited negative correlation with ΔDERS (r = –0.39, p = 0.028) and ΔPSQI (r = –0.38, p = 0.032). To demonstrate the practice effect across the 3 conditions, Figure 4 illustrates scatter plots between FC and ReHo of the specific region lMFG in the MBSR group, which highlights the relationships between distant and local connectivity during the mindfulness practices. Before the MBSR training (Figure 4A), FC and ReHo only presented non-significant correlations across the 3 conditions ($r < 0.3$, $p > 0.05$); however, after the MBSR training (Figure 4B), the $FC_{dACC-lMFG}$ presented positive correlation with ReHo in both *Breathing* (r = 0.68, p = 0.002) and *BodyScan* (r = 0.51, p = 0.029), but not in the resting state (r = –0.15, p = 0.56).

TABLE 1 Demographics.

	MBSR	CTRL	Statistical analysis
Sample size	18	14	
Sex (F/M)	17/1	11/3	$p = 0.465$ ($\chi_1^2 = 0.533$, n.s.)
Age (years)	47.50 (9.6)	45.87 (8.1)	$p = 0.604$ ($t_{31} = 0.524$, n.s.)
Education (years)	16.89 (2.0)	17.60 (2.5)	$p = 0.377$ ($t_{31} = 0.897$, n.s.)

Mean (standard deviation). *$p < 0.05$. n.s.: non-significant.

4. Discussion

Most studies employing mindfulness-based interventions have focused on overall changes in participants' subjective perceptions and objective neurophysiology or immunology (Black and Slavich, 2017), and few have identified the brain functional differences across different mindfulness practices (Lumma et al., 2015; Kok and Singer, 2017); However, each mindfulness practice yields differential psychological characteristics and changes in brain function. Therefore, this study investigated the differences among resting, breathing and body scan states in terms of brain connectivity. The results of both the questionnaires and brain FC indices suggested that the practices of *breathing* and *body scan* over the 8-week MBSR program allowed the participants to hone their interoceptive awareness. In the questionnaire results, the increased FFMQ scores indicated enhanced mindfulness level, and the reduction in DERS and PSQI scores indicated improvements in emotional regulation and sleep quality. The FC indices (both FC and ReHo) effectively reflected the effects of the mindfulness training as well. Specifically, the SN-FC linked to different brain regions between breathing and body scan, which was particularly pronounced after the MBSR program (Figure 1). In the traditional mindfulness training, the mindful breathing involves the single-point fixated attention to the exhalation/inhalation, either on the nostrils or abdomen, without shifting the target. Body scan, in contrast, involves the continuous attention shift on the physical sensation, from one body part and to the next. Both of them require the attention on the body sensations, but the distinction between breathing and body scan might be from the attention shift in the body scan, which might be the reason that the more engagement between SN and the lMFG (part of DLPFC) in the body scan, instead of the breathing. We also compared the association between FC and ReHo and identified the underlying information processing patterns of the resting state and the two mindfulness practices. After the MBSR program, the elevated FC and the sustained ReHo were observed during both breathing and body scan compared to the resting state, indicating increased distant connectivity along with maintenance of local connectivity. This result supports the conjecture that a focus on mindfulness task coincides with an increase in long-distance communications (especially on between-network connectivity) without sacrificing the local communications (Figures 2, 3). After the MBSR training, the stronger correlation between FC and ReHo at the body scan compared with at the resting state (Figures 3, 4) indicates that the body scan exercises the SN into an alternative information processing pattern. To assess the time/training effect, we found that the altered FC or ReHo were significantly associated with the score changes of Observe, implying that the elevated connectivity, in certain brain regions, contributed to the interoceptive perception and emotion regulation. Although both mindfulness practices are based on interoceptive awareness, the emphasis enhances both long-distance and local information connectivity in the on specific

TABLE 2 Intervention effects of questionnaire scores between MBSR and CTRL groups.

Questionnaire	MBSR		CTRL		Group × Time interaction	
	Pre-test	Post-test	Pre-test	Post-test	*F*	*p*
FFMQ	114.90 (16.9)	142.60 (23.2)	116.60 (17.1)	115.90 (15.2)	13.3	0.001**
(a) Observe	23.28 (4.7)	30.22 (4.9)	23.71 (4.9)	24.93 (3.9)	11.3	0.002**
(b) Describe	22.94 (5.5)	26.22 (7.1)	24.21 (4.7)	24.07 (4.6)	5.6	0.025*
(c) Act with Awareness	25.11 (4.7)	29.89 (6.4)	26.07 (5.3)	24.50 (6.0)	8.7	0.006**
(d) Non-judge	23.94 (5.3)	32.33 (5.8)	22.64 (4.7)	22.79 (6.1)	15.2	<0.001***
(e) Non-react	19.67 (3.6)	23.89 (5.3)	19.93 (4.4)	19.64 (3.1)	8.8	0.006**
DERS	97.78 (20.7)	84.72 (23.2)	95.50 (23.2)	99.93 (16.1)	4.1	0.05*
PSQI	8.39 (3.9)	6.11 (3.8)	5.57 (2.9)	5.00 (2.8)	1.8	$0.196^{n.s.}$

Mean (standard deviation). *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$. n.s.: non-significant.

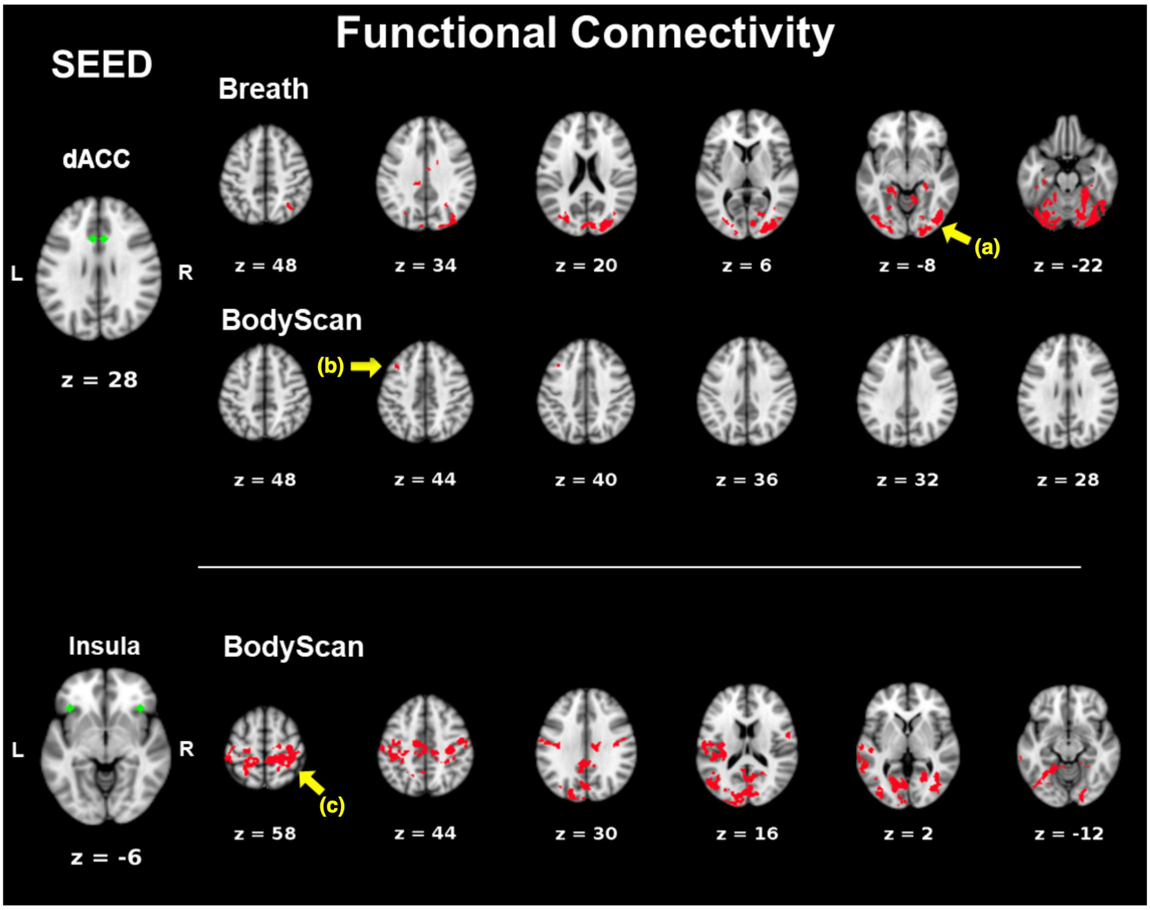

FIGURE 1
POST–PRE comparison of FC in the MBSR group using TFCE. Seeds are marked in green. Areas of significant post-pre differences ($p < 0.05$, FDR-corrected) in FC are marked in red. **(a)** The bilateral occipital lobe; **(b)** left middle frontal gyrus; **(c)** the precentral and post central gyri.

bodily sensations (breathing and body scan) yielded distinct spatial patterns of the SN connectivity, contributing to different facets of mindfulness. As compared with the normal resting state, both interoceptive mindfulness practices changed pattern of brain communication (distant-local in Figure 4), but this difference was only apparent after MBSR program. The functional specificity of mindfulness practices offers a novel viewpoint on the altered information processing across mindfulness practices.

4.1. MBSR training effect

In standard MBSR programs, practitioners are taught the breathing and body scan practices at the beginning of the formal practice phase, indicating that these are fundamental techniques for honing attention and interoceptive awareness. The body scan practice involves attentional shifts to multiple body parts, whereas the breathing practice encourages participants to focus on a single

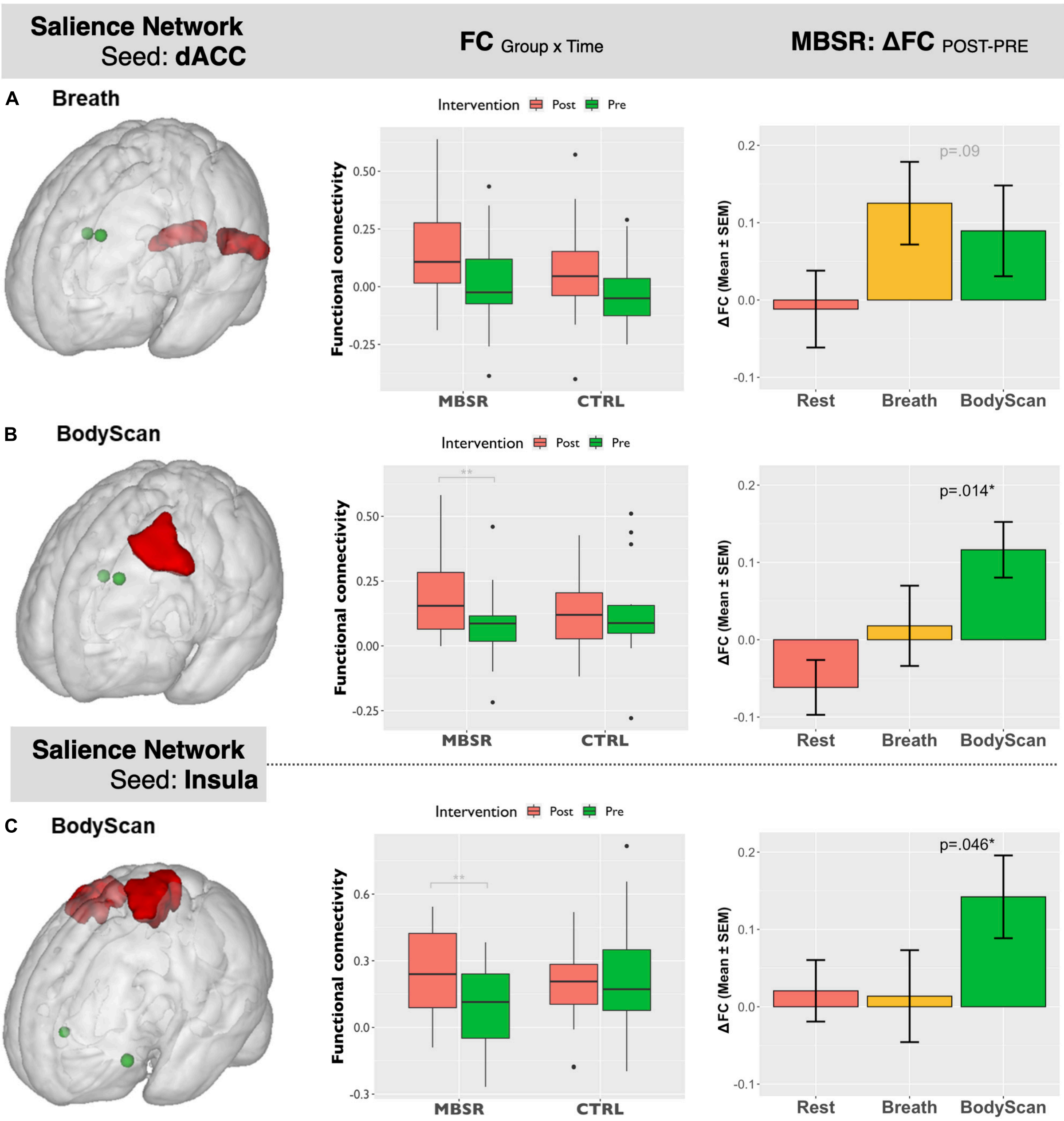

FIGURE 2
Salient Network-seeding at dACC: **(A)** (left) ROI of bilateral occipital lobe extracted from Yeo_{400} template, (middle): the ROI-based boxplot presenting the group × time interactions, and (right) the repeated-measure ANOVA of the FC changes across the 3 conditions (Rest, Breath, and BodyScan) in the MBSR group; **(B)** (left) ROI of the left middle frontal gyrus from Yeo_{400} template, (middle): the ROI-based boxplot presenting the group × time interactions, and (right) the repeated-measure ANOVA of the FC changes in the MBSR group. Salient Network-seeding at Insula: **(C)** (left) ROI of bilateral pre/postcentral gyri from Yeo_{400} template, (middle): the ROI-based boxplot presenting the group × time interactions, and (right) the repeated-measure ANOVA of the FC changes in the MBSR group. The error bars in the third column stands for standard error of the means (SEM).

bodily region. At the outset, when none of the participants had prior knowledge of the two mindfulness techniques, their brain function indices suggested no functional changes associated with either technique relative to the resting condition. This was observed in both the preprogram MBSR group (Figure 4) and the CTRL group. However, after the 8-week program, significant differences in the functional effects of breathing and body scan in terms of the SN connectivity were observed. SN exhibited enhanced internetwork connectivity with the posterior brain during the breathing practice and increased connectivity with the frontal lobe during the body scan practice (Figure 1). By contrast, our results did not reveal any change in SN connectivity during the resting state, and it remained the same in the POST session (Figure 2). These observations demonstrate the link between enhanced functional connectivity and increased interoceptive awareness.

This specificity was only observable after long-term practice. During the breathing practice, dACC showed enhanced

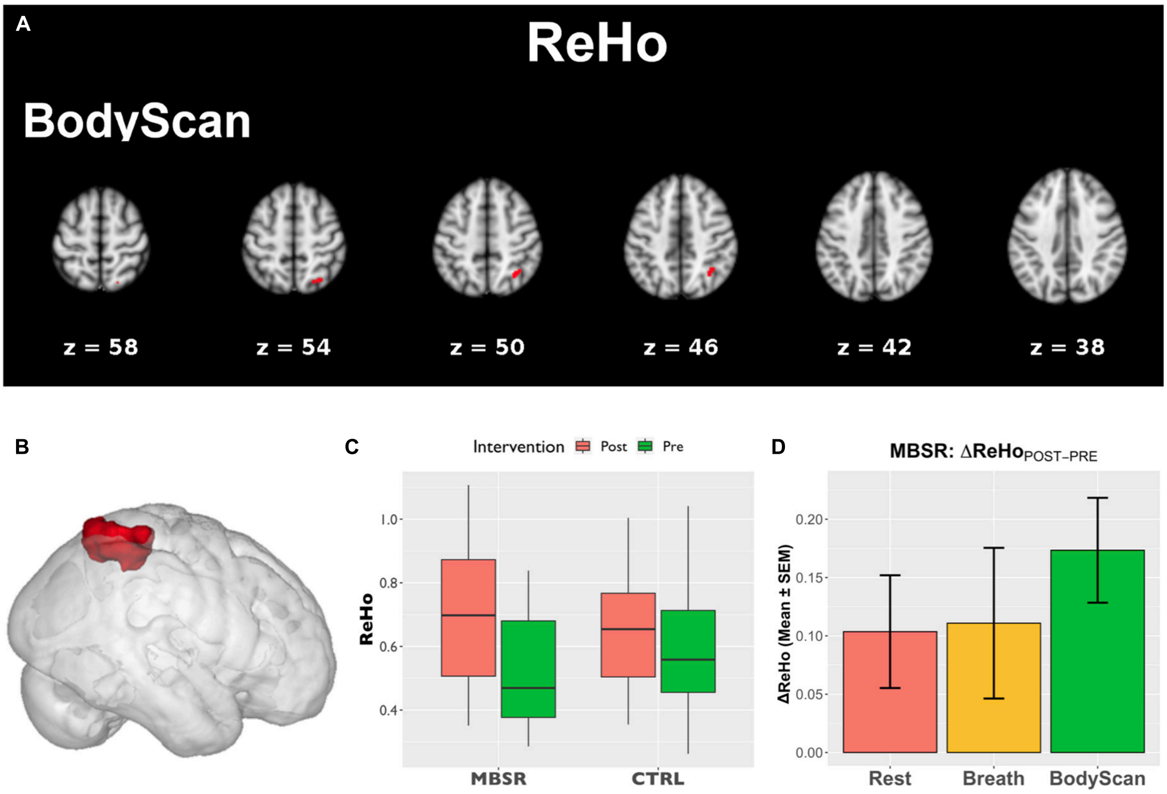

FIGURE 3
The analysis of ReHo. **(A)** Areas that showed POST−PRE differences of ReHo in TFCE ($p < 0.05$, FDR-corrected); **(B)** ROI of the right angular gyrus and parietal lobe extracted from Yeo_{400} template; **(C)** the ROI-based boxplot presenting the group × time interactions; **(D)** the repeated-measure ANOVA of the ReHo changes in the MBSR group, and the error bars in **(D)** stands for standard error of the means (SEM).

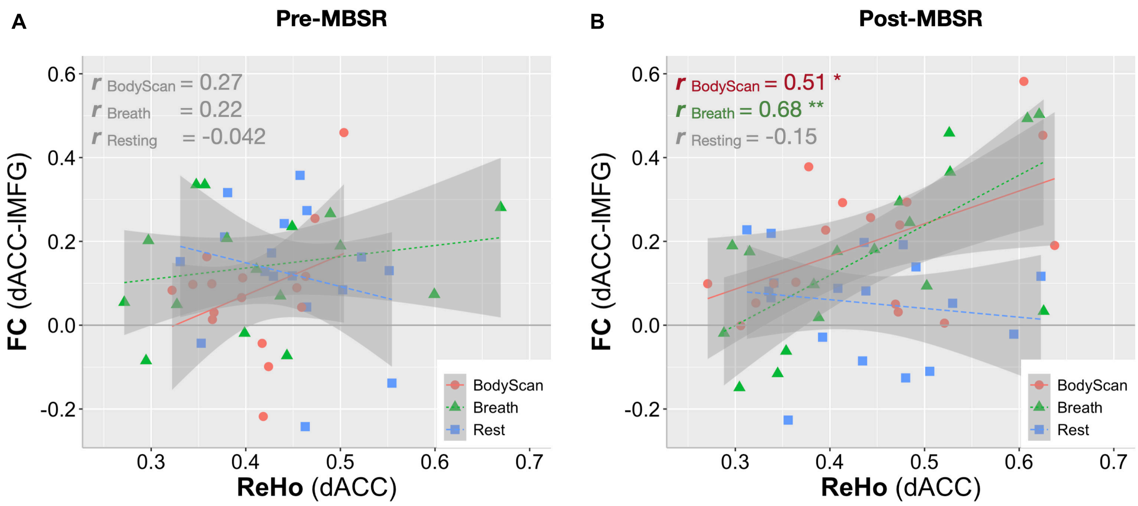

FIGURE 4
Correlation analysis between FC and ReHo for the left middle frontal gyrus in each of the 3 conditions (Rest, Breath and BodyScan) of the MBSR group. **(A)** Before the MBSR training, no significant FC-ReHo relationship was observed. **(B)** After the MBSR training, post-intervention FC_{dACC} exhibited a positive relationship with ReHo during both the breathing and the body scan, indicating a changed pattern of information processing in the salience network.

internetwork connectivity with the occipital regions (ROI 2a). These results may be attributable to the involvement of visual imagery perception when novice participants tend to envision airflow through their nostrils (Ganis et al., 2004; Haruna et al., 2019; Weaver et al., 2020). By contrast, during the body scan, enhanced internetwork FC between dACC and lMFG (ROI 2b) and between insula and the SMN (ROI 2c) was observed. The enhanced dACC-lMFG connectivity might reflect the attention engagements toward the interoceptive awareness, and the insula–SMN connectivity might be attributable to the interaction between interoceptive awareness and bodily sensations (Blatow et al., 2007; Ferri et al., 2012). Although we did not conduct counterbalancing in our experiment of mindfulness practices, the spatially distinctive changes in connectivity substantiated our presumption that the two mindfulness techniques yield different effects at the neurophysiological level. Subsequent studies should identify subtle differences between these two mindfulness techniques in a counterbalanced order.

4.2. Information processing between breathing and body scan in the MBSR group

In this study, the two brain functional metrics, FC and ReHo, were adopted to investigate underlying information processing mechanisms from the perspective of distant and local neural communications, respectively. After the MBSR program, although an elevated FC was observed in SN, ReHo increased only in the inferior parietal lobe during the body scan practice. Hence, long-distance connectivity increased during the mindfulness practices, while local connectivity remained the same. The results indicate that the pattern of information processing in the brain shifted toward one of the enhanced internetwork communications with the preservation of local information communication during both practices. Studies implementing meditation training programs of similar durations reported decreased ReHo during the postintervention testing (Xiao et al., 2019; Zhao et al., 2019). Our results suggest that the ReHo values remained largely unchanged during the mindfulness practices. However, **Figure 4** highlights strong association between FC and ReHo (FC-ReHo correlation) in the lMFG after training. Compared with the resting state, the stronger positive FC-ReHo correlations during the breathing and body scan practices indicates simultaneous increases in distant and local connectivity during the mindfulness practices, with levels varying by participant. Steiger's Z test revealed stronger FC-ReHo correlation in the dACC-lMFG connectivity during the mindfulness practices compared with those recorded during resting (p = 0.01 and 0.03 for *BodyScan* and *Breathing*, respectively). FC-ReHo correlations were only discernible after the 8-week MBSR program, and no significant FC-ReHo correlation was observed during the mindfulness practices (breathing and body scan) before program attendance. Although the FC-ReHo correlation varied by participant, these findings provide preliminary evidence that mindfulness practices alter information processing associated with SN connectivity in various brain regions. Future studies should investigate the functional changes specific to other types of mindfulness techniques and brain networks.

Previous literature mentioned that longitudinal mindfulness training is related with the most prominent three networks—SN, default-mode network (DMN), and executive control network (ECN) (Sezer et al., 2022), but it was not reported for the practice-specific FC changes after mindfulness training. In this work, we targeted on the SN because the mindfulness practices—breathing and body-scan—are related to the interoception (the function of SN), instead of the mind-wandering (the function of DMN) and goal-oriented execution (the function of ECN). Even though, the other two networks were also evaluated in both mindfulness practices and training. The DMN-FC presented significant training effects on the $FC_{PCC-superior\ temporal}$ and $FC_{insula-PCC}$, but there was a lack of significance finding in the between-condition comparisons (see **Supplementary Figure 1** in **Supplementary material**), but neither the training effect nor the condition effect was found in the ECN-FC. The functional roles of DMN and ECN in mindful breathing and body-scan await further investigations.

4.3. Limitations

This study had several limitations. First, the sample size was small and may have had insufficient statistical power because of the two-group interventional design. Relatively, the CTRL group exhibited no significant longitudinal differences in both behavioral and brain functional indices over the 8-week study period, hence we did not present their imaging findings, so as the between-group comparisons in the imaging data. The between-group comparisons of the questionnaires were shown in **Supplementary Table 1**, in which we found that the MBSR group showed higher mindfulness scale and marginally lower difficulty in emotion regulation compared to the CTRL group after MBSR training. Studies with more sample size are warranted to verify the practice specificity. Second, although the total home-based practice times of all MBSR group were recorded (mean $\pm$ SEM: 43.3 $\pm$ 0.7 h), we did not identify a relationship between practice time and the changes in FFMQ score (r = 0.18, p = 0.47) or changes in the SN connectivity ($|r| < 0.39$, $p > 0.11$). This might be attributable to the small sample size or considerable between-individual differences. Third, we conducted the *Resting*, *Breath* and *BodyScan* conditions in a fixed order because most of the mindfulness practitioners would start with the breathing and then proceed to the body scan practice. In this study, the practitioners were able to sufficiently engage in the appropriate mindfulness practice. However, without a counterbalanced design, separating the effects of the breathing practice from those of the body scan practice was difficult. Nevertheless, our findings indicate spatial differences in the connectivity patterns of these practices (**Figure 1**) after the MBSR training, which supports our hypothesis that each mindfulness practice affects brain functions distinctively. Subsequent studies can improve the experimental design by including a brief period of breathing at the start of all mindfulness practices to address the practice interaction problem.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Taipei Medical University Joint Institute Review Board (TMU-JIRB, N201905049). The participants provided their written informed consents to participate in this study.

Author contributions

CW and C-MH: conception and experiment design. F-YH, Y-TC, and H-YN: mindfulness training and data collection. S-FG and Y-PC: data analysis. S-FG, Y-PC, C-FH, and C-HC: preparation of the manuscript. All authors reviewed and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2023.1008086/full#supplementary-material

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Classification of temporal lobe epilepsy based on neuropsychological tests and exploration of its underlying neurobiology

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Objective: To assist improving long-term postoperative seizure-free rate, we aimed to use machine learning algorithms based on neuropsychological data to differentiate temporal lobe epilepsy (TLE) from extratemporal lobe epilepsy (extraTLE), as well as explore the relationship between magnetic resonance imaging (MRI) and neuropsychological tests.

Methods: Twenty-three patients with TLE and 23 patients with extraTLE underwent neuropsychological tests and MRI scans before surgery. The least absolute shrinkage and selection operator were firstly employed for feature selection, and a machine learning approach with neuropsychological tests was employed to classify TLE using leave-one-out cross-validation. A generalized linear model was used to analyze the relationship between brain alterations and neuropsychological tests.

Results: We found that logistic regression with the selected neuropsychological tests generated classification accuracies of 87.0%, with an area under the receiver operating characteristic curve (AUC) of 0.89. Three neuropsychological tests were acquired as significant neuropsychological signatures for the diagnosis of TLE. We also found that the Right-Left Orientation Test difference was related to the superior temporal and the banks of the superior temporal sulcus (bankssts). The Conditional Association Learning Test (CALT) was associated with the cortical thickness difference in the lateral orbitofrontal area between the two groups, and the Component Verbal Fluency Test was associated with the cortical thickness difference in the lateral occipital cortex between the two groups.

Conclusion: These results showed that machine learning-based classification with the selected neuropsychological data can successfully classify TLE with high accuracy compared to previous studies, which could provide kind of warning sign for surgery candidate of TLE patients. In addition, understanding the mechanism of cognitive behavior by neuroimaging information could assist doctors in the presurgical evaluation of TLE.

KEYWORDS

temporal lobe epilepsy, machine learning, structural magnetic resonance imaging, neuropsychology, cognitive impairment

1. Introduction

Nowadays, temporal lobe epilepsy (TLE) remains the most common type of epilepsy, with an incidence of more than 50% among patients with epilepsy. TLE is also the most common form of drug-resistant epilepsy, and about 70% of patients are drug-resistant (Abarrategui et al., 2021). Typical anterior temporal lobectomy (ATL) is the most effective treatment to control seizure, about 63.8% will have seizure freedom after surgery (Xu et al., 2020). However, even after complete removal of the anterior temporal lobe and mesial structures, a significant number of patients will experience seizures again which suggests that some epileptogenic tissue has not been resected. It is possibly due to pseudotemporal epilepsy whereby a extratemporal epileptogenic zone (extraTLE) was misdiagnosed, dual pathology combining an extratemporal epileptogenic lesion and temporal plus epilepsy (TPE), which could mimic the semiology and electroencephalographic (EEG) patterns including interictal and ictal features (Eryurt et al., 2015; Suresh et al., 2015; Barba et al., 2016). The most frequent ictal presentations of TLE include loss of responsiveness preceded by aura, oral automatism, ipsilateral gestural automatisms and contralateral limb dystonia or immobility. Abdominal and psychic auras are most common, which are not always pathognomonic of a temporal origin. They can also be elicited by the other regions of limbic system including insula, orbitofrontal region, anterior cingulum. And interictal and ictal scalp EEG could not distinguish them, especially to TLE and TPE, which make more complicated for accurate localization (Barba et al., 2016; Abarrategui et al., 2021). Distinguishing TLE from extraTLE and TPE has important clinical significance for surgical outcome before performing anterior temporal lobectomy (Frank et al., 2018). To determine who would benefit from ATL, presurgical evaluation of TLE is usually performed using high-resolution magnetic resonance imaging (MRI) due to its high sensitivity and specificity for hippocampal sclerosis (HS), the most common pathologic basis of TLE. However, seizure-free rates for those with normal MRI results about 50% (Muhlhofer et al., 2017). Therefore, it is necessary to propose a new method to assist clinicians in the identification of TLE patients whose disabling seizures could be resolved by standard anterior temporal lobectomy, improve long-term postoperative seizure-free rates, and improve patients' quality of life, especially for MRI negative patients. Or there will be signs that could send red flag to the non-TLE patients who are misdiagnosed as TLE undergoing ATL procedure.

Neuropsychological assessment is an essential diagnostic tool for evaluating human brain function. Before the advent of MRI, clinicians used the patterns of cognitive strengths and weaknesses derived from a neuropsychological assessment to lateralize and localize cerebral pathology. The difficulties on particular neuropsychological tasks represent dysfuncion within the underlying network that subserves this function, which could be related to many factors. Epilepsy is considered as the disorder of cerebral networks. It is hard to assigning one cognitive dysfunction to a certain brain structure. Vice versa, one focal lesion could related to multiple cognitive dysfunctions. Cognitive impairment is a common comorbidity in patients with TLE. Moreover, memory decline is a major cognitive impairment in patients with TLE. However, most studies have reported the TLE have the involvement of other cognitive abilities, including attention, language, praxis, executive function, judgment, insight, and problem solving (Hermann et al., 2006; Keary et al., 2007; Allone et al., 2017). Besides, currently the interpretation of relies immensely on clinicians' experience. They need to take into account the results of multiple neuropsychological assessment, the influence factors such as education, gender and intelligence, which is complicated, subjectives and time-consuming. Therefore, it is difficult to draw a conclusion through neuropsychological tests alone as patients with epilepsy often have multiple cognitive impairments (Hermann et al., 1997; Martin et al., 2000; Sung et al., 2013; Hamberger, 2015). State-of-the-art analysis techniques, such as machine learning, may be more objective and helpful for neuropsychological analysis. Studies have employed support vector machine (SVM) and neuropsychological tests to classify TLE and extraTLE with an accuracy of 78% (Frank et al., 2018). Another study reported 74% accuracy when distinguishing TLE from the healthy control group, which was distinguished using SVM with 14 neuropsychological tests (Hwang et al., 2019). These studies indicated that using machine learning methods with neuropsychology tests can effectively assist clinicians in preoperative evaluation. However, this technique has not been well developed in epilepsy research. Moreover, different tests have different effects on the classification results. Therefore, it is necessary to explore which tests are most effective for TLE classification.

Understanding the brain structural mechanism of cognitive behavioral changes can provide a theoretical basis for locating the epileptogenic zone in presurgical evaluation. Some studies have explored the relationship between cognitive impairment and abnormal brain structure in patients with TLE. Studies have shown that abnormalities in gyrification are associated with a significantly lower performance intelligence quotient (IQ), poorer verbal and visual memory, significant slowing across measures of simple and complex psychomotor processing as well as the speed of fine motor dexterity (Oyegbile et al., 2004). Decreased volume of cerebral gray matter is significantly associated with a lower IQ, as well as a decline in immediate and delayed memory, executive function, and speed of motor dexterity (Oyegbile et al., 2006). The lower IQ is a typical symptom of TLE. Although studies have investigated the changing patterns of cortical surface in patients with TLE, the mechanism underlying abnormal cognitive behavior remains unclear.

This study aimed to identify which neuropsychological tests may be effective for distinguishing TLE from extraTLE and explore the structural mechanism underlying abnormal cognitive behavior using MRI. We hypothesized that neuropsychological test could distinguish TLE from extraTLE. Furthermore, we expected that the brain differences between TLE and extraTLE would be associated with the selected neuropsychological test and can provide a theoretical basis for TLE classification.

2. Materials and methods

2.1. Data acquisition

Patients diagnosed with drug-resistant focal epilepsy who were either had seizure-related lesion or underwent stereoelectroencephalogram (SEEG) in the epilepsy centers of Shenzhen University General Hospital and Shenzhen secondary people's Hospital from 2016 to 2019, were selected by retrospective review. They initially underwent phase one non-invasive pre-surgical evaluation that included patient and family history followed by video electroencephalography and neuropsychological testing. Consequently, each patient underwent 3T magnetic resonance imaging (MRI) and functional imaging (inter-ictal FDG-PET scan). Invasive exploration using SEEG was considered necessary to delineate the epileptogenic zone, map the functional cortex and to determine the limits of the resection. All patients underwent surgery and had postsurgical outcome consistent with Engel I or II criteria. Patients were included if they (1) were right-handed; (2) were aged $\geq$ 18 years; (3) can complete the neuropsychological tests independently, and attained a normal level on the Wechsler Adult Intelligence Scale-Revised Chinese version (WAIS-RC); (4) followed-up at least for 1 year after surgery. Patients were excluded if they had any of the following: multifocal epilepsy; medical illness with central nervous system impact other than epilepsy; drug abuse; or serious organ diseases, such as brain tumor, intracranial hemorrhage, and metabolic diseases. Twenty-three patients were classified as TLE by experienced neurologists and neurosurgeons based on the International League Against Epilepsy diagnosis criteria (Fisher et al., 2017; Scheffer et al., 2017), SEEG results, surgical plan and postsurgical outcome. Mesial temporal lobe epilepsy and the neocortical epilepsy over anterior temporal lobe were included in the TLE group, whose resection regions were located within the areas of standard temporal lobectomy. Similarly, there were 23 patients in the extraTLE group. The extraTLE group included patients with frontal lobe, parietal lobe, and occipital lobe epilepsy. The temporal plus epilepsy patients were defined based on SEEG results, whose primary temporal lobe epileptogenic zone extending to the insula, the suprasylvian operculum, the orbito-frontal cortex and the temporo-parieto-occipital junction, were also included in the extraTLE group. The reason of this grouping criterion is to provide warning sign for forecasting the poor postsurgical outcome of standard temporal lobectomy.

We collected detailed information, including demographic data, history, seizure semiology, long-term scalp video-EEG monitoring, neuropsychological tests, and neuroimaging findings. The Ethics Committee at the Department of Neurosurgery, Shenzhen University General Hospital, approved this study, and all participants provided written informed consent.

A comprehensive neuropsychological evaluation explores several cognitive domains, mainly including perception, memory, attention, executive function, language, motor and visuomotor function (Baxendale et al., 2019), which were included in our neuropsychological testing battery. Neuropsychological testing could provide important information about the cognitive conditions of epilepsy patients, but it could be influenced by multiple factors, such as antiseizure medications, pre-testing seizures, psychiatric comorbidity (e.g., depression) and sleep (Baxendale et al., 2019). All patients underwent neuropsychological tests at their first visit to the hospital. We controlled the influence factors by choosing the time without pre-testing seizures, good sleep before testing and stopping topiramate for at least 3 days before testing. Wechsler Adult Intelligence Scale-Revised Chinese version (WAIS-RC), revised by Gong (1983), is the most popular intelligence scale used in China. Five subtests were choosed to roughly evaluate the general cognitive function, including Similarity Test, Arithmetic Test, Digital Span Test (forward and backward), Block-design Test and Object Assembly. The subtest score was converted to a standardized score based on age and living background (Urban vs. Rural). The standardized score of verbal IQ was calculated by the average of standardized score of Similarity, Arithmetic and Digital span and the standardized score of performance IQ was calculated by the average of standardized score of Block-design and Object Assembly. The average standardized IQ score is above 9 was considered as normal. Memory ability was assessed using the Abstract Figures Learning Test (AFLT), Abstract Verbal Learning Test (AVLT) (Majdan et al., 1996), Real Auditory Verbal Learning Test (RAVLT), and the Batterie d'Efficience Mnésique (BEM) Test. Visuoperceptual skills were assessed using the Face Recognition Test, Line Orientation Test, Right-Left Orientation Test, and Rey Complex Figure Test. Executive functions were assessed using the Self-Ordered Pointing Test (SOP) (Ross et al., 2007), Selective Attention Test, Stroop Test, Conditional Association Learning Test (CALT) (Petrides, 1985, 1997), Figure Fluency Test, Category Verbal Fluency Test, Phonic Verbal Fluency Test, and Component Verbal Fluency Test.

TABLE 1 Magnetic resonance imaging (MRI) acquisition parameters.

Instrument manufacture	Slices	Slice thickness (mm)	TR, TE (ms)
SIEMENS	176	1	1900, 2.9/2530, 3.0
	192	1	5000, 3.0
	176	1.2	2200, 1.5
GE	352/336	1	8200, 3.2
uMR790	176/160	1	7200, 3.1

TR, repetition time; TE, echo time.

The Token Test (De Renzi and Vignolo, 1962) and Boston Naming Test (Tombaugh and Hubiey, 1997) were administered to assess language functions. All neuropsychological tests are shown in the **Supplementary Table 1**.

Magnetic resonance imaging scans of 46 patients were performed on three different scanners. A total of 39 patients were scanned with the SIEMENS 3.0 Tesla MR scanners, 2 patients with the uMR790 3.0 Tesla MR scanner, and 5 patients with the GE 3.0 Tesla MR scanner. The detailed scanning parameters are listed in **Table 1**.

2.2. Classification of TLE and extraTLE with neuropsychological tests

Twenty-three neuropsychological tests were included in this study, and the neuropsychological test data were normalized using min-max normalization. All neuropsychological tests may contain some redundant or highly relevant features that affected the performance of the model. Herein, we used the least absolute shrinkage and selection operator (LASSO) algorithm for feature selection. Feature selection was achieved by adding L1 penalty to the objective function, which caused many coefficients to be close to zero, with only a small subset to be non-zero. LASSO regression can better deal with multicollinearity (Oyeyemi et al., 2015).

A logistic regression algorithm was employed for TLE classification using scikit-learn toolkit.[1] The classification performance was evaluated using leave-one-out cross-validation with N (N = total number of instances) iterations. At each iteration, a single subset was retained as the validation data for test the model, and the remaining N-1 subsets were used as the training data. In the first step, the LASSO algorithm was applied to the training data for feature selection. The neuropsychology tests that occurred most times in the training data at all iterations were considered as the significant neurologic signatures for TLE classification. Thereafter, the selected features were input into the logistic regression classifiers to predict the classification outcome using leave-one-out cross-validation.

The performance of the classification models was evaluated using the receiver operating characteristic curve (ROC) and the area under the ROC curve (AUC) was calculated. We also evaluated the models by evaluating the accuracy, specificity, and sensitivity, which were calculated as follows:

$$\text{Sensitivity} = TP/(TP + FN)$$

$$\text{Specificity} = TN/(TN + FP)$$

$$\text{Accuracy} = (TP + TN)/(TP + FP + FN + TN)$$

where, TP, TN, FP, and FN denote true positive, true negative, false positive, and false negative, respectively, calculated according to the optimal cut-off value that maximized the Youden index.

2.3. Correlations of neuroimaging and neuropsychological tests

It is no doubt that analysis of the pattern of cognitive behavior change could provide the clue for lateralization and localization of the epileptogenic zone especially for the MRI negative patients. Overall assessment covering different cognitive domain could give us some information, but it still need experienced neuropsychologists in epilepsy. By exploring the underlying the relationship between structural alterations with the cognitive abnormalities, it might not only help us to understand the underlying mechanism of behavior change, but also could backstep the location of possible lesion or dysfunction of certain brain network.

Images were preprocessed and analyzed using FreeSurfer (version stable v6.0.0).[2] The image preprocessing includes skull stripping, volumetric labeling, intensity normalization, white matter segmentation, surface atlas registration, surface extraction, and gyral labeling. To improve the signal-to-noise ratio, a 10-mm full width at half-maximum was used for smoothing. Cortical thickness, sulcal depth, mean curvature, gray-white matter contrast, and gray matter volume were computed after image preprocessing and reconstruction. Cortical thickness was measured as the shortest distance at the corresponding vertex between the white matter surface and the pial surface (Fischl and Dale, 2000). The sulcal depth is defined as the geodesic from the vertex located within the sulci to the closest vertex within the gyral crown (Fischl et al., 1999). The mean curvature is the reciprocal of the radius of the inscribed circle measured at the gray-white matter boundary, which is equal to the average of the main curvatures k1 and k2 (Pienaar et al., 2008). The gray-white matter contrast is calculated as the ratio of gray matter signal intensity to white matter signal intensity (Salat et al., 2009). Gray matter volume is defined as the amount of gray matter that lies between the gray-white interface and the pia matter (Winkler et al., 2010).

1 https://scikit-learn.org/stable

2 http://surfer.nmr.mgh.harvard.edu

TABLE 2 Patient demographics characteristics.

Characteristics	TLE (n = 23)	ExtraTLE (n = 23)	p-value[a]
Age, mean ± SD, years	33.6 ± 2.2	30.7 ± 1.8	0.422
Sex			0.234
Men	11	15	
Women	12	8	
Background			0.536
Urban	9	7	
Rural	14	16	
Age at onset, mean ± SD, years	20.7 ± 2.6	15.3 ± 1.5	0.079
Education, mean ± SD, years	11.9 ± 0.6	10.3 ± 0.8	0.136
IQ, mean ± SD	12.6 ± 0.3	10.5 ± 0.4	<0.001

TLE, temporal lobe epilepsy; extraTLE, extratemporal lobe epilepsy; IQ, intelligence quotient; SD, standard deviation.
[a]Comparison between the TLE group and the extraTLE group.

A generalized linear model was used to explore the relationship between the MRI features and the selected neuropsychological test, and then the coefficient that differed between TLE and extraTLE were compared. Statistical maps were generated using FreeSurfer's Query, Design, Estimate, Contrast interface tools, accounting for the effects of the covariates of sex and age. If two or more neuropsychological tests that evaluate the same cognitive function were selected, one neuropsychological test was considered as an independent variable, whereas the others were considered as nuisance for generalized linear model analysis. Multiple comparisons were corrected with a Monte Carlo simulation using a p-value < 0.05. The results were visualized by overlaying significant areas onto the inflated cortical surface.

2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 20. Demographic data (i.e., age, sex, background, education, age at onset, and IQ) were compared between the groups with TLE and extraTLE using Chi-square test for categorical variables, two-sample t-test for continuous variables, if they had a normal distribution, or using Mann–Whitney U test for continuous variables with non-normal distribution. Statistical significance was defined as a p-value < 0.05.

3. Results

3.1. Participant demographic characteristics

There were ninety-nine patients with refractory epilepsy had finished evaluation with full datas of MRI and neuropsychological testing in Shenzhen University General Hospital and Shenzhen Second People Hospital from 2016 to 2019. Fifty-five patients have done epileptogenic zone resection and their outcome are consistent with Engel Ia and Ib. Among them, nine patients were excluded due to IQ below normal range. Twenty-three patients with TLE (ages 19–51 years, mean age: 33.6 ± 2.2 years) and 23 patients with extraTLE (ages 18–55 years, mean age: 30.7 ± 1.8 years) met the criteria for inclusion in this study. The extraTLE group included patients with 12 frontal lobe epilepsy(52.2%), 6 temporal plus temporo-parieto-occipital (TPO) junction epilepsy (26.1%), 1 parietal lobe epilepsy (4.3%), 2 insular & operculum epilepsy (8.7%) and 2 others (ventricular heterotopia and hypothalamus hamartoma epilepsy, 8.7%). Participant demographic characteristics are shown in **Table 2**. There were no differences in age, sex, background, age at onset, or education between groups. The TLE group showed higher IQ than the extraTLE group, and the difference was statistically significant ($p < 0.001$).

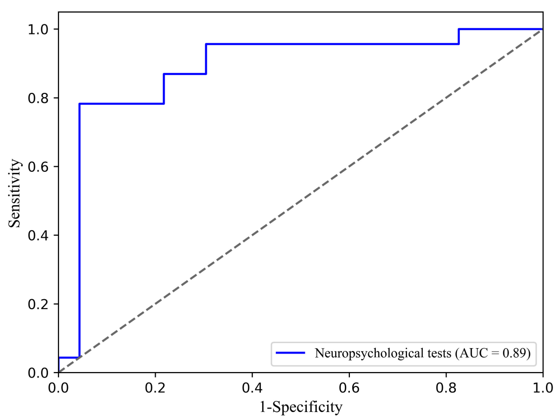

FIGURE 1
Receiver operating characteristic (ROC) curve of the TLE classification based on neuropsychological tests and logistic.

3.2. Classification of TLE and extraTLE with neuropsychological tests

The neuropsychology tests of the Right-Left Orientation Test and Component Verbal Fluency Test occurred 46 times in the training data sets, and the CALT occurred 45 times in the training data sets, while other neuropsychological tests occurred less than twice in the training data sets. Hence, three neuropsychological tests of the Right-Left Orientation Test, CALT, and Component Verbal Fluency Test were finally selected as significant neuropsychological signatures for the diagnosis of TLE.

The logistic regression classification based on selected neuropsychological tests in distinguishing TLE from extraTLE was achieved with an average accuracy of 87.0%, sensitivity of 95.7%, specificity of 78.3%, and AUC of 0.89. The ROC curve is shown in **Figure 1**.

3.3. Correlations of neuroimaging and neuropsychological tests

The correlations between structural abnormalities and cognitive impairment are presented in **Figure 2** and **Table 3**. The Right-Left Orientation Test difference was related to the difference in gray matter volume in the superior temporal region, the difference in sulcal depth in the banks of the superior temporal sulcus (bankssts), and the mean curvature difference in bankssts between TLE and extraTLE, while accounting for sex, age and total intracranial volume. CALT was associated with the cortical thickness difference in the lateral orbitofrontal area between the two groups. The Component Verbal Fluency Test was associated with the cortical thickness difference in the occipital pole between the two groups.

4. Discussion

In this study, the Right-Left Orientation Test, CALT, and Component Verbal Fluency Test were finally selected as significant neuropsychological signatures for the diagnosis of TLE according to the analysis of the LASSO algorithm. An 87% accuracy was achieved when using logistic regression with selected

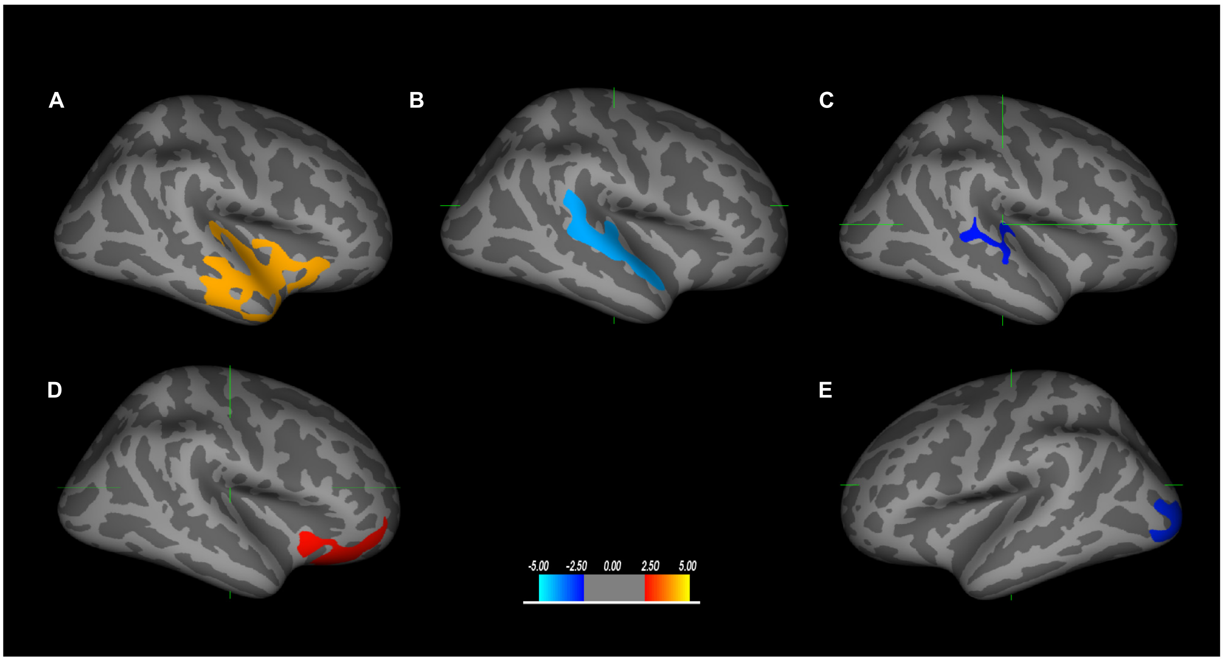

FIGURE 2
The brain regions correlated with neuropsychological tests are significantly different between TLE and extraTLE, accounting for age and sex. The relationship between the Right-Left Orientation Test and the gray matter volume difference in the superior temporal area **(A)**, the sulcal depth difference in the banks of the superior temporal sulcus (bankssts) **(B)**, and the mean curvature difference in the bankssts area **(C)**, respectively. The relationship between the Conditional Association Learning Test (CALT) and the cortical thickness difference in the lateral orbitofrontal **(D)**. The relationship between the Component Verbal Fluency Test and the cortical thickness difference in the occipital area **(E)**. The values in the color bar represent log10 (p-value) ($p < 0.05$).

TABLE 3 Correlations between the brain region and the neuropsychological tests.

Cognitive function	Neuropsychology	Brain regions associated with neuropsychological tests						
		Hemisphere	Brain region	Talairach coordinates			Lobes	Cortical surface features
				TalX	TalY	TalZ		
Visuoperceptual skill	Right-Left Orientation Test	R	Superior temporal	49.2	−0.2	−6.8	Temporal	Gray matter volume
		R	Bankssts	54.8	−31.9	4.9	Temporal	Sulcal depth
		R	Bankssts	49.4	−33.6	6.4	Temporal	Mean curvature
Executive functions	Conditional Association Learning Test (CALT)	R	Lateral orbitofrontal	34.4	42.5	−10.3	Frontal	Cortical thickness
	Component Fluency Test	L	Lateral occipital	−23.0	−90.2	6.0	Occipital	Cortical thickness

neuropsychological tests for TLE classification. Similar research has shown that 78% accuracy was obtained when using multiple neuropsychological assessment and SVM methods to distinguish the TLE from the extraTLE (Frank et al., 2018). The application of machine learning approaches with the neuropsychological test for epilepsy classification is extremely uncommon, but these studies have verified the feasibility and validity of the method.

Among these selected neuropsychological tests, the Right-Left Orientation Test was used to assess visuospatial perceptual skills. Traditional models confirmed that the visual pathway is segregated into two distinct streams: the temporal-occipital ventral pathway and the occipital-parietal dorsal pathway (Sheth and Young, 2016). The dorsal pathway mainly processes information about object location, developing relations to several areas of the cortex, such as the frontal, temporal, and limbic lobes (Trés and Brucki, 2014). Our results showed that the Right-Left Orientation Test difference was related to the difference in gray matter volume in the anterior to posterior superior temporal region (including temporoparietal junction), the sulcal depth difference in bankssts, and the mean curvature difference in the bankssts; the coefficient is significantly different between TLE and extraTLE, which may indicate that this region plays a key role in the behavior difference between the two groups in Right-Left Orientation Test. Left-right disorientation was one symptom of Gerstmann syndrome, and was considered as the dysfunction of dominant parietal lobe, especially in angular gyrus. However, insular and operculum lesion also could cause Gerstmann syndrome, resulting in a pseudoparietal presentation (Bhattacharyya et al., 2014). Superior temporal gyrus, neighboring to angular gyrus, have close connectivity with insular and parietal lobe, which may influence the capacity of left-right orientation. Due to the limited number of the patients with parietal lobe epilepsy in the extraTLE group, it may be the reason why we did not obtain the significant difference in gray matter volume of parietal cortex between the two groups.

The CALT and the Component Verbal Fluency Test were used to assess executive function skills. More specifically, the parts of the brain that deal with memory and conditional associative learning are activated during the CALT. Our results showed that CALT was associated with the cortical thickness difference in the lateral orbitofrontal cortex, and that the coefficient was significantly different between TLE and extraTLE. Conditional associative learning can facilitate memory processing. Consequently, repeated memory is also an important part of conditional response formation. The lateral orbitofrontal is the main brain area connecting with them. Previous reports have indicated that the orbitofrontal cortex is strongly connected with the limbic area of the medial temporal lobe, which is closely related to the establishment of declarative memory (Petrides, 2007; Barbey et al., 2011). OFC neuronal activity represents a long-term associative memory to support behavioral adaptation (Namboodiri et al., 2019). Orbitofrontal damage may impair the exclusionary aspect of attention. Our result is also consistent with previous findings that executive function is associated with the frontal lobe (Della Sala et al., 1998; Schnider et al., 2020), and these findings may indicate that these two groups have different degrees of correlation in the frontal lobe, which may be the reason that the CALT can distinguish TLE from the extraTLE. Previous studies have shown that the frontal lobe plays an important role in executive function, which is an extensive efferent and afferent connection to most brain regions (Heyder et al., 2004). Cortico-subcortical circuits that connect the prefrontal cortex, the basal ganglia, and the cerebellum via the thalamus are considered as the neuroanatomical basis for executive function (Bostan et al., 2010). Therefore, frontal impairment may cause damage to other brain regions associated with executive dysfunction. The integrity of the frontal cortex is necessary but not sufficient for intact executive function (Della Sala et al., 1998). Executive dysfunction may not always reflect frontal lesions, but probably indicate damaged neural networks throughout the brain. Fluency was defined as the ability to maximize unique response productions, and at the same time to avoid or minimize response repetition, including verbal and non-verbal categories (Ruff et al., 1994). It has been suggested that all forms of fluency, independent from modality, represent general executive functions (Zalonis et al., 2017). Non-verbal fluency is related not only to executive function but also to visuomotor abilities (Ruff et al., 1987). Right-posterior parietal cortex and left temporal cortex are more especially involved in figural and semantic fluency (Ghanavati et al., 2019). Chinese is one kind of non-alphabetic language, originating from hieroglyphs with dual features of verbal and graphic, and may involve diffuse brain region, especially in frontal and temporal lobe. This may be the reason that Component Verbal Fluency Test was associated with the cortical thickness difference in the occipital pole region. This also proposed a supermodal contribution to the executive function, which was consistent with the previous study (Zalonis et al., 2017). Occipital lobe has very close connectivity with the frontal lobe by frontooccipital fasciculus. The dysfunction of occipital lobe may also can cause the decline of visual executive function.

A few limitations of this study should be noted. First, the small sample size of patients with epilepsy may result in decreased power to distinguish TLE from extraTLE using a machine learning algorithm. Models developed based on such a small sample size may not yet be adequate for the clinical diagnosis of TLE. The relatively small sample size may also affect the analysis of the correlations between structural abnormalities and cognitive impairment. Second, we only used structural MRI, but not functional MRI, DTI, or other modalities to analyze the correlations between the structural abnormalities and the cognitive impairment, which may not be comprehensive. Most studies have demonstrated that TLE not only shows hippocampal atrophy and signal change on magnetic resonance images, but also shows functional connectivity abnormalities (Miró et al., 2015; Bharath et al., 2019). We did not analyze from the perspective of functional connectivity. Third, the MRI scanning parameters were significantly different between individuals, which may lead to the deviation in preprocessing and can further influence the result. Future studies with a larger sample size of patients should continue to investigate the mechanism of cognitive impairment in patients with TLE and to build a more reliable machine learning model for TLE classification. Moreover, use of additional multimodalities may be necessary for in future studies in patients with TLE. From clinical observation, frontal vs. temporal lobe epilepsy patients could combine different psychiatric comorbidity, depression and anxiety more popular in temporal lobe epilepsy and schizophrenia with higher occurrence in frontal lobe epilepsy. Psychiatric evaluation as well as more sensitive neuropsychological test, like Logical Memory and Recognition Test (discriminating frontal vs. temporal), could be added to the testing battery in future (Paradiso et al., 2001; Conradi et al., 2020).

5. Conclusion

Our work advocated that using a machine learning model with neuropsychological data can successfully classify TLE with high accuracy. Furthermore, we explored significant neurologic signatures for TLE classification, providing a new path for the diagnosis of TLE. Our study send a potential red flag for ATL when the patients had abnormal performance of Right-Left Orientation Test, CALT and Component Verbal Fluency Test. The findings about the relationship between structural abnormalities and cognitive impairment can better assist physicians in the preoperative assessment, surgical planning, surgical outcome prediction, and surgical rehabilitation planning for patients with TLE.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Department of Neurosurgery, Shenzhen University General Hospital, Shenzhen, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FC, XM, and YY conceived and designed the experiment. FC provided the administrative support. XM collected and delineated the images and collected the clinical data on patients. KD performed the experimental design, analyzed the data, and prepared the graphs. XM and KD wrote the manuscript. BH, XL, YW, WT, and CL assisted with the manuscript writing and data analysis. All authors read and approved the final version of the manuscript.

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Conflict of interest

KD was employed by Philips Healthcare.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Increased neurocardiological interplay after mindfulness meditation: a brain oscillation-based approach

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Background: Brain oscillations facilitate interaction within the brain network and between the brain and heart activities, and the alpha wave, as a prominent brain oscillation, plays a major role in these coherent activities. We hypothesize that mindfully breathing can make the brain and heart activities more coherent in terms of increased connectivity between the electroencephalogram (EEG) and electrocardiogram (ECG) signals.

Methods: Eleven participants (28–52 years) attended 8 weeks of Mindfulness Based Stress Reduction (MBSR) training. EEG and ECG data of two states of mindful breathing and rest, both eye-closed, were recorded before and after the training. EEGLAB was used to analyze the alpha band (8–12 Hz) power, alpha peak frequency (APF), peak power and coherence. FMRIB toolbox was used to extract the ECG data. Heart coherence (HC) and heartbeat evoked potential (HEP) were calculated for further correlation analysis.

Results: After 8 weeks of MBSR training, the correlation between APF and HC increased significantly in the middle frontal region and bilateral temporal regions. The correlation between alpha coherence and heart coherence had similar changes, while alpha peak power did not reflect such changes. In contrast, spectrum analysis alone did not show difference before and after MBSR training.

Conclusion: The brain works in rhythmic oscillation, and this rhythmic connection becomes more coherent with cardiac activity after 8 weeks of MBSR training. Individual APF is relatively stable and its interplay with cardiac activity may be a more sensitive index than power spectrum by monitoring the brain-heart connection. This preliminary study has important implications for the neuroscientific measurement of meditative practice.

KEYWORDS

alpha peak frequency, mindfulness meditation, heart coherence, brain-heart connection, effective connectivity, resting-state EEG

1. Introduction

Mindfulness meditation, a popular form of meditation, has demonstrated a wide range of benefits across various domains such as education, clinical settings, commercial industries, and the military (Goldberg et al., 2020; Duff, 2022). Mind-body connection is central to mindfulness meditation, and recent studies suggest that meditation can modulate brain network organization and the neural representation of cardiac activity within the default mode network (Jiang et al., 2020; Lurz and Ladwig, 2022; Wong et al., 2022). Nevertheless, research on the potential neural mechanisms underlying brain-heart connection remains relatively scarce when compared to enormous research on other mechanisms of mindfulness (Ng et al., 2005; Minhas et al., 2022). Our previous study demonstrated brain-heart entrainment in mindfulness meditation practitioners, however, it only examined the data at a group-level (Gao et al., 2016). To better understand how the brain and body interact during meditation, this study focuses on instantaneous brain-heart entrainment during mindfulness meditation practice at an individual level, which would support a greater application in mindfulness practice.

Naturally, immediate mind-body connections can be felt by individuals in their response to significant events or intense emotions, with the heart being particularly responsive. This is because that central nervous system modulates visceral organ activity through the autonomic nervous system, with most visceral organs functioning autonomously but exhibiting a clear circadian rhythm (Tran et al., 2021; Chambers et al., 2022). Maintaining coherent mind-body activity and circadian rhythms is essential for our well-being, and disruptions can lead to visceral organ dysfunction or even cardiac arrest (Tran et al., 2021). Recognizing the importance of mind-body coherence, the bio-medical-social model has been proposed for promoting health (Heidger, 2011).

To simplify the investigation of the mind-body connection, this study examines the relationship between cerebral and cardiac activities, as the heart is the most responsive organ to external stimuli (Lutwak and Dill, 2012). Electroencephalography (EEG) and electrocardiography (ECG) can easily measure brain and cardiac activities, respectively. Different EEG frequency bands, such as delta, theta, alpha, beta, and gamma, reflect various mental states. Among these, the alpha wave is the primary human brain oscillation, with changes in alpha wave activity being the most reliable outcomes in EEG meditation studies (Lomas et al., 2015).

Different meditation forms can induce changes in distinct brain wave bands; for example, traditional Tibetan Buddhist meditation is associated with gamma band changes (Lutz et al., 2004; Ferrarelli et al., 2013; Jiang et al., 2020). Research has also shown that the anterior cingulate cortex connects to the autonomic nervous system (Devinsky et al., 1995), and frontal midline theta rhythm correlates with heart rate variability during meditation (Kubota et al., 2001). Nonetheless, increased alpha wave activity, particularly in the occipital and frontal regions, has been universally observed during various meditations (Cahn and Polich, 2006).

In this study, we focus on alpha wave analysis due to its significance in brain rhythm and dominance during eyes-closed relaxation which has been proposed as a form of "cortical idling" (Vanwinsum et al., 1984). The alpha power is inversely proportional to the fraction of cortical neurons recruited for any given task (Gevins and Schaffer, 1980). There is similarity of alpha peak frequency (APF) to the central processing unit's main frequency within the brain network (Bera, 2015). The APF has been implicated in cognitive preparedness (Angelakis et al., 2004) and is positively correlated with processing speed, memory, and cognitive performance in healthy individuals (Vogt et al., 1998; Clark et al., 2004; Moretti et al., 2013; Sanchez-Lopez et al., 2018). Clinical patients typically exhibit reduced APF and lower cognitive performance compared to healthy individuals (Klimesch et al., 1993; Bertaccini et al., 2022). Higher alpha frequency is associated with better academic performance (Klimesch, 1999) and intelligence (Anokhin and Vogel, 1996).

Alpha peak frequency is a largely heritable trait, with heritability accounting for most individual APF (iAPF) variance (Mierau et al., 2017). Although iAPF is highly stable across time and considered a heritable neurophysiological marker and true endophenotype, evidence suggests that APF can be volatile during different mental states and may reflect a change in cerebral oxygenation (Angelakis et al., 2004). Alpha wave activity can be measured by averaging alpha band power within the 8–12 Hz range, and alpha peak power can be specified to calibrate the highest alpha power in 8–12 Hz range. Slight peak power of variations across brain regions may occur due to differences in brain network interactions (Mierau et al., 2017).

To measure the interactive activity among brain network, the topography of this interactive synchronization can be calculated by alpha coherence (Zheng et al., 2007). Coherence is typically calculated using mean cross-power density over respective mean auto-power spectral densities. Different methods have been developed to calculate brain connectivity, and mindfulness training has been shown to modulate brain connectivity in diverse populations (Kilpatrick et al., 2011; Jovanovic et al., 2013; Lifshitz et al., 2019; Li et al., 2022).

Alpha waves are generated by thalamo-cortical information interactions, such as feedback loops between excitatory and inhibitory neurons (Dasilva, 1991; van Schie and Bekkering, 2007). These loops facilitate cortical information processing and communication with the thalamus, potentially causing slight iAPF shifts in different mental states. The interplay between the thalamus and cortex plays a critical role in various brain functions, including consciousness and perception, and may contribute to brain-heart activity interactions (Min et al., 2020).

The dynamic interaction between cerebral and cardiac electrical activities can be directly reflected by the heartbeat evoked potential (HEP). The R-peak of QRS waves in ECG is considered an event related to ongoing cerebral electrical activity, allowing HEP calculation using event-related potential methods. HEP varies among individuals due to differences in body structure and function, with higher HEP observed in those with greater interoception (Jiang et al., 2020; Coll et al., 2021).

This study aims to investigate brain-heart interaction with a focus on alpha oscillation, given its prominence in meditation research. We primarily analyze the oscillation and synchronization of neurophysiological systems between the brain network and cardiac activity. By examining the fundamental synchronization, we would demonstrate the critical role of brain-heart coherence in a meditative state. Additionally, we did coherence analysis in quantitative EEG to provide cortico-cortical interactions and further topographical information on coherent oscillatory activity during mindfulness meditation.

2. Materials and methods

2.1. Participants

Thirteen healthy participants from a local Mindfulness Based Stress Reduction (MBSR) class were recruited for this EEG study. Each of them was paid $HK200 to compensate for their time. The Beck Depression Inventory (BDI) was used to exclude participants with depression (Yeung et al., 2002). All participants had completed education at or above the undergraduate level. None of them had experience in MBSR. During the experiment, they were requested to only practice the mindfulness breathing technique learned from their MBSR course. The course was taught following the standard MBSR program consisting of one pre-program orientation session, eight weekly classes and one all-day class when the teacher provided direct instructions. Also, participants had to make a strong commitment to practice 45 min of MBSR training each day as home assignments for 8 weeks individually, which included body scanning and mindful breathing. The research was approved by the local Institutional Review Board (IRB) and participants provided their written informed consent before participating in this study. One participant dropped out, and another participant had unusable EEG data due to technical issues. Eventually, data from eleven participants (6 males, 5 females, mean age 35.7 years; 7 Asians and 4 Caucasians) were used for the final data report in this brief research.

2.2. Experiment procedure

Electroencephalogram data were recorded first at the beginning of the MBSR training (within 2 weeks), which was taught by a qualified MBSR teacher. The second round of EEG data collection was collected less than 1 month after the MBSR course, resulting in two data sets with two conditions. One condition was having the participants undergo 10 min of eye-closed normal rest, while the other condition was 10 min of eye-closed mindful breathing. Participants were instructed before each task not to ruminate or fall asleep, and the experiment took place in a quiet room. To make sure that trainees knew the correct way to perform the MBSR mindful breathing, the early-stage MBSR condition was set as 2 weeks after of training MBSR. All of the participants confirmed they did follow the instructions after the experiment and their practice of mindfulness breathing was generally good. The Five Facets Mindfulness Questionnaire (FFMQ) was used to measure the change in mindfulness practice quality, and the score of non-reacting facet increased from 22.8 ± 6.5 to 23.9 ± 7.3 (p = 0.042). Please refer to the previous paper for more details (Gao et al., 2016). The sequence of rest and mindful breathing was counter-balanced, with half of the participants randomly assigned to perform the mindful breathing task first and the other half doing the rest task first.

2.3. Data acquisition and analysis

The data were acquired by a 128-channel NeuroSCAN system in a quiet room. The sampling rate was set at 1,000 Hz. The system has the reference default at the left mastoid, and we recomputed the reference to the combination of both mastoids afterward during data processing. The ECG electrodes were placed at the left and right infraclavicular fossae after cleaning the area with alcohol.

Heart coherence was calculated by peak power divided by total power (McCraty and Zayas, 2014; McCraty, 2022), where peak power was determined by calculating the integral in a window 0.03 Hz wide, centered on the highest peak in the 0.04–0.4 Hz range of the HRV power spectrum, and the total power was determined by calculating the integral in a window of 0.0033–0.4 Hz wide. Heart coherence has a value between 0 and 1 and indicates the magnitude of similarity between the waveform of the HRV tachogram and a sinusoidal wave (McCraty and Zayas, 2014; McCraty, 2022).

EEGLAB was used to extract the power of alpha peak, peak frequency of the alpha wave, and alpha coherence. Eye movement and ECG artifacts in the EEG data were cleaned using independent component analysis (ICA). To evaluate the instantaneous heart and brain coupling of each participant, we found the interval RR from ECG data using the detect function of FMRIB toolbox, then calculated the participant's heart coherence. Using the RR interval obtained, we set the window length accordingly for further power spectrum analysis of the EEG data. Given the prominence of the alpha wave, this study mainly focused on the alpha wave band (8–12 Hz).

Functional connectivity between brain regions was estimated from EEG coherence between electrodes overlying the participant's head (Bowyer, 2016). Coherence is one mathematical method used to determine if two or more sensors, or brain regions, have similar neuronal oscillatory activity. Coherence ranges from zero to one, with a value near one indicating that EEG signals have similar phase and amplitude differences at all time points and a value near zero indicating that signals have a random difference in phase and amplitude (Bowyer, 2016). In this study, we used lagged coherence to exclude the non-lagged part of coherence which is believed to be effects of volume conduction (Milz et al., 2014). The lagged coherence calculation details can be calculated as following,

$$LagCoh\left(f\right) = \frac{\left[ImG_{xy}(f)\right]^2}{G_{xx}\left(f\right) G_{yy}\left(f\right) - \left[ReG_{xy}(f)\right]^2}$$

where $G_{xy}(f)$ is the cross-power spectral density and $G_{xx}\left(f\right)$, $G_{yy}\left(f\right)$ are the auto-power spectral densities for each channel X and Y.

To calculate the instantaneous brain-heart interplay, a sliding window of 60 s was used, and the Pearson correlation coefficient was calculated between heart coherence and these alpha wave indexes (Kim et al., 2013, 2014). This process returned an r-value for each channel and each condition. The r-value difference between before and after intervention was then calculated, and finally, paired-sample t-tests were used to compare this r-value difference between the mindful breathing and rest conditions. Similar indices were calculated for the gamma wave.

Heartbeat evoked potential (HEP) was also calculated, as HEP can reflect the interaction between cardiac and cerebral activities (Jiang et al., 2020; Coll et al., 2021). The HEP was calculated by extracting epochs that were time-locked to the R peaks of QRS wave identified earlier in ECG channel, with the time window set as −200 to 600 ms around the R peak event onset. Then epochs were averaged to obtain the HEP data for each participant. For each channel, paired-sample *t*-tests were used to analyze the difference between conditions. Instantaneous correlation between HEP and alpha wave indexes were also explored. Finally, we also calculated brain effective connectivity with partial directed coherence (PDC) (Baccala and Sameshima, 2001). Significant differences were determined using $p < 0.05$. The flowchart of data collection and analysis is shown in **Supplementary Figure 1**.

3. Results

After MBSR training, participants had a greater brain-heart connection during mindful breathing than that at the early-stage training. This training effect did not happen during close-eye rest.

This higher brain-heart connection is most obvious between the alpha peak and heart coherence but also appears between alpha-coherence and heart coherence, with a similar distribution. The increased brain-heart connection is most apparent in the middle frontal and also appears in the temporal and occipital regions of the scalp. See **Figures 1**, **2**.

Figure 1 shows an overall 2-D map of brain areas with increased brain-heart connection after 8-week mindfulness training; while **Figure 2** shows a single channel with significantly increased brain-heart connection in terms of alpha coherence and heart coherence. That is, a dark dot means a significant change of brain-heart connection after mindfulness training (see **Supplementary Tables 1**, **2** for statistic).

Additionally, we calculated heart coherence and gamma coherence, which did not show a significant result. See **Supplementary Figure 2**. Also, results of HEP analysis did not show any difference after mindfulness training. Correlational analysis between HEP and various alpha indexes were also done. See **Supplementary Figures 3–5**. The power spectral analysis of alpha power, alpha peak power, alpha peak frequency, and alpha coherence are shown in the **Supplementary Figures 6–9**, respectively.

With regard to connectivity among brain regions only, these brain connectivity results are shown in the **Supplementary Figure 10** and **Supplementary Tables 3**, **4**. It demonstrates significantly increased brain connectivity was found after MBSR training, in terms of PDC indices, while less increased brain connectivity is found during the resting state. The increased brain connectivity was found mainly in the middle frontal with other regions, including the temporal, parietal and occipital regions.

4. Discussion

The current study finds that the link between the brain and heart during meditation may follow coherent rhythms rather than amplitudes of neurophysiological activity due to a stronger correlation between heart coherence and alpha wave peak frequency instead of its peak power. Our previous study on mindfulness meditation found entrainment between brain and heart, but only in a group of meditators (Gao et al., 2016). That study did not examine any longitudinal effect of mindfulness meditation either, as only spectrum analysis was made on EEG. Similarly, we did not find significant longitudinal change in MBSR training when directly comparing the spectral analysis of alpha band, including the alpha power, alpha peak power, APF, alpha coherence in the current study. However, we demonstrated that instantaneous brain-heart connection considering both central and peripheral physiological activities can be more sensitive to mental state, and to measure the longitudinal effect of mindfulness training.

By measuring the simultaneous interplay between the EEG and ECG, we found that APF becomes more correlated with heart activities after 8 weeks of mindfulness meditation. This longitudinal change did not happen during normal rest conditions. We did not find a similar brain-heart connection in the gamma wave band (see **Supplementary material**). This implies the importance of alpha wave and heart coherence when calculating brain-heart connectivity. Our results demonstrated that APF can be a better EEG measure than alpha power (amplitude) as it is more stable in test-retest reliability (Salinsky et al., 1991; Rocha et al., 2020). The greater between-session variability in EEG power may lead to insignificant findings, as shown in the current results that no significant finding in alpha peak power and its correlation with heart coherence.

Although APF is relatively stable and largely heritable, accumulating evidence indicates that APF can shift slightly during different states, such as sleep, sensorimotor processing or neurological disorders (Uhhaas and Singer, 2006). Mindfulness breathing meditation may modulate the frequency of synchronous neural activity and tune the alpha oscillation to be synchronized with the heart activity. As shown by current results, the instant correlation between APF and Heart coherence became more positive after 8 weeks of MBSR training.

Heart coherence was calculated by the ratio of low and high frequency of heart rate, which partially reflects the balance between the parasympathetic nervous system and sympathetic nervous system (McCraty and Zayas, 2014; McCraty, 2022). Heart coherence is associated with greater levels of emotion regulation and cognitive flexibility. The authors suggested that heart coherence may reflect a state of physiological coherence that is associated with better emotional and cognitive functioning (Shaffer et al., 2014). Heart coherence represents the ordering degree in the oscillation of heart rhythm intervals (Kim et al., 2013). This study found heart coherence is a sensitive marker for meditation states, given its strong correlation with middle-frontal APF and alpha coherence. We did not find a similar correlation between heart coherence and gamma waves. It is plausible that gamma wave is generated by neurons in a firing state and communicating with local cortical areas. Bursts of fast waves, such as gamma and beta waves, play a supportive role in working memory and volitional control.

In contrast, the alpha wave as the slow wave is generated by the thalamo-cortical information interaction, such as feedback loops of excitatory and inhibitory neurons (Dasilva, 1991; van Schie and Bekkering, 2007). This loop enables the cortex to poll information from the thalamus and process it, and then relay the processed information back to the thalamus. Furthermore, the interplay between the thalamus and cortex plays a critical role

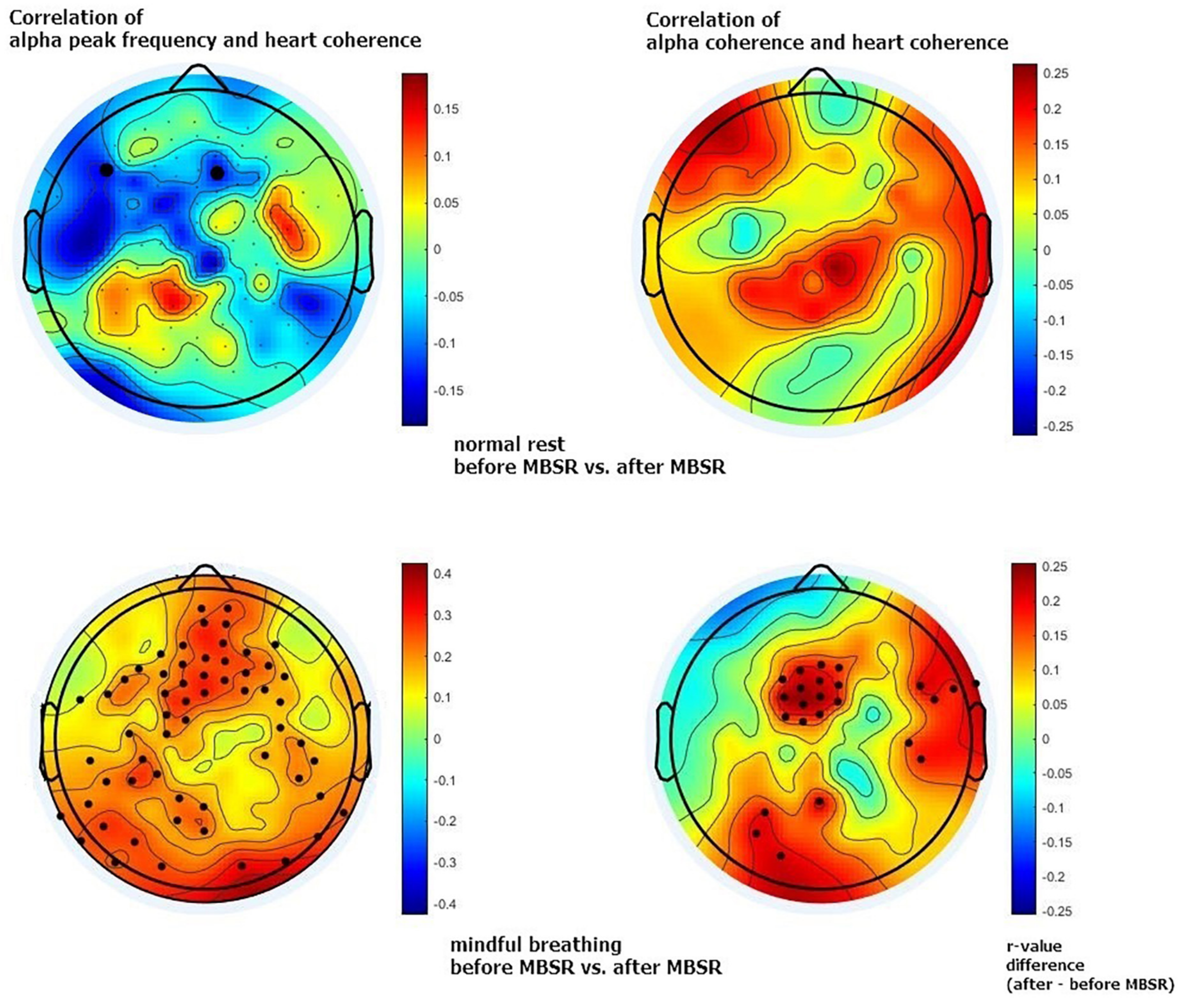

FIGURE 1
Maps of brain-heart connections. This connection (*r*-value) was calculated based on correlation of alpha peak frequency and heart coherence **(left column)**, and correlation of alpha coherence and heart coherence **(right column)**. The upper row is showing normal rest control condition before and after 8-week mindfulness-based stress reduction (MBSR) training; the lower row is showing mindful breathing condition before and after MBSR training. Color represents the *r*-value differences between before and after MBSR training. The black dots indicate electrodes with significant differences before and after MBSR training ($p < 0.05$, uncorrected).

in a variety of brain functioning, including consciousness and perception (Min et al., 2020). During mindfulness breathing, the practitioner needs to consciously monitor their breath-in and -out. Breathing activity can be either conscious or unconscious. It is assumed that mindful breathing may contribute to increased interaction between brain-heart activities and improve the dynamic oscillatory integration between the peripheral vegetative system (including the cardiovascular system) and the central nervous system. This is vital for individuals to maintain hemostasis, and physical and mental health (Gebber et al., 1999).

Animal studies have found that the rhythmic activity in the respiratory pathway can dynamically modulate the coupling of central oscillators and peripheral targets (Gebber et al., 2004). The discharges of sympathetic nerves generated by central oscillators are around 10 Hz, parallel to the alpha wave band (Gebber et al., 1999). Our results demonstrate that mindfully controlled breathing can cause a slight shift of iAPF in different mind states. This may modulate the coupling of central oscillators and peripheral targets, including cardiac activity, and enhance the cardio-respiratory coordination and, broadly, body-mind connection. Future studies are needed to investigate the role of respiratory activities in connecting cardiac and cerebral activities to determine their potential mediative relationship.

In addition to APF, we found that heart coherence is also correlated with alpha coherence, which is involved in alpha wave generation. A previous study of alpha coherence demonstrated that functional interaction between posterior and anterior brain regions might be involved in generating alpha rhythm during the waking time (Wang et al., 1992). Alpha coherence can be applied to illustrate the functional relationship between different brain regions (Achermann and Borbely, 1998; Cantero et al., 1999; Jorge et al., 2017). The fronto-occipital fasciculi physiologically supports this long-range interaction (Mai et al., 2004). Alpha coherence can discern different arousal levels and is a sensitive index to evaluate various mental states (Cantero et al., 1999). For example, alpha coherence is reduced in patients with Alzheimer's disease during

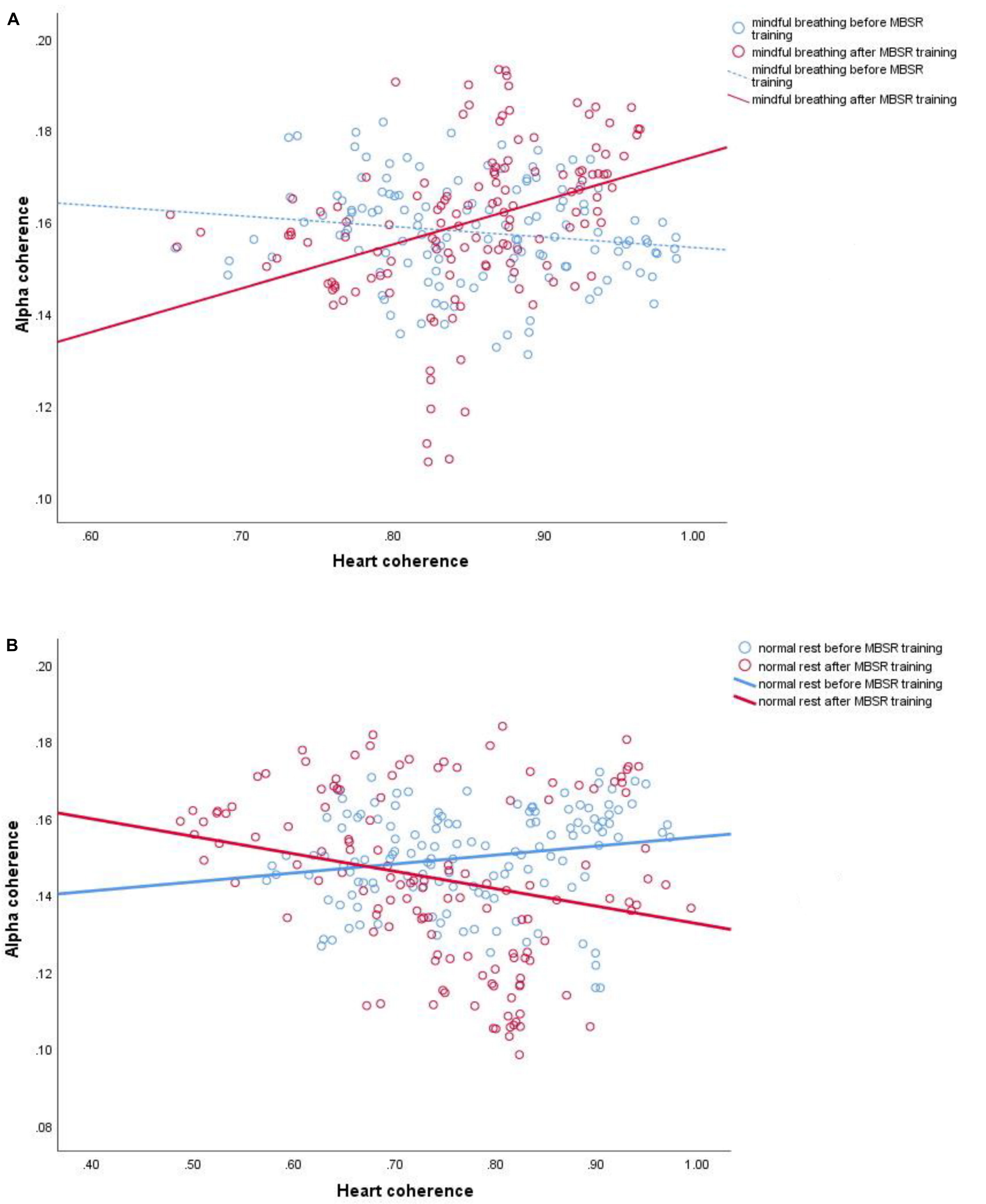

FIGURE 2
Examples of linear regressions for channel Fz of one participant. **(A)** Instantaneous correlation (60 s, with 4 s sliding) of alpha coherence and heart coherence during mindful breathing before ($r = -0.153$, $p = 0.077$; blue line) and after ($r = 0.361$, $p < 0.0001$; red line) mindfulness-based stress reduction (MBSR) training; **(B)** normal rest before ($r = 0.190$, $p = 0.028$; blue line) and after ($r = -0.226$, $p = 0.008$; red line) MBSR training. Solid line represents significant correlation ($p < 0.05$).

task that needs memory activity (Hogan et al., 2003). On the other hand, how the sinusoidal oscillations of alpha wave creates coherence among brain regions and its generation mechanism has not been fully illustrated (Miranda de Sá and Infantosi, 2005).

Heartbeat evoked potential reflects the relationship of cardiac electric activity and cerebral electric activity, and it is found to be related to the sense of interoception. In this study, we did not find any longitudinal change in HEP, or any correlation between the HEP and alpha band power, alpha peak frequency, or alpha coherence. We did find great variability of HEP among individuals, and also HEP could be easily contaminated by direct cardiac electric activity. This may contribute to the negative finding of HEP in mindfulness training.

Several limitations are worth noting. Firstly, the number of participants in this brief report is relatively small and no control group was recruited. More participants are in future studies to ensure statistical power after correction for multiple comparisons. The limited sample size and absence of a control group may restrict the generalizability of the findings to broader populations. A second limitation is that although there is a significant increased correlation between cardiac and cerebral activities after mindfulness training, no causal relationship can be made. Additional measurement of breath rate may help explore the causal and mediative relationship between brain, cardiac and respiratory activities.

In sum, 8-week MBSR training can promote brain-heart coherence. Additionally, brain connectivity between two signals provides richer information compared to undirected functional connectivity (Baccala and Sameshima, 2001; Kaminski et al., 2016). The increased alpha rhythm-ECG synchronization at the frontal lobe during MBSR after 8-week training indicates the importance of coherence to maintain an optimal psychophysiological state. It is suggested that the coherence of neurophysiological activity, especially the neurocardiological interplay, plays a vital role in mind and body wellbeing (McCraty et al., 2009). This rhythm-based analysis can also be used to explore other types of meditations which may have different effects on APF and heart coherence.

Data availability statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB), The University of Hong Kong. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JG conducted the experiment and prepared the manuscript. RS analyzed the data and experiment design. HL assisted on data analysis, and together with AR and BW, helped prepare the manuscript and shared important ideas. ET and AT helped on statistics and experiment data analysis. HS helped on the experiment design and coordinated the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1008490/full#supplementary-material

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Inhibitory dysfunction may cause prospective memory impairment in temporal lobe epilepsy (TLE) patients: an event-related potential study

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Introduction: Prospective memory (PM) is the ability to remember future intentions, and PM function is closely related to independence in daily life, particularly in patients with temporal lobe epilepsy (TLE). As PM involves various cognitive components of attention, working memory, inhibition and other executive functions, this study investigated how TLE may affect PM components and the underlying neural mechanisms.

Methods: Sixty-four subjects were recruited, including 20 refractory TLE patients, 18 well-controlled TLE patients and 26 age-matched healthy controls. A set of neuropsychological tests was administered to assess specific brain functions. An event-related potential (ERP) task was used to further explore how PM and its components would be differentially affected in the two TLE types.

Results: Our findings revealed that: (1) refractory TLE patients scored lower than the healthy controls in the digit span, Verbal Fluency Test and Symbol Digit Modalities Test; (2) refractory TLE patients exhibited impaired PM performance and reduced prospective positivity amplitudes over the frontal, central and parietal regions in ERP experiments when compared to the healthy controls; and (3) decreased P3 amplitudes in the nogo trials were observed over the frontal-central sites in refractory but not in well-controlled TLE patients.

Discussion: To our knowledge, this is the first ERP study on PM that has specifically identified PM impairment in refractory but not in well-controlled TLE patients. Our finding of double dissociation in PM components suggests that inhibition dysfunction may be the main reason for PM deficit in refractory TLE patients. The present results have clinical implications for neuropsychological rehabilitation in TLE patients.

KEYWORDS

temporal lobe epilepsy (TLE), prospective memory (PM), working memory, inhibition, event-related potential (ERP), Go/Nogo, Oddball

Highlights

- Refractory temporal lobe epilepsy (TLE) patients performed worse than healthy controls in neuropsychological tests.
- Prospective positivity amplitudes were lower in refractory TLE patients and correlated with their impaired prospective memory (PM) function.
- Impairment in inhibition function may be the main reason for worse PM in refractory TLE patients.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common type of epilepsy. TLE patients can have frequent seizures and cognitive dysfunction. The latter may severely compromise TLE patients' daily functirons and social life (Black et al., 2010). Prospective memory (PM) performance relies on a set of cognitive abilities to enable us to maintain an intention for future actions by responding to event- or time-based cues which, in turn, trigger the intended action at the appropriate time (Kourtesis et al., 2021). Numerous studies in TLE patients have shown cognitive impairment, particularly in memory and executive functions (Stafstrom, 2007; Jackson-Tarlton et al., 2020; Kloc et al., 2022). As these functions are essential for PM performance, it is plausible that TLE patients have PM impairment.

Several studies in epilepsy patients have reported poor PM performance alongside memory and executive dysfunction (Adda et al., 2008; Wandschneider et al., 2010; Rai et al., 2015; Mills et al., 2022). For instance, Adda et al. (2008) reported that PM impairment in patients with mesial TLE is associated with hippocampal sclerosis, suggesting a significant role of the hippocampus in PM. PM may be impaired in other epilepsy syndromes. For example, PM impairment in patients with juvenile myoclonic epilepsy is genetically determined (Wandschneider et al., 2009, 2010). Despite these findings, there is a scarcity of neurophysiological research focused on PM in TLE patients, particularly concerning the underlying neural basis. This underscores the need for further investigation into the neural mechanisms of PM impairment in TLE and other epilepsy syndromes.

To successfully perform a PM task, an individual must execute a planned action upon encountering an external or internal cue. Paying attention to the cue is necessary for PM performance. In addition, the ongoing tasks must be ceased to allow for accomplishment of the PM task (Graf and Uttl, 2001). Another critical component of PM is memory itself, which is called the retrospective memory component in PM tasks. Memory impairment can cause PM failure. Our previous studies have found that patients with dementia and healthy elderly individuals exhibit varying degrees of PM impairment with long- and short-range brain fasciculi potentially playing differential roles (Gao et al., 2013, 2014). Innumerable neural fasciculi contribute to the dynamic function of the brain networks.

Similar to dementia and schizophrenia, epilepsy is also considered a neural network disease affecting not only local brain regions such as the temporal lobe but also other more distant brain areas (Kanner et al., 2017; Scharfman et al., 2018). Such network dysfunction may impact various cognitive functions in epilepsy patients, including attention, working memory, inhibition and execution. Several studies, together with a review, have reported evidence of working memory dysfunction in TLE patients (Wagner et al., 2009; Stretton and Thompson, 2012; Stretton et al., 2013). As the brain network responsible for executive function overlaps with that for working memory function, working memory deficits in TLE patients may lead to executive dysfunction.

Numerous studies have reported pathological brain network activity that may cause memory impairment in epilepsy (Kucewicz et al., 2013), and these altered brain networks could induce other cognitive dysfunction in TLE patients (Yang et al., 2018). Memory impairment is well-known in epilepsy (Hall et al., 2009; Parra-Diaz and Garcia-Casares, 2019). However, fewer studies in epilepsy patients have focused on PM performance. Investigating PM performance in TLE patients is essential because PM impairment adversely affects short-term tasks, long-term episodic tasks, and repetitive routine activities. Adequate PM function is crucial for the independence of all patients with any neurological disease in daily activities such as taking medication after meal and turning off the stove on time.

Recent studies on cognitive profile have provided valuable insights into the neuropsychological deficits and neural correlates in TLE (Hermann and Seidenberg, 2007; Reyes et al., 2019). Furthermore, a recent study has documented a large scale disorganization of memory and executive function in adult TLE patients (Caciagli et al., 2023); these findings corroborated with results in pediatric TLE patients (Oyegbile et al., 2018). Taken together, these studies highlight our evolving understanding of cognitive impairments in TLE and the importance of further investigation into the underlying neural mechanisms.

Neuropsychological questionnaires have been used to assess executive and other cognitive functions in TLE patients, including the Faux Pas test (Black et al., 2010), Wisconsin card sorting task (Ma et al., 2007), Stroop test (Labudda et al., 2009), Trail-making test (Ma et al., 2007), and Delis-Kaplan executive function system test (Takaya et al., 2006). These questionnaires could help researcher evaluate and understand PM function. However, questionnaires typically cannot differentiate among neural correlates such as attention, working memory, inhibition and execution, which are required for PM performance.

Executive function also plays a significant role in PM performance. Taxing the central executive processes of working memory can reduce the efficiency of PM (West et al., 2007). The executive system facilitates PM by tuning the responsiveness of neural systems within the extrastriate, posterior temporal, and frontal association cortices that support performance processing in PM (McNerney, 2006; West et al., 2007). It has been reported that PM performance requires several cognitive processes, mediated by brain regions including the subcortical-frontal-parietal network

Abbreviations: ANCOVA, analysis of covariance; BDI, Becker's Depression Inventory; DS, digit span; DSF, digit span forward; DSB, digit span backward; ERP, event-related potential; fMRI, functional MRI; HEA, healthy; ISI, inter-stimulus interval; PM, prospective memory; REF, refractory; SDMT, Symbol Digit Modalities Test; TLE, temporal lobe epilepsy; VFT, Verbal Fluency Test; VFT1, Verbal Fluency Test of vegetables and fruits; VFT2, Verbal Fluency Test of animals; WEL, well-controlled.

and limbic-hippocampal memory network (Adda et al., 2008; Burgess et al., 2011; Alves et al., 2019). Regarding the two most specific functions, attention allocation and ongoing task inhibition, however, their relevant neural mechanisms have not yet been clarified. Clarification of these mechanisms can permit specific treatment or clinical application.

This study aimed to use the event-related potential (ERP) technique to investigate attention and inhibition in PM. ERP offers a high temporal resolution and can help delineate potential impairments through typical neuropsychological paradigms like the Oddball experiment and Go/Nogo experiment (Adda et al., 2008; Burgess et al., 2011; Alves et al., 2019). To delineate the neural mechanism of PM and prospective positivity, this study also examined the roles of attention/working memory and inhibition in PM using behavioral and ERP methods. Specifically, we aimed to differentiate between these key components in PM performance of TLE patients using a series of ERP experiments. We hypothesized that TLE patients might exhibit worse PM performance than healthy controls and that PM impairment might differ between refractory and well-controlled TLE patients. This distinction can only be made through further investigation into the different components of PM.

2. Experimental procedures

2.1. Participants

Adult patients aged 61 years or younger and having a clinical diagnosis of TLE with or without secondary generalization were recruited from the Epilepsy Clinic of Queen Mary Hospital, Hong Kong. They were divided into the refractory (REF) group and well-controlled (WEL) group. TLE diagnosis was based on medical history, seizure semiology, MRI findings and multiple EEG recordings in accordance with the International League against Epilepsy guidelines (Reynolds, 2002). All patients have a temporal lobe lesion on MRI and/or temporal lobe epileptiform discharges on EEG and/or other evidence of TLE. REF group of patients had experienced three or more complex partial epileptic seizures per half-year in the preceding 1-year period despite using at least three antiepileptic drugs. WEL group of patients had had no epileptic seizures within the same period. All the patients have a TLE history of at least 3 years. There was no significant difference between the two epilepsy groups concerning the age of epilepsy onset using an independent t-test. However, the REF group had a significantly longer duration of epilepsy. Patients with other neurological or psychiatric diseases were excluded. Healthy age- and sex-matched native Cantonese-speaking controls with no neurological or psychiatric history were also recruited as the healthy (HEA) group. Becker's Depression Inventory (BDI) was used to exclude participants with severe depression (Steer et al., 1999). Only right-handed subjects were included. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster for human research. All participants were well informed about the study and provided informed written consent. Results were expressed in mean ± standard deviation.

2.2. Neuropsychological tests and analysis

Each participant underwent a set of neuropsychological tests using three questionnaires administered in a random order. These included the digit span (DS) Forward/Backward (DSF/DSB), the Verbal Fluency Test (VFT) of vegetables and fruits (VFT1) and the VFT of animals (VFT2), and the Symbol Digit Modalities Test (SDMT) written part and the SDMT oral part (Silva et al., 2018; Zhang et al., 2021). Univariate analysis of covariance (ANCOVA) with education level set as a covariate was used to compare among the three groups regarding their demographic and clinical characteristics as well as concerning (a) DSF and DSB, (b) VFT1 and VFT2, and (c) SDMT written and SDMT oral using SPSS software (Version 22.0).[1] The Turkey *post-hoc* test was used to detect the difference between any two groups. A $p < 0.05$ was taken to infer statistical significance.

2.3. ERP task

2.3.1. Task design

Four tasks were administered, including the Ongoing Task, the PM Task, the Oddball Task, and the Go/Nogo Task. They were adapted from the arrow-and-color bar task of previous studies (Burgess et al., 2001; Gao et al., 2013). To differentiate among various cognitive components, the same PM cue of the PM task was used in the Oddball Task and the Go/Nogo Task albeit with different instructions. The Ongoing Task was used to measure basic cognitive function and reaction speed. The Oddball Task and the Go/Nogo Task were designed to separately measure attention/working memory and inhibitory function. Measuring these cognitive functions may help identify the components responsible for impaired PM performance in TLE patients.

The computer screen background was in black. A white arrow pointing to the left or right was horizontally placed in the center of the screen with two parallel bars of different colors horizontally positioned at equal distances above and below the arrow (Burgess et al., 2001). The colors of the bars were randomly chosen from standard red, green and blue. Two horizontally arranged keyboards were used in the tasks with the left one for the left index finger and the right one for the right index and middle fingers (Gao et al., 2013). The Ongoing Task was always performed first, and this was followed by the PM Task, the Oddball Task and the Go/Nogo Task in a random but counterbalanced sequence among all the participants.

In the Ongoing Task, the participants were instructed to disregard the bar colors and press the right keyboard buttons with their right index finger for the left-pointing arrow and with their right middle finger for the right-pointing arrow (**Figure 1A**). The Ongoing Task had a total of 120 trials with 30 trials in each of the four sessions and a 5-s resting period between sessions.

In the PM Task, the participants were instructed to press the right keyboard buttons according to the arrow direction using the right index or middle finger like that of the Ongoing Task when the

1 www.ibm.com/products/spss-statistics

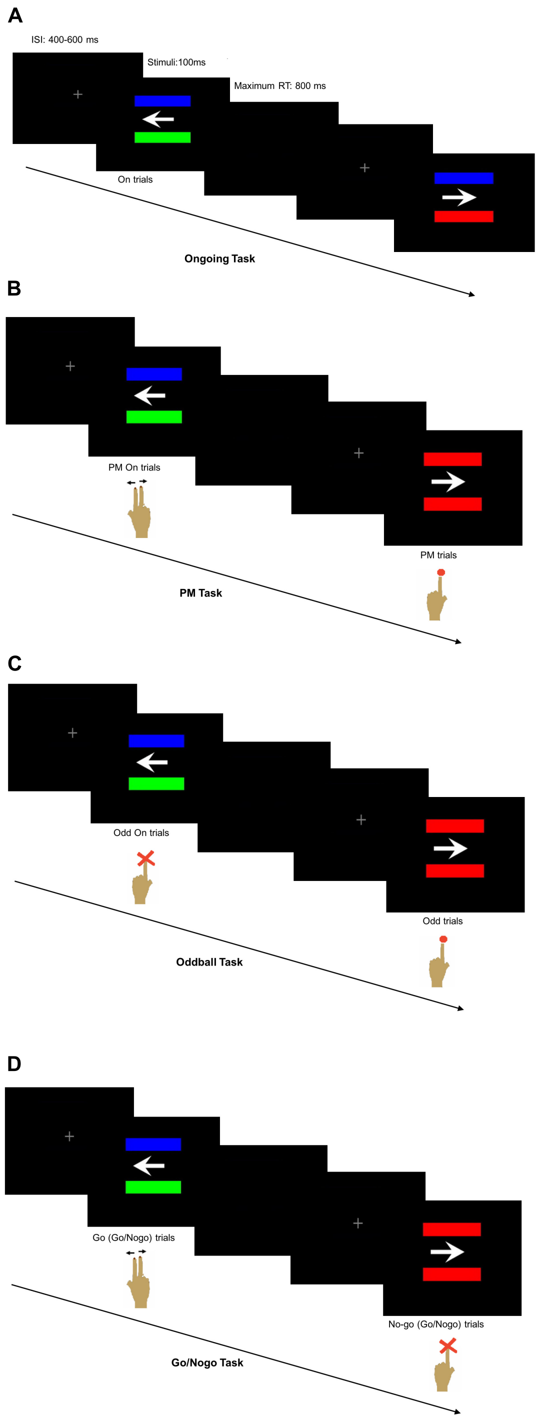

FIGURE 1
Computer screen appearance with two horizontally positioned parallel bars **(A)** of different colors in the Ongoing Task reminding the participant to press the right keyboard buttons according to the arrow direction, **(B)** either of different colors in the ongoing trials of prospective memory (PM) Task reminding the participant to press the right keyboard buttons according to the arrow direction or of same colors in the PM trials reminding the participant to press the left keyboard button, **(C)** either of different colors in the ongoing trials of Oddball Task reminding the participant not to press any button or of the same colors reminding the participant to press the left keyboard button, and **(D)** either of different colors reminding the participant to press the right keyboard buttons according to the arrow direction or of same colors reminding the participant not to press any button.

two bars were of different colors. Occasionally, the PM cues with two same-colored bars would appear, and the participants would disregard the arrow direction and press the left keyboard button using the left index finger (**Figure 1B**). The PM Task had a total of 240 trials with 30 trials in each of the eight sessions and a 5-s resting period between sessions. Six trials per session had the PM cues, making up a total of 48 randomly interpolated PM cues for all eight sessions of the PM Task. The first seven trials of each session would not contain the PM cues. The inter-stimulus interval (ISI) was randomly set at 400, 500, or 600 ms to avoid stimuli expectation.

In the Oddball Task, the participants were required to pay attention to the PM cues, disregard the arrow direction and respond to press the left keyboard button using their left index finger (**Figure 1C**). They would not press any button when the two bars were of different colors. In the Go/Nogo Task, the participants had to respond with their right index or middle finger according to the arrow direction when the bars were of different colors. They were instructed to disregard the arrow direction and refrain from pressing any button when seeing the PM cues (**Figure 1D**). The number of trials per session, the number of session per task, the number and random appearance of the PM cues, and the stimuli settings were similar to the PM Task. All the participants were given explicit instructions about the tasks so that they fully understood what to do for each task. In addition, the participants were given sufficient practice to ensure their accurate performance in each task.

2.3.2. ERP data acquisition

Each participant would sit comfortably and calmly in an armchair inside a dimly lit room with a computer screen set about 60 cm in front of the face. A continuous recording of 128-channel scalp EEG (QuikCap, Compumedics Neuroscan, El Paso, TX, USA) and 4-channel horizontal and vertical electrooculography was made using Neuroscan 4.3 software (Compumedics, Neuroscan, El Paso, TX, USA). A band-pass filter of 0.01 to 100 Hz and a gain of 1,000 were used. Two reference electrodes were placed behind the left and right mastoids. The midline frontal electrode located on the EEG cap was the ground electrode. Electrode impedances were maintained below 30 kΩ (Sik et al., 2017).

2.3.3. Behavioral data analysis

The behavioral data from the computer-based tests were recorded by the E-prime program.[2] Trials with a reaction time more than 800 ms were excluded because these results reflected occasional inattention rather than poor test performance. All data sets were reassembled after primary data processing and then further analyzed using SPSS (Version 22.0). Missing data were excluded using listwise deletion. Repeated measures ANCOVA was used to test group differences in the four tasks with education level set as a covariate. The Turkey *post-hoc* test was also used. The strength of the linear relationship between the ERP behavioral data of each task and the results of psychological tests was evaluated using the Pearson correlation.

2 https://pstnet.com/products/e-prime/

2.3.4. ERP components of interest

Prospective positivity component: This component is an EPR indicator of switching from an ongoing to PM activity (Bisiacchi et al., 2009; West, 2011). Task switching is essential for PM performance in daily living (Costa et al., 2015; Faraut et al., 2021). PM deficits has been reported to adversely affect the recall of information about COVID pandemic (Aizpurua et al., 2021). The prospective positivity is related to the inhibition of the ongoing activity upon detection of a PM cue and the switching process (Joly-Burra et al., 2018).

P300 component: Oddball stimuli would generate a positive ERP wave at around 300 ms, which is the P300 component. P300 was calculated and measured in the time window of 300–600 ms after the stimuli, which is related to attention and working memory (Yao et al., 2014; Gregory et al., 2015). P300 may be generated from the functional interaction between the frontal lobe and hippocampus/temporal-parietal lobes (Huang et al., 2015). Utilizing a deviant oddball experiment, TLE patients have been found to exhibit reduced P300 amplitudes in the temporal region and, to a lesser extent, in the frontal region (Bocquillon et al., 2011; Artemiadis et al., 2014; Mukheem Mudabbir et al., 2021).

P3 component: It was measured in the Go/Nogo Task. P3 generally represents the inhibition process, which is another essential aspect of PM performance to suppress/delay a response or interrupt an activity and avoid interference (Johnstone et al., 2005). It is necessary for PM performance because participants often need to inhibit an ongoing task and switch to the PM task at the appropriate time (Schnitzspahn et al., 2013). The P3 component, an ERP marker associated with inhibition process (Polich, 2007), has been widely studied in neurological diseases such as schizophrenia (Farzan et al., 2010), attention-deficit hyperactivity disorder (Cubillo et al., 2010), and idiopathic generalized epilepsy (Chowdhury et al., 2014). Neuroimaging studies have shown evidence of prefrontal cortex involvement in the inhibitory response (Apsvalka et al., 2022; De Vis et al., 2022), with several types of inhibition mediated by other different cortical areas (Bokura et al., 2001; Ridderinkhof et al., 2004).

2.4. ERP data analysis

Event-related potential data were analyzed using Neuroscan 4.3 Software (Neurosoft, Inc., Sterling, VA, USA). The raw EEG data were filtered off-line with a zero phase-shift digital filter and a 0.1 to 30 Hz bandpass. Eye blink artifacts were mathematically corrected by the ocular reduction function of the software. EEG data were segmented into 800 ms epochs with a 100 ms pre-stimulus baseline according to the event markers. Time point zero indicated the start of the visual stimulus. Segments exceeding 100 μV were automatically discarded. Individual epochs were normalized relative to a 100 ms pre-stimulus baseline, and the calculated linear trend was removed across the entire epoch according to the pre-stimulus baseline. Same types of stimuli for trials of different tasks were averaged across all sessions to generate the group ERP. ERP components of interest, including the prospective positivity component, P300 component and P3 component, were identified (Schmiedt-Fehr and Basar-Eroglu, 2011; Cruz et al., 2016; Sowndhararajan et al., 2018). The mean amplitudes were calculated for selected ERP components with latencies from 400 to 700 ms in the PM Task, from 300 to 600 ms in the Oddball Task and from 350 to 600 ms in the Go/Nogo Task.

Scalp maps were obtained using the software to illustrate different ERP components, i.e., prospective positivity component in PM trials, P300 component in the Oddball trials, and P3 component in the nogo trials. Afterward, the mean amplitudes were compared among the HEA, WEL, and REF groups using ANCOVA with education level set as a covariate (SPSS Version 22.0). The Turkey *post-hoc* test was also used.

3. Results

3.1. Demographics of the participants

Sixty-four subjects aged 24–61 years participated in this study. The REF group had 20 patients (43.9 $\pm$ 11.6 years; 8 with left-sided TLE), and the WEL group had 18 patients (48.0 $\pm$ 12.0 years; 10 with left-sided TLE). Patients of the REF group had 16.0 $\pm$ 20.8 simple partial seizures and/or partial seizures with generalization in the past 6 months, whereas patients of the WEL group had no seizure within the same period. The HEA group had 26 subjects (43.0 $\pm$ 12.4 years). Years of education were not comparable among the groups with the HEA group having longer years of education than the two TLE groups but having no difference between REF and WEL groups. There were more left-sided or bilateral epileptic foci in the WEL group whilst the REF group had more right-sided epileptic foci. There were no significant differences among the groups in age, sex, epilepsy duration, age of onset of epilepsy, MRI/EEG/other evidence, and BDI scores (**Table 1**). The current drug treatment for each patient in the two TLE groups is listed in **Supplementary Table 1**.

3.2. Neuropsychological tests

After controlling for education level, ANCOVA revealed a significant difference in the DSF scores [$F(2,61) = 3.756$, $p = 0.029$] among the groups (**Table 2**). *Post-hoc* test showed that the HEA group had significantly higher scores than the WEL group ($p = 0.025$) and the REF group ($p = 0.024$). There were also significant intergroup differences in the VFT1 scores [$F(2,61) = 3.360$, $p = 0.040$] and the VFT2 scores [$F(2,61) = 3.950$, $p = 0.019$]. *Post-hoc* test showed that the HEA group scored higher than the REF group in VFT1 ($p < 0.01$) and VFT2 ($p = 0.033$). In addition, the REF group scored lower than the WEL group in VFT2 ($p < 0.01$; **Table 2**). There was a trend for intergroup difference in SDMT oral scores because of the low score in REF group when compared to the HEA group.

3.3. Behavioral results from ERP tasks

Across all the groups, the participants tended to perform the ongoing trials faster than other trials with the shortest reaction time (**Supplementary Figure 1**). The reaction time tended to be progressively longer in odd trials of the Oddball Task, nogo trials of

TABLE 1 Demographic and clinical characteristics of the three groups of participants.

	HEA group (*n* = 26)	WEL group (*n* = 18)	REF group (*n* = 20)	*P*-value*
Age, years	43.0 ± 12.4	48.0 ± 12.0	43.9 ± 11.6	0.854
Sex, male/female	13/13	11/7	11/9	0.752
Education, years	15.8 ± 3.5	12.0 ± 4.9	11.6 ± 4.0	0.568
Epilepsy duration, years	NA	16.4 ± 7.6	24.2 ± 9.2	0.004
Onset age, years	NA	30.8 ± 14.9	19.0 ± 12.1	0.600
Location, left/right/bilateral	NA	10/2/5	8/11/1	0.009
Evidence, MRI/EEG/others	NA	14/12/0	17/12/3	0.084
Becker's Depression Inventory	6.9 ± 4.3	8.3 ± 6.1	10.0 ± 5.0	0.178

HEA, healthy group; WEL, well-controlled; REF, refractory. *ANOVA or independent *t*-test.

TABLE 2 Neuropsychological tests.

	HEA group	WEL group	REF group	ANCOVA *P*-value		*Post hoc*	
					HEA vs. WEL	HEA vs. REF	WEL vs. REF
DSF	9.7 ± 1.1	8.3 ± 1.2	8.1 ± 1.8	0.029*	0.025*	0.024*	0.960
DSB	7.7 ± 1.9	6.3 ± 1.7	6.0 ± 2.1	0.528	0.320	0.345	0.968
VFT1	21.2 ± 3.3	17.3 ± 9.6	14.2 ± 4.3	0.040*	0.244	0.006**	0.162
VFT2	21.8 ± 4.0	20.0 ± 10.8	14.3 ± 4.2	0.019*	0.775	0.033*	0.008**
SDMT written	59.0 ± 10.6	52.7 ± 17.3	47.0 ± 13.6	0.386	0.761	0.197	0.313
SDMT oral	66.9 ± 12.2	58.4 ± 16.0	51.3 ± 15.3	0.093	0.383	0.038*	0.197

DSB, digit span backward; DSF, digit span forward; HEA, healthy; WEL, well-controlled; REF, refractory; SDMT, symbol digit modalities test; VFT1, verbal fluency test1 (fruits); VFT2, verbal fluency test2 (animals). ANCOVA: $^*p < 0.05$; $^{**}p < 0.01$.

TABLE 3 Behavioral results from ERP tasks.

	HEA group	WEL group	REF group	ANCOVA *P*-value	*Post hoc*		
					HEA vs. WEL	HEA vs. REF	WEL vs. REF
Accuracy (%)							
On	94.8 ± 8.9	93.6 ± 9.4	89.4 ± 10.9	0.165	0.916	0.154	0.378
Odd on	99.9 ± 0.3	99.6 ± 0.7	99.6 ± 0.6	0.163	0.179	0.344	0.913
Odd	96.7 ± 7.3	96.5 ± 4.6	94.5 ± 12.0	0.65	0.996	0.657	0.752
Go/Nogo on	96.4 ± 8.0	93.6 ± 10.4	82.8 ± 24.8	0.015*	0.832	0.014*	0.095
Go/Nogo	90.2 ± 7.0	92.1 ± 5.7	88.8 ± 5.8	0.296	0.592	0.761	0.266
PM on	89.1 ± 4.9	87.2 ± 6.2	85.0 ± 5.0	0.043*	0.501	0.033*	0.406
PM	90.9 ± 6.2	85.5 ± 6.3	79.7 ± 7.1	<0.001**	0.024*	<0.001**	0.023*
Reaction Time (ms)							
On	435.7 ± 55.3	444.4 ± 73.2	459.2 ± 62.7	0.46	0.895	0.428	0.751
Odd on	NA	NA	NA	NA	NA	NA	NA
Odd	459.0 ± 49.6	455.9 ± 61.6	466.1 ± 52.6	0.833	0.981	0.898	0.831
Go/Nogo on	490.8 ± 50.5	495.8 ± 77.1	502.8 ± 45.3	0.786	0.956	0.767	0.928
Go/Nogo	NA	NA	NA	NA	NA	NA	NA
PM on	498.4 ± 52.9	511.2 ± 75.0	533.4 ± 42.3	0.128	0.746	0.108	0.463
PM	548.2 ± 66.0	561.0 ± 65.7	568.9 ± 45.1	0.504	0.768	0.484	0.914

ERP, event-related potentials; HEA, healthy; Go/Nogo, Nogo trials in the Go/Nogo Task; Go/Nogo on, ongoing trials in the Go/Nogo Task; NA, not available; Odd, oddball trials in the Oddball Task; Odd on, ongoing trials in the Oddball Task; On, ongoing trials in Ongoing Task; PM, prospective memory (PM) trials in the PM Task; PM on, ongoing trials in the PM Task; WEL, well-controlled; REF, refractory. ANCOVA: $^*p < 0.05$; $^{**}p < 0.01$.

the Go/Nogo Task, ongoing trials of the PM Task and, finally, PM trials of the PM Task. Owing to the small sample sizes with relatively large variations, the trends were not significant statistically.

Table 3 summarizes the accuracy and reaction time of the three groups during different ERP tasks. The REF group tended to be less accurate than the other two groups in all except ongoing trials of the Oddball Task. Repeated measures ANCOVA with education level as the covariate revealed that the differences in accuracy were not significant except for doing the ongoing trials in Go/Nogo Task ($p = 0.015$) and PM task ($p < 0.05$) with the REF group being worse than HEA group as well as responding to PM cues in the PM Task ($p < 0.001$) with the REF group being worse than the other two groups and the WEL group worse than the HEA group. The HEA group tended to have a shorter reaction time than the TLE groups whilst the REF group tended to have a longer reaction time than the other two groups (**Table 3**). Nevertheless, the differences were not significant according to ANCOVA.

Supplementary Table 2 summarizes the Pearson correlation analysis results between the ERP behavioral data and neuropsychological tests of the questionnaires. Except for responding to PM cues of the Oddball Task and SDMT written scores in ongoing trials of the Go/Nogo Task, the accuracy of performing ongoing trials of the Ongoing Task, Go/Nogo Task and PM task as well as the accuracy of responding to PM cues of the PM Task were positively correlated with the results of neuropsychological tests ($p < 0.05$). The reaction time of performing ongong trials of the Ongoing Task was negatively correlated with the results of neuropsychological tests ($p < 0.05$; **Supplementary Table 2**). The reaction time of performing ongoing trials of the Go/Nogo Task was negatively correlated with the VFT1 and VFT2 scores ($p < 0.01$), and the reaction time of performing ongoing trials of the PM Task was negatively correlated with the DSF, VFT1 and VFT2 scores ($p < 0.05$).

3.4. ERP components of interest

3.4.1. PM Task

As an ERP indicator of responding to PM cues of the PM Task, prospective positivity between 400 and 700 ms was found over the frontal, central and parietal sites, and the outlined region in the scalp map represented the activated areas (**Figure 2**; see **Supplementary Figure 2** for the grand average ERP waveforms). The mean amplitudes of prospective positivity were as follows: the HEA group, Fz 6.49 ± 5.79 μV, Cz 7.84 ± 6.22 μV, Pz 5.15 ± 5.00 μV; the WEL group, Fz 4.67 ± 4.36 μV, Cz 5.03 ± 5.87 μV, Pz 3.85 ± 4.83 μV; and the REF group, Fz 1.98 ± 2.01 μV, Cz 1.59 ± 1.85 μV, Pz 1.46 ± 1.91 μV. ANCOVA with education level set as the covariate revealed a significant intergroup difference in the frontal, central and parietal sites [e.g., Fz, $F(2,61) = 4.054$, $p = 0.022$] with the *post-hoc* tests showing a significant difference between the HEA and REF groups ($p < 0.01$) but not between the HEA and WEL groups ($p = 0.287$) and between the WEL and REF groups ($p = 0.084$).

3.4.2. Oddball Task

The amplitude of P300 between 300 and 600 ms over the central-parietal sites in response to PM cues of the Oddball Task was used to measure attention and working memory, and the outlined region in the scalp map represented the activated areas (**Figure 3**; see **Supplementary Figure 3** for the grand average ERP waveforms). The mean amplitudes of P300 were as follows: HEA group, Fz 6.64 ± 4.78 μV, Cz 10.97 ± 6.04 μV, Pz 9.98 ± 5.09 μV; WEL group, Fz 3.80 ± 5.77 μV, Cz 6.37 ± 7.75 μV, Pz 5.10 ± 6.37 μV; and the REF group, Fz 7.18 ± 6.39 μV, Cz 9.16 ± 8.25 μV, Pz 6.78 ± 6.99 μV. ANCOVA with education level set as the covariate revealed a significant intergroup difference in the central-parietal sites [e.g., Pz, $F(2,61) = 3.185$, $p = 0.048$] with the *post-hoc* tests showing a significant difference between the HEA and WEL groups ($p < 0.05$) but not between the HEA and REF groups and between the WEL ($p > 0.05$) and REF groups ($p > 0.05$).

3.4.3. Go/Nogo Task

A P3 component between 350 and 600 ms and peaked at around 500 ms was observed over the frontal-central sites to indicate inhibition in response to PM cues of Go/Nogo Task, and the outlined region in the scalp map represented the activated areas (**Figure 4**; see **Supplementary Figure 4** for the grand average ERP waveforms). The mean amplitudes of Nogo P3 were as follows: the HEA group, Fz 10.94 ± 4.35 μV, Cz 10.40 ± 6.87 μV, Pz 7.85 ± 3.33 μV; the WEL group, Fz 9.63 ± 3.29 μV, Cz 9.88 ± 3.99 μV, Pz 4.78 ± 4.42 μV; and the REF group, Fz 8.34 ± 3.98 μV, Cz 8.67 ± 5.30 μV, Pz 5.29 ± 4.44 μV. ANCOVA with education level set as the covariate revealed a significant intergroup difference in the frontal-central sites [e.g., Fz, $F(2,61) = 3.786$, $p = 0.033$] with the *post-hoc* tests showing a significant difference between the HEA and REF groups ($p = 0.04$) but not between the HEA and WEL groups ($p > 0.05$) and between the WEL and REF groups ($p > 0.05$).

4. Discussion

Medial temporal lobe damage is associated with PM impairment to indicate the role of episodic memory (Burgess et al., 2007; Kliegel et al., 2008). TLE patients have temporal lobe dysfunctions, including impairment in episodic memory and PM (Jain et al., 2018; Li et al., 2022). Successful PM performance requires not only memory function but also attention, inhibition, and other execution functions of the frontal lobe. Indeed neurological and psychiatric patients with frontal neural circuitry damage frequently exhibit PM deficits (Kliegel et al., 2008). Thus, PM deficits in TLE patients warrant further investigations especially on its relatively less well studied prospective component of PM. In this first ERP study on PM impairment in TLE patients, the REF group have more left temporal lobe abnormalities. Patients with mesial temporal sclerosis on the left side have greater PM impairment than those with lesion on the right side (Adda et al., 2008).

The present results in DS, VFT and SDMT indicated impaired working memory, verbal function, and information processing speed, respectively, in TLE patients. The impairments are primarily found in the REF group of patients whereas the WEL group's worse DSF score indicated impaired working memory. VFT2 score was lower in the REF group of patients when compared to the WEL group to reveal an impairment of semantic fluency which is a

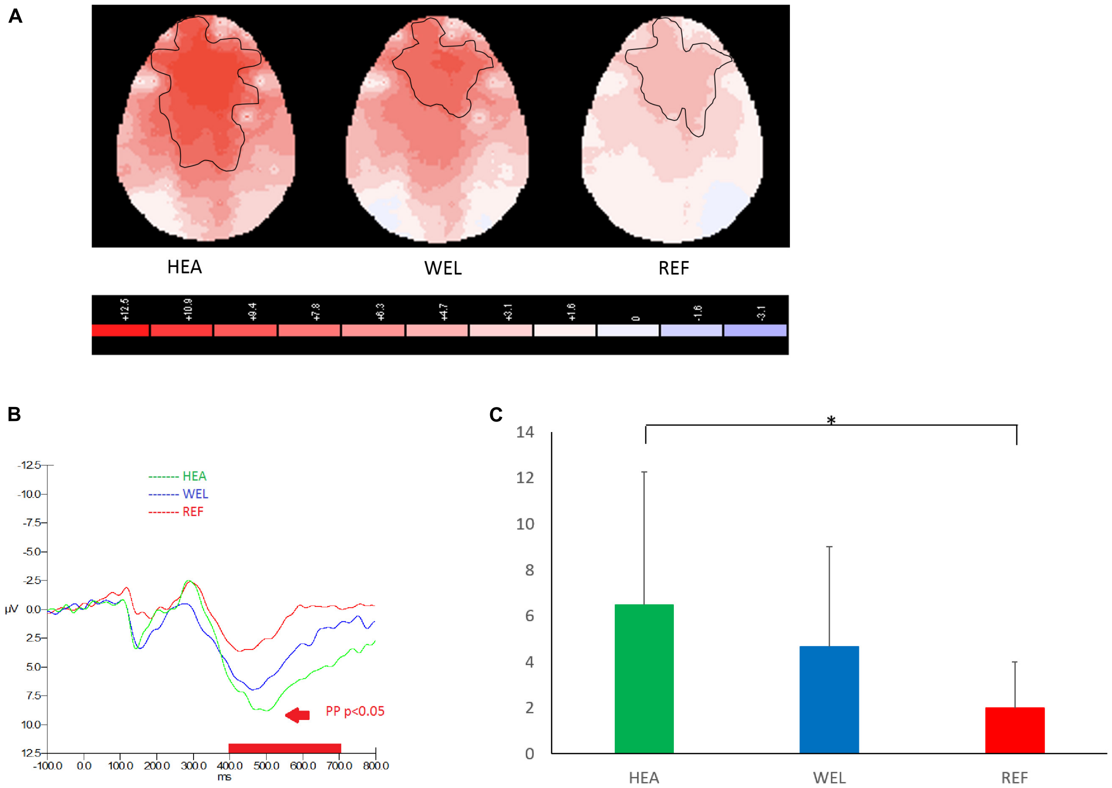

FIGURE 2
Prospective positivity (PP; 400–700 ms) during prospective memory (PM) trials of the PM Task with **(A)** 2-D scalp maps showing strongest and largest activations over the frontal, central and parietal sites in the healthy (HEA) controls, weakest and smallest activations in the refractory (REF) group of epilepsy patients and intermediate activations in the well-controlled (WEL) group, **(B)** grand average waveforms at Fz of the three groups, and **(C)** mean amplitudes at Fz of the three groups. Significant intergroup difference according to ANCOVA with education level set as the covariate. *$p < 0.05$ between the HEA and REF groups on the *post-hoc* test.

frontotemporal lobe function (Troyer et al., 1998; Lepow et al., 2010).

Recent literature has reported generalized cognitive impairment, particularly executive function and processing speed, in TLE to implicate a more extensive network dysfunction beyond the frontotemporal areas responsible for working memory and executive function (Oyegbile et al., 2018). Our neuropsychological results are in line with global cognitive impairment in TLE patients. Further correlation analysis has revealed potential association between PM task accuracy and working memory, semantic fluency, and processing speed. Our earlier study showed that declined processing speed in verbal and non-verbal tasks could explain the cognitive deficits in abnormal aging (dementia) and normal aging (Gao et al., 2013). As a network disease, therefore, it is plausible that TLE patients have various cognitive deficits.

Various cognitive resources such as attention, inhibition, and execution are required in successful PM performance. Behavioral results of our ERP experiments have revealed a longer response time in the PM Task when compared to other tasks in both groups of TLE patients and HEA group of controls. The REF group of patients tended to have the longest reaction time during the PM Task but the intergroup differences are not significant. Worst PM Task accuracy in the REF group of patients would indicate their impaired PM function. ERP studies on the PM Task could elucidate the potential neural mechanisms underlying PM dysfunction (Trimmel et al., 2017). In addition, we employed the Oddball Task and Go/Nogo Task to distinguish between attention/executive function and inhibitory functions which are critical in successful PM performance (McDaniel and Einstein, 2007, 2011).

Prospective positivity was clearly observed in all three groups during the PM Task with the lowest amplitude in the REF group of patients which is significantly reduced when compared to the HEL group of controls. As a key EPR indicator of PM function, prospective positivity is broadly seen over the central, parietal, and occipital regions of the scalp (West and Krompinger, 2005). In the present study, prospective positivity is mainly observed in the frontocentral brain regions responsible for task configuration, coordination, and task switching (Bisiacchi et al., 2009; Cruz et al., 2016; Mitra et al., 2022). Our findings suggest a role of prospective positivity in switching between ongoing activities and the PM Task. This is consistent with reported findings (Cona et al., 2014; Cejudo et al., 2022; Crook-Rumsey et al., 2022). The late positive complex has been postulated to reflect different cognitive processes, depending on whether the instructions would involve a dual-task or task-switch approach (Bisiacchi et al., 2009).

It has been proposed that patients with refractory TLE may have disrupted brain networks especially the fronto-central-temporal network (Lin et al., 2020). Other investigators and theorists have stressed on an interplay between the medial

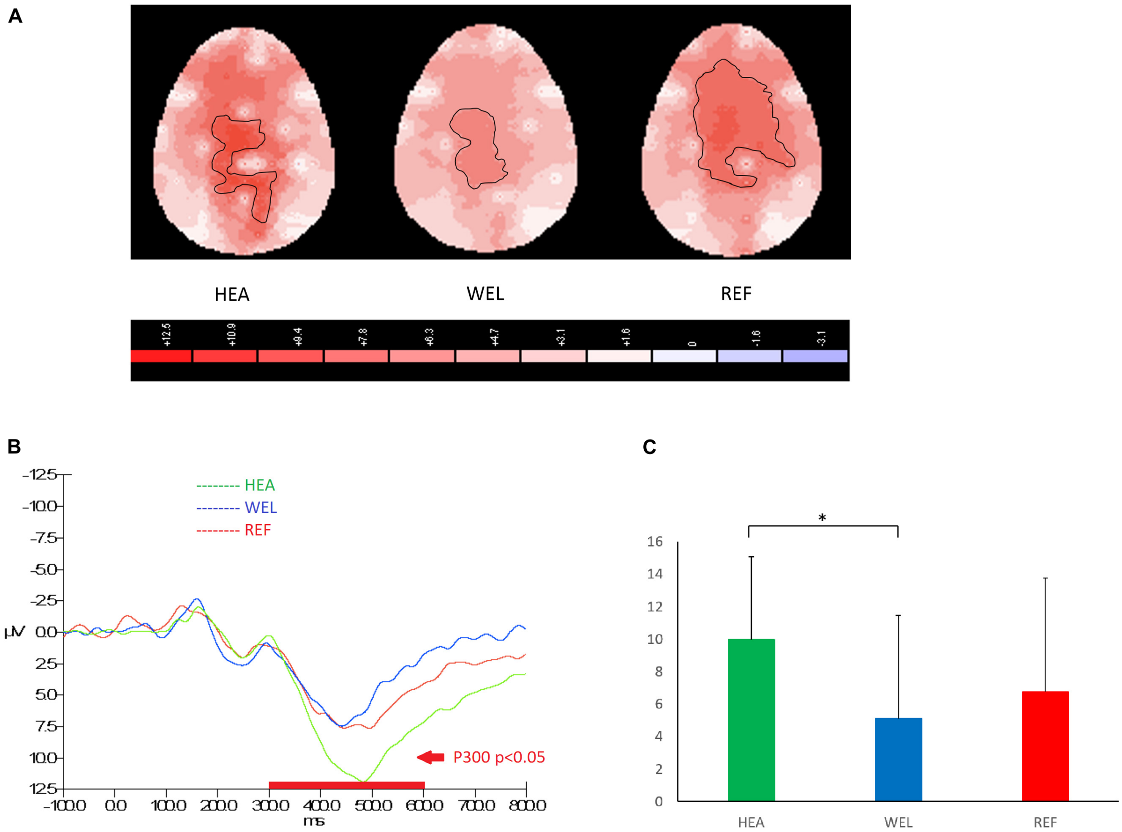

FIGURE 3
P300 component (300–600 ms) during oddball trials of the Oddball Task with **(A)** 2-D scalp maps showing stronger and larger activations over the central-parietal sites in the healthy (HEA) controls and refractory (REF) group of epilepsy patients but weaker and smaller activations in the well-controlled group, **(B)** grand average waveforms at Pz of the three groups, and **(C)** mean amplitudes at Pz of the three groups. Significant intergroup difference according to ANCOVA with education level set as the covariate. $^{*}p < 0.05$ between the HEA and WEL groups on the *post-hoc* test.

temporal lobe memory system and the frontal executive system in supporting PM function (Palmer and McDonald, 2000; Zimmer et al., 2001). PM studies using both functional neuroimaging and neuropsychological techniques including positron emission tomography, functional MRI (fMRI) and magnetoencephalography have revealed consistent activations in the lateral and orbital prefrontal cortices (Burgess et al., 2007, 2008) as well as the medial temporal lobe (Martin et al., 2007) during PM activities. Depending on the nature of different PM activities (Luck, 2014), prospective positivity is consisted of a variety of ERP components, including the P3b component (West and Wymbs, 2004; West et al., 2006), the late positive complex associated with task configuration (Bisiacchi et al., 2009) and the old-new recognition effect (West and Krompinger, 2005).

P300 component of the EPR response during the Oddball Task was mainly seen in central-parietal leads (Chen et al., 2001; Rocha et al., 2010). P300 components of lower amplitudes and longer latencies have been reported in other studies (Grunwald et al., 1999; Rocha et al., 2010). Two recent studies have reported decreased frontoparietal connectivity in TLE patients (Riley et al., 2010; Liao et al., 2011). TLE patients with unilateral hippocampal sclerosis have impaired working memory, patients with left or right-sided TLE have decreased right superior parietal lobe activation during working memory tasks, and progressive hippocampal deactivation is observed upon increasing task demands (Stretton and Thompson, 2012; Duarte et al., 2014). On the other hand, several imaging studies have also reported hippocampal activation during working memory tasks involving encoding, maintenance and retrieval processes (Axmacher et al., 2007; Mainy et al., 2007; Schon et al., 2009). Taken together, temporal lobe dysfunction plays a critical role of in working memory impairment, and the parietal lobe may also be involved. The propagation of epileptic activity from the epileptogenic zone to the eloquent cortex may lead to specific cognitive dysfunction (Hermann et al., 1988).

In the present study, P300 amplitudes in the Oddball Task were significantly lower in the WEL group but not REF group of patients when compared to the HEA group of controls, revealing impaired attention/working memory in stable but not unstable TLE patients. Our P300 amplitude results of WEL group but not REF group are in agreement with the literature (Schomaker et al., 2021). P300 amplitude has also been found to reflect treatment effectiveness (Sun et al., 2008). For example, increased P300 amplitude at the parietal midline (Pz) electrode was observed when the epilepsy responded well to vagus nerve stimulation therapy (De Taeye et al., 2014; Wostyn et al., 2017). Further studies are needed to explain our P300 amplitude findings in REF group. A plausible explanation is that there are more left-sided epileptic

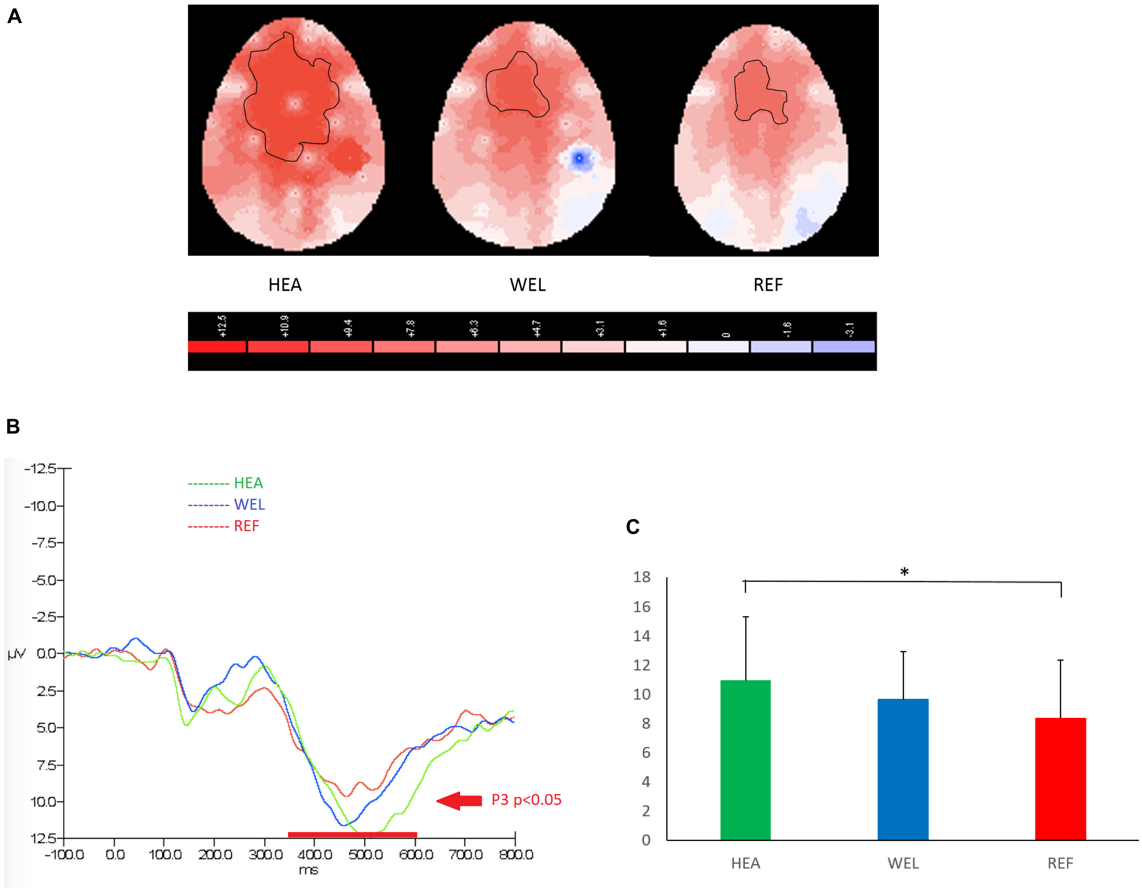

FIGURE 4
P3 (350–600 ms) during nogo trials of the Go/Nogo Task with **(A)** 2-D scalp maps showing strongest and largest activations over the frontal-central sites in the healthy (HEA) controls, weakest and smallest activations in the refractory (REF) group of epilepsy patients and intermediate activations in the well-controlled (WEL) group, **(B)** grand average waveforms at Fz of the three groups, and **(C)** mean amplitudes at Fz of the three groups. Significant intergroup difference according to ANCOVA with education level set as the covariate. $^{*}p < 0.05$ between the HEA and REF groups on the *post-hoc* test.

foci in the WEL group whilst patients of the REF group have more right-sided epileptic foci. In TLE patients with mesial temporal sclerosis, reduced P300 is seen especially in those with left-sided sclerosis (Grunwald et al., 1999). Another ERP study has reported that patients with left-sided mesial temporal sclerosis had P300 with lower amplitude and longer latency than controls, mainly at the central C3 and C4 regions (Rocha et al., 2010). The present study did not find any significant difference in P300 latency. Some ERP studies on epilepsy patients have reported longer latency of P300 (Naganuma et al., 1997; Wu et al., 1997; Sowndhararajan et al., 2018). Nevertheless, other studies have reported no change in P300 latency in epilepsy patients and no effect from epilepsy treatment (Sun et al., 2008; Boscariol et al., 2015).

Nogo P3 is linked to inhibitory neural activity in the frontal lobe. To our knowledge, there is no published ERP study on inhibitory function in TLE patients; P3 component of the EPR response during the Nogo Task was mainly seen in frontocentral leads. An important role of frontocentral sites in inhibition is in line with the literature (Aron et al., 2004; Swick et al., 2008). On the other hand, there is a good correlation between orbitofrontal cortex activity on fMRI and behavioral performance in Go/Nogo tasks (Criaud and Boulinguez, 2013). Previous EPR studies have localized the Nogo P3 to the left orbitofrontal cortex (Falkenstein et al., 1999) or the left lateral orbitofrontal area (Bokura et al., 2001). Patients with frontal cortex damage have abnormal social behavior, including inappropriate activities and disinhibited behavior (Deets et al., 1970; Kratsman et al., 2016), and they also have impaired PM function (Burgess et al., 2008).

Nogo P3 amplitudes were significantly lower in the REF group but not WEL group of patients when compared to the HEA group of controls, revealing impaired inhibition in unstable but not stable TLE patients. Taken together with the amplitudes of prospective positivity and P300 components, the neuromechanism for PM impairment in REF group of patients may involve impaired task switching and inhibition rather than attention deficit. Despite the attention deficit in the WEL group of patients, PM impairment was not observed when their frontal inhibitory function was unaffected. In other words, the present findings of double dissociation in EPR components suggest that inhibition dysfunction is a more important mechanism than attention deficit in causing PM deficit. It is speculated that frequent seizures in REF group of patients may spread to affect other brain regions, such as the frontal lobe, anterior cingulate cortex and thalamus, resulting in compromised inhibitory process (Akinci et al., 2023).

There has been a growing body of research on the neuropsychological deficits and large-scale disorganization of memory and executive function in TLE patients (Hermann and Seidenberg, 2007; Reyes et al., 2019; Caciagli et al., 2023). The present results support the notion that epilepsy is a disorder of brain network and that refractory TLE is associated with significant cognitive impairments. More research on the underlying neural mechanisms of cognitive deficits is needed to improve our diagnosis, treatment and management. Given the importance of PM performance in daily living and the dependence of PM on various cognitive components, disrupted neural network information processing would cause PM impairment in TLE and other epilepsies. PM deficit can be an important biomarker of severity in TLE. As such, research on antiepileptic drugs should go beyond seizure control and include cognitive functions and PM performance as potential benefits or adverse effects (Barr, 2002; Mattson, 2004).

This study has two limitations. First, the number of left- and right-sided lesions was imbalanced in the two groups of TLE patients. This important confounder should be addressed in future studies to better understand the role of lateralization in PM deficits of TLE patients. Second, the Pearson correlation analysis results between the ERP behavioral data and neuropsychological tests of the questionnaires are both exploratory and preliminary findings. Larger sample sizes with increased statistical power are needed to study on the correlation between ERP components and neuropsychological tests.

In summary, three ERP components were studied in TLE patients and healthy subjects during the PM Task, Oddball Task and Go/Nogo Task with ERP results correlated with neuropsychological tests and behavioral data to delineate the relevance of attention and inhibition in PM function. TLE patients were separated into two groups according to their seizure control. Impaired PM function in refractory TLE patients may be attributed to their impaired inhibition over frontal-central sites since well-controlled TLE patients had no PM deficit despite their deficit in attention. Our findings on this double dissociation suggest that the adverse effects of TLE on PM function may be more dependent on inhibitory dysfunction than attention dysfunction. Nevertheless, there are other factors for PM impairment in refractory TLE patients, including antiepileptic drugs, depression, and sociological stigma. Further studies are needed. The current finding of PM deficits in refractory TLE patients have clinical implications in their daily living and neuropsychological rehabilitation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HY and JG conducted the experiment and drafted the manuscript. RS-KC designed the experiment. WM recruited the patients and revised the manuscript. T-QT reviewed the statistical analyses and revised the manuscript. RC supervised and coordinated the study and critically revised manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1006744/full#supplementary-material

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EEG-based investigation of effects of mindfulness meditation training on state and trait by deep learning and traditional machine learning

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Introduction: This study examines the state and trait effects of short-term mindfulness-based stress reduction (MBSR) training using convolutional neural networks (CNN) based deep learning methods and traditional machine learning methods, including shallow and deep ConvNets as well as support vector machine (SVM) with features extracted from common spatial pattern (CSP) and filter bank CSP (FBCSP).

Methods: We investigated the electroencephalogram (EEG) measurements of 11 novice MBSR practitioners (6 males, 5 females; mean age 35.7 years; 7 Asians and 4 Caucasians) during resting and meditation at early and late training stages. The classifiers are trained and evaluated using inter-subject, mix-subject, intra-subject, and subject-transfer classification strategies, each according to a specific application scenario.

Results: For MBSR state effect recognition, trait effect recognition using meditation EEG, and trait effect recognition using resting EEG, from shallow ConvNet classifier we get mix-subject/intra-subject classification accuracies superior to related previous studies for both novice and expert meditators with a variety of meditation types including yoga, Tibetan, and mindfulness, whereas from FBSCP + SVM classifier we get inter-subject classification accuracies of 68.50, 85.00, and 78.96%, respectively.

Conclusion: Deep learning is superior for state effect recognition of novice meditators and slightly inferior but still comparable for both state and trait effects recognition of expert meditators when compared to the literatures. This study supports previous findings that short-term meditation training has EEG-recognizable state and trait effects.

KEYWORDS

meditation state classification, deep learning, electroencephalogram (EEG), state and trait characteristics, convolutional neural networks (CNN), mindfulness-based stress reduction (MBSR), filter bank common spatial pattern (FBCSP)

1. Introduction

With the popularization of mindfulness meditation, especially the mindfulness-based stress reduction (MBSR) developed in a behavioral medicine environment suitable for people suffering from chronic pain, stress, depression and various other diseases (Khoury et al., 2015), this intrinsic neuromodulation method has gradually attracted widespread attention in the field of psychology and neuroscience. Since an 8 weeks short-term training of MBSR is effective on behavioral and brain function modulation even for novices (Kirk et al., 2016; Kral et al., 2018; Kwak et al., 2019; Favre et al., 2021; Rahrig et al., 2021; Guendelman et al., 2022), MBSR training is helpful for emotion and attention regulation, as well as decision making and executive functions, therefore has many clinical applications. It is important to assess the training effectiveness of MBSR practitioners and provide feedback to improve their performance (Farkhondeh Tale Navi et al., 2022; Yu et al., 2022). Therefore, mindfulness meditation state recognition is of great importance for online or offline feedback during MBSR training and practice (Brandmeyer and Delorme, 2020).

Neural mechanism of mindfulness meditation and neural characteristics of meditation state can be investigated by neuroimaging and neurophysiology using magnetic resonance imaging (MRI) (Gotink et al., 2016; Valk et al., 2017), functional magnetic resonance imaging (fMRI) (Engström et al., 2022; Li et al., 2022; Sezer et al., 2022; Snyder et al., 2022), functional near-infrared spectroscopy (fNIRs) (Bergen-Cico et al., 2021; Xie et al., 2022), electroencephalogram (EEG) (Ahani et al., 2014; Lomas et al., 2015; Ng et al., 2021; Wang et al., 2022), event-related potential (ERPs) (Gao et al., 2017; Lasaponara et al., 2019; Kaunhoven and Dorjee, 2021), magnetoencephalogram (MEG) (Berkovich-Ohana et al., 2013; Wong et al., 2015; Lardone et al., 2022), and various other biomedical engineering methods.

The most convenient method for characterizing meditation state is EEG, which is the physiological electrical activity of the brain recorded from the human scalp. Though short term mindfulness training may affect EEG functional connectivity (Xue et al., 2014; Travis, 2020; Trova et al., 2021), characteristics of mindfulness meditation can be more conveniently described in the spectral domain of EEG, especially in five standard frequency bands, namely delta band (1–4 Hz), theta band (5–8 Hz), alpha band (8–12 Hz), beta band (13–30 Hz), and gamma band (31–80 Hz), and reliable meditation characteristics have been found in theta and alpha bands (Cahn and Polich, 2006). In the meditation state, the theta rhythm in the frontal and temporal lobes is significantly stronger than in the occipital lobe. There is also a significant increase in amplitude and decrease in frequency of the posterior alpha rhythm at meditation states compared with resting condition (Lagopoulos et al., 2009). In addition, some studies have suggested that alpha regulation in the meditative state is a dynamic process: from amplitude increase to frequency decrease to alpha activity propagation in the frontal lobe, and finally the appearance of theta wave due to frequency decrease (Lee et al., 2018). Nonetheless, these results have not been consistently reported and no consistent patterns have been observed in the delta, beta and gamma bands in many EEG studies (Kerr et al., 2011; Ng et al., 2021; Śliwowski et al., 2021). Moreover, different meditation techniques and different aspects of the meditation may have their own specific EEG characteristics (Schoenberg and Vago, 2019).

Recognition of meditation state from EEG signal has gained some research interests, especially in the context of neurofeedback. Traditional machine learning techniques have been extensively applied for many different meditation styles using various feature extraction methods. Features used for meditation state recognition are from either frequency domain such as Fourier transform and time-frequency analysis, or spatial-temporal domain such as linear analysis using independent component analysis (ICA), common spatial patterns (CSP), and linear discriminator (LD), as well as non-linear analysis using entropy, correlation dimension (CD), largest Lyapunov exponent (LLE), and hurst exponent (HE) (Goshvarpour and Goshvarpour, 2012; Lin and Li, 2017; Han et al., 2020; Tee et al., 2020; Huang et al., 2021; Kora et al., 2021; Panachakel et al., 2021b). Brain connectivity features have also been exploited (Dissanayaka et al., 2015; Pandey et al., 2021). The classification techniques used for meditation state recognition include linear discriminant analysis (LDA) (Panachakel et al., 2021b), support vector machine (SVM) (Shaw and Routray, 2016; Han et al., 2020), random forest (RF) (Huang et al., 2021), and artificial neural network (ANN). Recently, deep learning techniques including long short-term memory (LSTM) framework (Panachakel et al., 2021a) as well as various deep convolutional neural networks (CNN) such as VGG16, ResNet50, and MobileNet (Pandey and Miyapuram, 2021), have also been exploited for meditation state recognition.

There are only a small number of publications reporting meditation state classification, mostly on yoga meditation (Han et al., 2020), including Raja yoga (Panachakel et al., 2021a,b), Kriya yoga (Shaw and Routray, 2016), and Himalayan yoga (Pandey and Miyapuram, 2021), with only one on non-specified meditation (Goshvarpour and Goshvarpour, 2012).

There is a still lack of research effort on meditation state classification during mindfulness meditation, especially on the well adopted MBSR training, and to the best of our knowledge only one publication is on brain state classification during mindfulness meditation which is not a standard 8-week MBSR but a 6-week program adapted from MBSR and mindfulness-based cognitive therapy (MBCT) (Ahani et al., 2014).

In this paper, we aim to perform EEG-based mindfulness meditation state classification during MBSR training, using deep learning methods as well as state-of-the-arts (SOTA) traditional machine learning approaches. Many deep learning and traditional machine learning methods have been applied to EEG-based brain state classification problems, as reviewed in Craik et al. (2019), Roy et al. (2019), Li et al. (2020), Gao et al. (2021), Saeidi et al. (2021), and Gong et al. (2022). While the popular deep learning architecture such as restricted Boltzmann machine (RBM), deep belief network (DBN), CNN, generative adversarial network (GAN), LSTM and gated recurrent unit (GRU) based recurrent neural networks (RNN), autoencoder (AE) and stacked AE (SAE), as well as some others such as capsule network (CapsNet), extreme learning machine (ELM), echo state network (ESN), Spiking neural network (SNN), and deep polynomial network (DPN), have all find applications for EEG analysis, those famous and effective deep network structures for audio, video, and image processing such as ImageNet, AlexNet, VGG, ResNet, and MobileNet are not suitable for most EEG applications, especially when only a small dataset is available.

Multi-channel EEG data are essentially spatio-temporal data, which have both the sampling of the two-dimensional surface of the brain scalp and the sampling over the time series, therefore EEG signals are different from images, sounds and video data. Moreover, EEG signals have information encoded in various oscillations, such as the delta, theta, alpha, beta and gamma rhythms. Two representative CNN deep learning networks developed specifically for EEG analysis are EEGNet (Lawhern et al., 2018) and deep/shallow ConvNet (Schirrmeister et al., 2017). The shallow ConvNet contains a CNN layer for spatial filtering and a dense layer for classification, and after the end-to-end training it conceptually trained a data-adaptive filter bank common spatial patterns (FBCSP) (Ang et al., 2012) for feature extraction and a following ANN for classification. The deep ConvNet is basically the same as shallow ConvNet but with a deep CNN instead of an ANN for classification, and they have been successfully applied for many brain state classification tasks such as depression recognition (Li et al., 2019), drowsiness recognition (Chen et al., 2021), and eye states classification (Han et al., 2022). Therefore, in this paper, we use deep and shallow ConvNets as the deep learning approaches and compare them with SVM classification (Shen et al., 2010; Dai et al., 2013, 2017) using CSP (Koles et al., 1990) and FBCSP as feature extraction methods.

Instead of a binary classification of meditation and resting as adopted in most meditation state classification literatures, in this paper we try also differentiate early and late stages of MBSR training for the aim of assessing the level of mindfulness meditation.

2. Materials and methods

2.1. EEG data

2.1.1. Experimental procedure and EEG data collection

The EEG experiment was performed in the University of Hong Kong, and was approved by the Hong Kong Local Institutional Review Board (IRB). Eleven healthy participants volunteered to participate in the study (6 males, 5 females; mean age 35.7 years; 7 Asians and 4 Caucasians from local MBSR courses). All participants have a bachelor's degree or above and had no previous experience in any kind of meditation before taking the MBSR training.

In this study, participants were taught mindfulness meditation in accordance with the standard MBSR training course which is an 8 weeks program with a maximum of 30 participants. The course generally includes 2–2.5 h group meeting each week for guided practice of mindfulness meditation and stress management techniques, 45 min daily homework, and a 1-day (7–8 h) retreat between week 6 and week 7. Three formal techniques including mindfulness meditation, body scanning and simple yoga postures, are instructed by the certified trainers.

Mindfulness meditation states were investigated at two stages: the early stage (stage 1) after the beginning of the MBSR training (within 2 weeks, in weeks 1–2) and the late stage (stage 2) after the end of the training (within 4 weeks, in weeks 9–12). The experiments were performed in a quiet room, and at each stage, the participants were asked to do 10 min resting with eyes closed but do not think too much or fall asleep, with this period denoted as the resting state (REST1 and REST2 for stages 1 and 2, respectively), and then do 10 min mindfulness breathing taught in the MBSR course, with this period denoted as the mindfulness meditation state (MBSR1 and MBSR2 for stages 1 and 2, respectively), as shown in **Figure 1**. Scalp EEG data were recorded with a 128-channel Neuro-SCAN EEG system. More details about the experiment and data collection are described in Gao et al. (2016).

Two experiments were performed for each participant, with the first experiment in weeks 1–2, and the second experiment in weeks 9–12. Each experiment investigated two brain states: resting (denoted as REST1 and REST2, respectively) and mindfulness meditation (denoted as MBSR1 and MBSR2, respectively).

2.1.2. EEG data pre-processing

The EEG data were preprocessed using the MATLAB toolkit EEGLAB (Delorme and Makeig, 2004) with the following steps before making brain state classification.

A number of 15 EEG channels (channels 10, 11, 17, 28, 59, 63, 64, 72, 74, 84, 85, 110, 111, 115, and 118) were excluded due to high impedance, with 113 EEG channels left for further processing and analysis. The remaining EEG data was resampled at the sampling rate of 250 Hz from the original sampling rate of 1,000 Hz, and then re-referenced to whole brain average reference from the original left mastoid reference. After that, notch filtering at 50 and 100 Hz was performed to reduce powerline noise, and 0.1–120 Hz bandpass filtering was followed to reduce low frequency signal drifting. At last, eye movement, eye blinking (EOG) and movement (EMG) artifacts were removed using the Automatic Artifact Removal (AAR) method (Gómez-Herrero, 2007) implemented in the EEGLAB toolkit.

After the pre-processing, for each participant, the EEG data were segmented into four segments according to the four brain states REST1, MBSR1, REST2, and MBSR2, respectively. Each segment is then divided into trials of 5 s, so that each brain state has 120 trials of data.

2.2. Brain state classification methods

2.2.1. CSP + SVM

Support vector machine (SVM) is a robust and effective machine learning method which does not require very large dataset. Kernels can be used in SVM, with linear kernel for linear classification, and other kernels such as polynomial kernels and radial basis function (RBF) kernels for non-linear classification. Before applying SVM for brain state classification, EEG features rather than raw EEG data are preferred as the inputs to the classifier.

Common Spatial Pattern (CSP) analysis is a supervised spatial filtering method for multichannel EEG feature extraction. CSP applies basically to a two-classes classification problem and aims for both compression and discrimination. CSP analysis has mainly three steps. First get the covariance matrices for each group, denoted as C1 and C2, respectively, from the groups' EEG data matrices E1 and E2. Then a whitening matrix is constructed from C = C1 + C2 and applied to C1 and C2 to get the whitened covariance matrices S1 and S2, which have identical eigen matrices U and their corresponding eigen value pairs summed to 1. Finally, the first two and the last two eigen vectors (corresponding to totally four filters) are chosen to project the EEG data matrices E1 and E2 to feature signal matrices F1 and F2, each having four rows of data. The logarithm of variance of each row of F1 and F2 is

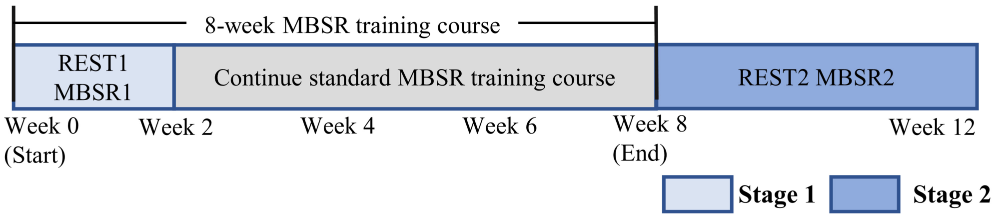

FIGURE 1
Flow chart of experimental design.

used as a feature, resulting in a feature vector of dimension 4, and then the feature vectors are used as inputs to the SVM classifier for training and classification. For multiple classes problem, we apply the one-vs.-rest (OVR) strategy for both CSP and SVM.

2.2.2. FBCSP + SVM

Common spatial pattern gets discriminative features from the full-band raw EEG signals. Since as have been demonstrated in the literature, different frequency bands of the EEG signals may represent different brain functions and contribute differently to the characteristics of mindfulness meditation state, a temporal filter bank which decompose the EEG signals to a number of distinct frequency bands may be helpful before the EEG signals are projected by CSP spatial filters. After the EEG signals are decomposed into different frequency bands by the filter bank, each band of the signal is then utilized to obtain its corresponding CSP filter and subsequently its specific feature vectors, and at last all these feature vectors are combined to feed into the SVM for training and classification. The approach of filter bank plus CSP is denoted as Filter Bank Common Spatial Pattern (FBCSP). In this study, we construct a filter bank of 10 bandpass filters, each have a bandwidth of 4 Hz, i.e., 0–4 , 4–8. . .36–40 Hz, to cover all the five EEG rhythms delta, theta, alpha, beta and gamma.

2.2.3. Shallow ConvNet

The shallow ConvNet designed in Schirrmeister et al. (2017) is inspired from FBCSP. The filter bank in FBCSP is replaced by a temporal convolution layer in shallow ConvNet, and the following CSP spatial filter is replaced by a spatial convolution layer, and the SVM classifier is replaced by a mean pooling layer and fully connected dense layer of ANN. In the FBCSP + SVM framework, filter bank is manually designed, CSP spatial filters are mathematically designed according to the signal in each frequency band, and the SVM classifier is trained using the CSP extracted features. In the shallow ConvNet network, the whole network is trained end-to-end, so the filter bank and CSP are not deterministically specified but jointly optimized from the data. Theoretically, joint optimization is in general better than sub-problem optimization. The shallow ConvNet can be regarded as composed of feature extraction function and classifier function.

In this study, the details of our shallow ConvNet adapted to our mindfulness meditation state classification problem are shown in **Figure 2**. In the temporal convolution layer, each trial of our EEG data has 113 channels (after bad channel removal) and 1,251 time points (5 s of data with a resampled sampling rate of 250 Hz), and we include 40 temporal filters in this layer to represent 40 filters in the filter bank. It should be noted that after the end-to-end training, these 40 filters are generally not non-overlapped bandpass filters but instead can be of any form. The spatial filter layer contains 40 spatial filters, corresponding to the 40 temporally filtering outputs. These spatial filters are expected to take the role of CSP spatial filters in FBCSP, but after end-to-end they may or may not get similar spatial filtering as those in FBCSP.

2.2.4. Deep ConvNet

The shallow ConvNet uses a single layer ANN to replace the SVM classifier in the FBCSP + SVM framework. Since deep CNN architecture has been demonstrated in many applications to be superior than shallow architectures for large dataset, the ANN in shallow ConvNet can be replaced by deep CNN to form a deep ConvNet architecture (Schirrmeister et al., 2017), which inserts three convolution-max-pooling blocks between the spatial filter block and the final classification block. There are four convolutional pooling blocks in the deep ConvNets. The deep ConvNet used in this study is described in **Figure 3**, where we use 25 temporal filters in the first layer instead of 40 in the shallow ConvNet, with the main purpose of reducing network complexity.

2.3. Classification and training strategy

In addition to the four-class (MBSR1, REST1, MBSR2, and REST2) classification, we also performed five binary classifications including MBSR1/REST1, MBSR2/REST2, and MBSR/REST for mindfulness/rest brain states classification at the two stages and their combination, as well as MBSR1/MBSR2 and REST1/REST2 for stage classification corresponding to mindfulness state and resting state, respectively. The class MBSR combines MBSR1 and MBSR2, and the class REST combine REST1 and REST2.

Since we have EEG data from a group of subjects, how to arrange training and classification across subject should be considered (Kamrud et al., 2021). In this study, four scenarios are investigated, including inter-subject classification, individual-subject classification, intra-subject classification, and transfer learning. For each scenario, we choose randomly 60% of the EEG trials as training set, 20% as validation set, and 20% as testing set, for deep and shallow ConvNets, while we use 80% as training and 20% as testing for CSP/FBCSP + SVM. We repeat this data-dividing and classification for 11 times to get an average performance. For the inter-subject classification scenario, leave-one-subject-out cross validation (LOOCV) is performed.

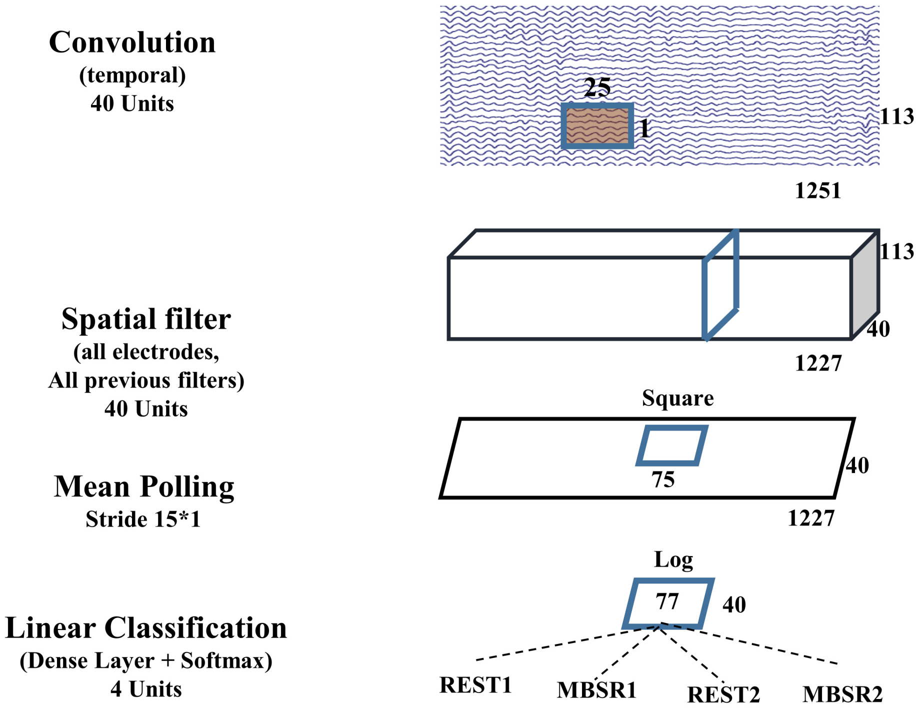

FIGURE 2
Shallow ConvNet.

2.3.1. Inter-subject classification

In order to be applicable to the general population whose EEG data are not available during the training of the classifier, the classifier should be trained on a specific group of training subjects and then applies to the general population. This training strategy is called inter-subject or cross-subject training. For inter-subject training/classification, the leave-one-subject-out cross validation (LOOCV) method was adopted in this study. Among the EEG data of 11 subjects, each of them was left in turn for testing and the data of the other 10 subjects are used for training, where 80% trials of the training subjects are used as training set and 20% trials were used as validation set for the training of deep and shallow ConvNets, whereas for CSP/FBCSP + SVM all EEG trials of the training subjects are used for training. Therefore, for each classification method, we have 11 trained classifiers, each for a specific testing subject. The principle of LOOCV is to guarantee that the subject used for testing cannot be mixed into the training set, so no data leakage occurs during LOOCV.

2.3.2. Mix-subject classification

In this so-called mix-subject classification scenario, we mix data from all subjects and divide the EEG trials as training, validation (for deep and shallow ConvNets) and testing set randomly. This classification strategy is user-independent, as pointed out by Kamrud et al. (2021), if an inter-subject model is intended to perform classification on only the same population where the training subjects are drawn, but not also unseen individuals, then testing the model on unseen subjects is unnecessary. This user-independent mix-subject classification strategy has been adopted by most previous studies for meditation state classification (Ahani et al., 2014; Shaw and Routray, 2016; Han et al., 2020).

2.3.3. Intra-subject classification

The purpose of both inter-subject and mix-subject classification strategies are for effective applications in unseen (by the training) subjects from the general population and the population same as the training subjects, respectively. However, inter-subject classification performs usually much poorer than mix-subject classification (Kamrud et al., 2021; Fu et al., 2022). If the mix-subject classification strategy is not applicable due to population shift and the inter-subject classification performs not good enough, the alternative intra-subject or within-subject classification strategy is to collect some EEG data from the target subject and use such EEG data for training and testing, and the classifier trained this way can be used by this specific subject for future mindfulness state recognition applications such as neurofeedback assisted mindfulness training. The advantage of the intra-subject classification strategy is that the classifier is dedicatedly trained for the specific target subject so does not suffer from the problem caused by individual differences, while its disadvantage is that the classifier is not readily available from the beginning because some training data need to be collected in advance and the classifier should be trained again from these training data. Although intra-subject classification may have some narrowly limited application scenario as discussed above for meditation states classification, it can hardly have any practical application for meditation experience classification. This strategy is studied only for state classification in this paper.

2.3.4. Subject-transfer classification

Another disadvantage of the intra-subject classification strategy is that in general the classifier can only be trained from a relatively

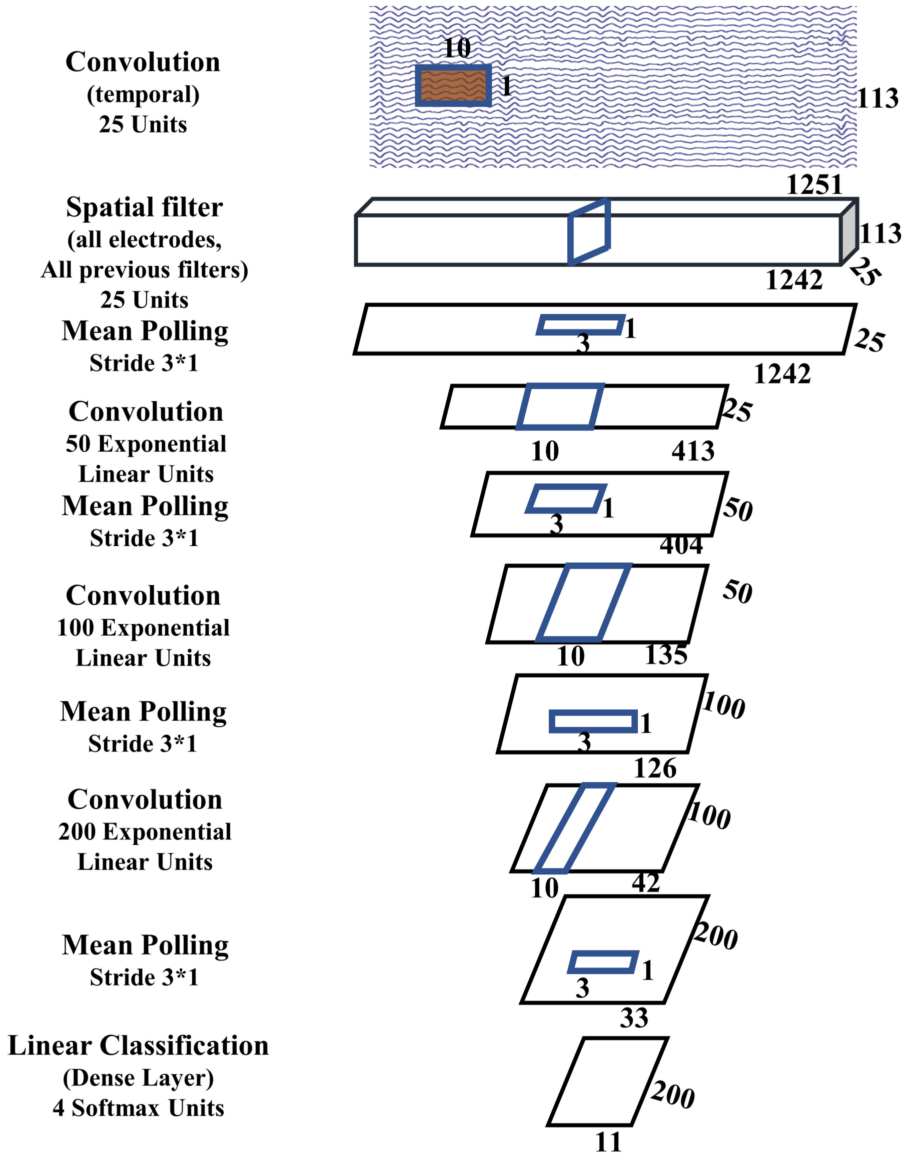

FIGURE 3
Deep ConvNet.

small dataset from a single subject and limited time span. For deep learning methods, especially those with very deep structures and thus a huge amount of model parameters to be learned from the data, a relatively large dataset is necessary for obtaining an effective model. To overcome this shortage of data problem, the idea of transfer learning (Pan and Yang, 2010; Niu et al., 2020) can be applied, and specifically we adopt a subject transfer strategy (Samek et al., 2013; Zhao et al., 2019). In this subject-transfer classification strategy, the inter-subject classification and intra-subject classification strategies are combined. For each target subject, we first train a subject-independent classifier using the same procedure as described in the inter-subject classification strategy, and then we finetune this classifier using the EEG data of the target subject and get a subject-transferred classifier. In the finetuning, the division of the EEG data of the target subject into training, validation, and testing sets follows the same as in the intra-subject classification strategy. In this study this subject-transfer classification strategy applies only to deep and shallow ConvNets but not CSP and FBCSP assisted SVM, since only deep networks can be trained by finetuning (Pan and Yang, 2010; Niu et al., 2020). For the same reason as in intra-subject classification, the subject-transfer classification strategy is also studied only for state classification.

3. Results

For each of the four classification strategies (inter-subject, mix-subject, intra-subject, and subject-transfer), each of the four classification methods (CSP + SVM, FBCSP + SVM, shallow ConvNet, and deep ConvNet), and each of the six classification tasks (MBSR1/REST1/MBSR2/REST2,

MBRS1/REST1, MBSR2/REST2, MBSR/REST, MBSR1/MBSR2, and REST1/REST2), we perform either 11 times of LOOCV or 11 times of training/classification with random division of the data, and then get the average classification accuracy for each combination of classification strategy and classification method. The results are then grouped according to the classification strategy and presented in the form of both tables and figures. Statistical tests on the performance of the two deep learning methods (deep and shallow ConvNets) using the non-parametric Mann-Whitney U-test of two independent samples (Nachar, 2008) and on six different classification tasks using k-independent sample Kruskal-Wallis test (Vargha and Delaney, 1998), are also presented for each classification strategy if applicable.

3.1. Inter-subject classification

The classification accuracies are presented in **Table 1** and also in **Figure 4**. The non-parametric Mann-Whitney U-test of two independent samples finds that the difference of classification accuracy between the deep and shallow ConvNets is not significant ($Z = -0.665$, $p = 0.512$), but the k-independent sample Kruskal-Wallis test shows that the difference among the six categories is significant ($Z = 34.344$, $p = 0.000$).

3.2. Mix-subject classification

The classification accuracies are presented in **Table 2** and also in **Figure 5**. We find that the classification accuracies between the two convolutional neural networks are significantly different ($Z = 2.795$, $p = 0.005$) using the non-parametric Mann-Whitney U-test. The classification accuracy of deep ConvNet is significantly better than that of the shallow ConvNet. The non-parametric k-independent sample Kruskal-Wallis test finds that the results of the six classification tasks are significantly different ($Z = 98.650$, $p = 0.000$).

3.3. Intra-subject classification

The classification accuracies are presented in **Table 3**.

3.4. Subject-transfer classification

The classification accuracies are presented in **Table 4**.

4. Discussion

4.1. Comparison with the literatures

4.1.1. State classification

In the literature there are four published studies on classifying meditation states and resting states of the same subject using EEG measurements, as detailed in **Table 5**, where the results of our study on meditation and resting state classification, represented by the average accuracy of the two stages, i.e., MBSR1/REST1 and MBSR2/REST2, are also presented for ease of comparison.

Mix-subject classification of mindfulness meditation state for a group of novice meditators participating in a short-term MBSR/MBCT adapted mindfulness training program is presented in Ahani et al. (2014), where SVM is used to obtain a classification accuracy of 78%, which is very close to our CSP and FBCSP based results (82.29 and 73.58%, respectively, with mean value of 77.94%), but is much inferior to the performance of our deep and shallow ConvNets (with classification accuracy of 99.65 and 95.43%, respectively).

Meditation state classification for expert and novice yoga meditators using SVM is reported in Han et al. (2020) with the accuracy of 74.31 and 62.16%, respectively, according to a mix-subject classification strategy, where it demonstrates that the discrimination between meditation and resting is much more difficult for novice than for expert meditators, since the meditation expertise of the novices is much lower than that of experts.

In the intra-subject classification scenario, using the traditional machine learning technique CSP + LDA, for Raja yoga experts, (Panachakel et al., 2021b) reports a classification accuracy of 97.9%, very much higher than our result (82.29%) using similar machine learning technique (CSP + SVM) but for MBSR novices. This implies that the task of meditation state recognition in the settings of our study for novice MBSR practitioners is much more difficult and challenging than that for Raja yoga experts. However, for the same intra-subject scenario for MBSR novices in our study, both shallow and deep ConvNets obtain very promising and improved classification accuracy, which are 98.40 and 90.45%, respectively, and the subject transfer learning further improves the accuracy to 98.80 and 96.00%, respectively.

The inter-subject classification accuracy using traditional machine learning technique FBCSP + SVM in our study is 68.50%, which is comparable to 74.0% reported in Panachakel et al. (2021b) using also traditional machine learning method, but as discussed above our task is much more difficult. The inter-subject classification accuracy for Raja yoga experts is greatly improved from 74.0% in Panachakel et al. (2021b) to 79.1, 86.5, 91.0, and 94.1% in Panachakel et al. (2021a) for using alpha, beta, low gamma, high gamma features, respectively, followed by the CSP + LDA + LSTM deep learning framework. However, the meditation state classification accuracy for our MBSR novices using deep and shallow ConvNets does not improve over the traditional FBCSP + SVM method but instead drops to around chance levels of 48.34 and 50.60%, respectively. Though in this study we use a CNN architecture ConvNet as the deep learning architecture, which is different from the RNN architecture LSTM in Panachakel et al. (2021a), the main reason accounting for the failure of ConvNet in the inter-subject classification scenario should be that ConvNet uses an end-to-end training architecture whereas in Panachakel et al. (2021a) the LSTM architecture does not work directly on raw EEG data but instead on EEG features extracted by CSP + LDA.

4.1.2. Stage classification

Meditation expertise increases through training and practice, and there will be both state and trait effects which can be characterized in either behavioral data or brain activities such as

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TABLE 1 Classification accuracies for inter-subject classification.

	Classification task	Shallow ConvNet	Deep ConvNet	CSP	FBCSP
State	MBSR1/REST1	48.95%	52.65%	59.93%	68.49%
	MBSR2/REST2	52.24%	44.02%	68.31%	70.17%
Stage	MBSR1/MBSR2	45.14%	35.90%	88.66%	85.00%
	REST1/REST2	60.66%	56.46%	63.35%	78.96%
Combined	MBSR/REST	50.42%	49.96%	56.85	63.17%
4-class	All four classes	30.12%	23.92%	40.69%	26.09%

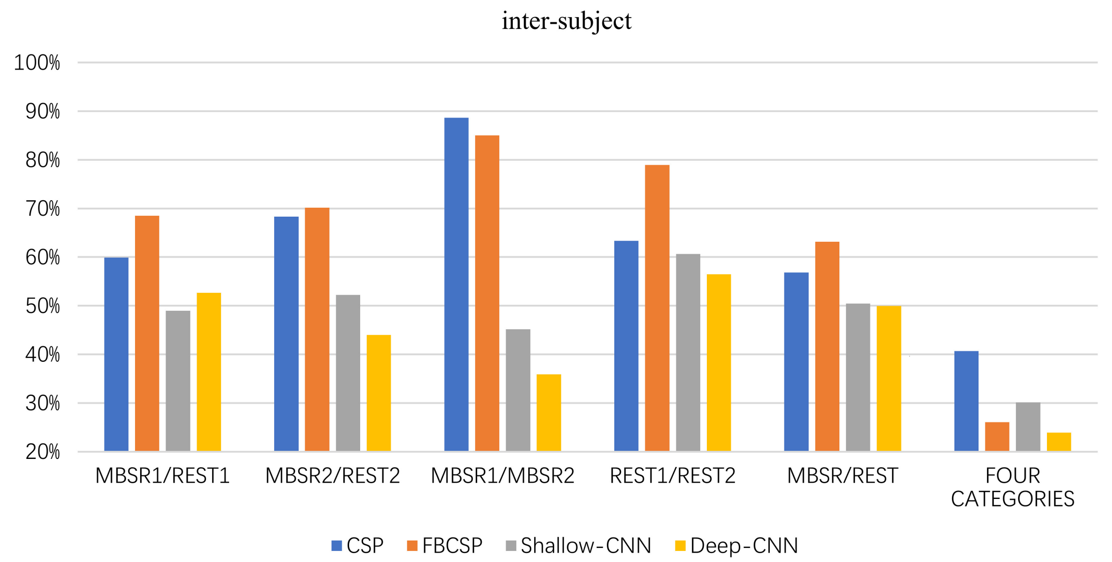

FIGURE 4
Classification accuracies for inter-subject classification.

TABLE 2 Classification accuracies for mix-subject classification.

	Classification task	Shallow ConvNet	Deep ConvNet	CSP	FBCSP
State	MBSR1/REST1	98.33%	99.59%	72.01%	73.92%
	MBSR2/REST2	92.53%	99.70%	92.56%	73.23%
Stage	MBSR1/MBSR2	99.81%	99.95%	71.67%	91.16%
	REST1/REST2	99.88%	99.78%	93.98%	95.13%
Combined	MBSR/REST	87.79%	81.83%	67.63%	72.10%
4-class	All four classes	96.72%	97.53%	79.32%	83.23%

resting EEG for trait effect and meditating EEG for state effect (Cahn and Polich, 2006; Zarka et al., 2022). There is lack of studies on classification of brain states for different training and practicing stages longitudinally for individual meditation practitioners, but some efforts have been spent on classifying subjects with different levels of meditation expertise using EEG in either the meditating states (Shaw and Routray, 2016; Lee et al., 2017; Pandey and Miyapuram, 2021) or the resting states (Sharma et al., 2019), as detailed in **Table 6**, where the results of our study in this paper on meditation stage classification using meditation EEG (MBSR1/MBSR2) and resting state EEG (REST1/REST2), are also presented for ease of comparison.

In Pandey and Miyapuram (2021), expert and non-expert Himalayan yoga meditators, along with non-meditator healthy controls are classified by their meditation experience/expertise according to the EEG data measured when they are asked to do a focused-attention (to breath sensations) meditation, using a variety of a variety of CNN deep learning architectures including VGG16, ResNet50, MobileNet, MobileNet-2, and a lightweight CNN, with high inter-subject classification accuracy of 97.27, 91.01, 90.57, 88.73, and 94.57%, respectively. The two stages of MBSR training/practicing in our study are chosen as Weeks 1–2 and Weeks 9–12 after the starting of MBSR training, for which the meditation expertise of the subject is relatively higher in stage 2 than in stage 1, but reasonably far not as discriminable as

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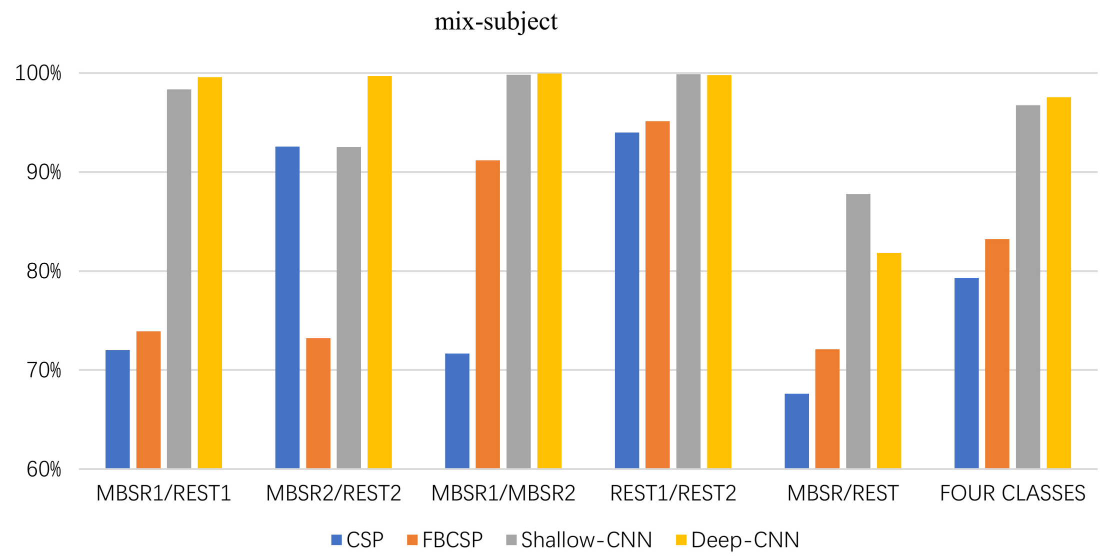

FIGURE 5
Classification accuracies for mix-subject classification.

TABLE 3 Classification accuracies for intra-subject classification.

	Classification task	Shallow ConvNet	Deep ConvNet	CSP	FBCSP
State	MBSR1/REST1	99.01%	97.05%	82.50%	94.60%
	MBSR2/REST2	97.99%	83.85%	80.24%	94.83%
Combined	MBSR/REST	99.26%	98.60%	85.12	87.40%

among experts, non-experts, and non-meditators. Nevertheless, our traditional machine learning method FBCSP + SVM, and the deep learning methods shallow and deep ConvNets for MBSR1/MBSR2 classification all perform almost perfectly on non-inter-subject classification scenarios, with respective classification accuracy as 91.16, 99.81, and 99.95% for mix-subject classification. As a comparison, in the mix-subject classification scenario, the classification of senior/junior/novice Tibetan Nyingmapa meditation expertise attains an average accuracy of 99.05% as reported in Lee et al. (2017), and the classification of expert/novice Kriya yoga meditation experience using SVM and kernel SVM (k-SVM) has classification accuracy of 85.54 and 90.83%, respectively, as reported in Shaw and Routray (2016). However, for inter-subject classification, the two deep learning ConvNets do not perform satisfactorily, while the traditional machine learning methods CSP + SVM and FBCSP + SVM still perform reasonably well with classification accuracy of 88.66 and 85.00%, respectively, comparable to 91.01, 90.57, and 88.73% reported in Pandey and Miyapuram (2021) for a theoretically more discriminative task of experts/non-experts/non-meditators classification.

For EEG-based classification of meditation experience using trait characteristics, in Sharma et al. (2019) an ANN is designed to recognize combined Yoga and Sudarshan Kriya meditation experience from resting state EEG data and its mix-subject classification accuracy is 87.2%, which is much inferior to the resting state EEG based stage classification performance for MBSR practitioners, where the REST1/RESR2 mix-subject classification accuracy is 93.98, 95.13, 99.88, and 99.78% for the classification methods CSP, FBCSP, shallow ConvNet, and deep ConvNet, respectively. However, as expected, since trait characteristics are not as discriminative as state characteristics, inter-subject classification of REST1/REST2 by FBCSP can attain the accuracy of only 78.96%, lower than 85.00% in the case of using meditation EEG.

4.2. Classification tasks

In addition to binary classifications of meditation states from resting states at each of the two stages and their combinations as well as stage combination using meditation and resting EEG, we also perform a multi-class classification on all the four different brain states across the two training stages. Both the traditional machine learning method FBCSP + SVM and the deep learning method shallow ConvNet perform quite well for mix-subject and intra-subject classification scenarios, demonstrating that there are both state and trait effects for the short-term MBSR training and such two kinds of effects are also discriminable from each other. Since no such longitudinal combined trait and state meditation recognition has ever been investigated in any previous research project, we could not find a proper previous study for comparison. One related study is a three-class (meditation/rest/attention) classification reported in Han et al. (2020) where the mix-subject classification accuracy is 74.31% for experts and 62.16% for novices, whereas in our study of novice MBSR practitioners, the four-class (MBSR1/REST1/MBSR2/REST2) mix-subject classification accuracy is 83.23% using FBCSP and 96.72% using shallow

TABLE 4 Classification accuracies for subject-transfer classification.

	Classification task	Shallow ConvNet	Deep ConvNet
State	MBSR1/REST1	99.64%	96.84%
	MBSR2/REST2	98.06%	95.15%
Combined	MBSR/REST	99.05%	98.29%

ConvNet, and this demonstrates the effectiveness of both our MBSR training program and our classification methods.

As shown in **Tables 1–4**, in total we have six classification tasks in this study, and statistical tests show that for each and all of the four classification scenarios, difference in classification accuracy among the six tasks is significant. This difference happens in part by the fact that the two classification tasks MBSR/REST and MBSR1/REST1/MBSR2/REST2 are more difficult than the other four binary classification tasks, and in part by the fact that meditation state is more discriminable from resting state at Stage 2 than at Stage 1 (MBSR1/REST1 is more difficult than MBSR2/REST2) and state meditation characteristics is more discriminative than trait meditation characteristics (REST1/REST2 is more difficult than MBSR1/MBSR2), which is well demonstrated by the inter-subject classification results of the CSP and FBCSP methods shown in **Table 1**.

Across all the four classification scenarios and all the four classification methods under investigation, there is a general and consistent trend that stage tasks (MBSR1/MBSR2 and REST1/REST2) are classified with higher accuracy than the state tasks (MBSR1/REST1 and MBSR2/REST2). This may imply that the short-term MBSR training is very effective that the brain functional networks have been greatly modulated to produce significantly different EEG characteristics in both the meditation and the resting state, as compared to the pre-training period. However, the EEG differences between the two stages may also be caused by some other meditation unrelated changes in either measurement or cognition environment that affect the EEG features. This may be investigated further in some future research.

4.3. Classification methods

4.3.1. Deep learning vs. traditional machine learning

For relatively larger dataset, in the mix-subject classification scenario, both shallow and deep ConvNets outperform greatly CSP and FBCSP, and for small dataset in the intra-subject classification scenario, the performance of shallow ConvNet is even more outstanding while the deep ConvNet performs comparably to FBCSB and better than CSP. However, for inter-subject classification, the pre-trained shallow and deep ConvNets fail to generalize to unseen subjects, while the performance of CSP and FBCSP work still reasonably well.

Within the two traditional machine learning methods, for all the three classification scenarios, FBCSP in general have overall performance better than CSP. This is expected since FBCSP extract EEG rhythms which contribute to the neuro-mechanisms of meditation so can better discriminate meditation states from resting states, while CSP mixes these rhythms into a wideband continuous signal so may not be as discriminative as FBCSP.

As for the two deep learning methods, their performance depends on the size of data available for model training. The more complex the network, the more data are needed. On one hand, for intra-subject, statistical test on the performance of deep ConvNet over shallow ConvNet find the statistics $Z = -1.923$ which is marginally significant ($p = 0.05$), where the negative Z shows the shallow ConvNet performs better than deep ConvNet. A possible reason is that for intra-subject classification we have training EEG data only from a single subject with a sample size not big enough for deep ConvNets to achieve sufficient optimization for better classification than shallow ConvNet which is simpler and requires less data for effective training, and this is also demonstrated by the subject-transfer learning where the classification accuracy for deep ConvNet is slightly but consistently improved for almost all the six classification tasks due to the additional data used for pre-training the network. On the other hand, for mix-subject classification, the statistical test gets $Z = 2.795$ and $p = 0.005$, which means deep ConvNet is significantly better than shallow ConvNet. It may be because the sample size in the mix-subject scenario is large enough for the more complex deep ConvNet to get sufficiently optimized to outperform the shallow ConvNet. Moreover, for inter-subject and subject-transfer classification, the statistical test gets $Z = -0.665$ ($p = 0.512$) and -1.590 ($p = 0.112$), respectively, meaning in such two cases the shallow ConvNet performs better but not to the level of statistical significance, implying that more data are needed in order to improve inter-subject classification using either shallow ConvNet or deep ConvNet.

4.3.2. End-to-end learning tries to catch subject-dependent features

The deep learning ConvNet architecture, especially the shallow ConvNet, performs much better than the traditional machine learning methods CSP and FBCSP for both mix-subject classification and intra-subject classification, where in the latter we have very few EEG samples for training the networks. This good performance is due to the extreme simplicity of shallow ConvNet which mimics a very simple FBCSP + ANN architecture with a small number of model parameters. Different from a two steps approach of first FBCSP and then ANN where each step is trained separately, the two blocks in the shallow ConvNet are jointly optimized through an end-to-end learning strategy. In the deep ConvNet, the single layer ANN in the shallow ConvNet is replaced by a deep CNN architecture with three more CNN-max-pooling blocks, and the whole network is also jointly optimized through end-to-end learning.

The better performance of shallow ConvNet than that of FBCSP in the intra-subject classification scenario is definitely due to this joint optimization, and better performance of deep ConvNet than shallow ConvNet in the mix-subject classification scenario is due to the availability of larger data that makes a deeper architecture get more discriminative features. However, the end-to-end joint optimization is a mixed blessing, which on the one hand gets very individualized subject-dependent features so as to attain superior intra-subject and mix-subject classification performance for that specific subject or population, but on the other hand is difficult to generalize to unseen subjects with big individual difference. This

TABLE 5 Comparison to the literatures on mediation state classification; the accuracy of our methods on meditation/resting classification is the average for MBSR1/REST1 and MBSR2/REST2; SCNN and DCNN represent shallow and deep ConvNets, respectively.

References	Meditation	Tasks	Experience	Strategy	Method	Accuracy
Panachakel et al., 2021a	Raja yoga	Med/rest	Expert	Inter-subj	LSTM-α	79.1%
					β	86.5%
					Low γ	91.0%
					High γ	94.1%
Panachakel et al., 2021b	Raja yoga	Med/rest	Expert	Inter-subj	LDA	74.0%
				Intra-subj		97.9%
Han et al., 2020	Yoga	Med/rest/attention	Expert	Mix-subj	SVM	74.31%
			Novice			62.16%
Ahani et al., 2014	Mindfulness	Med/rest	Novice	Mix-subj	SVM	78%
Ours	MBSR	Med/rest	Novice	Inter-subj	SCNN	50.60%
					DCNN	48.34%
					FBCSP	68.50%
					CSP	64.12%
				Mix-subj	SCNN	95.43%
					DCNN	99.65%
					FBCSP	73.58%
					CSP	82.29%
				Intra-subj	SCNN	98.40%
					DCNN	90.45%
					FBCSP	94.72%
					CSP	81.37%
				Transfer	SCNN	98.85%
					DCNN	96.00%

is why deep and shallow ConvNets perform badly in our study for inter-subject classification while FBCSP still has reasonably good performance.

To overcome this disadvantage of end-to-end ConvNets on inter-subject classification, we may either enlarge the dataset by collecting data from a large number of subjects for better covering broad individual features so as to reduce the problem of individual difference, or try not to use end-to-end learning for the case where only a small number of subjects are available, as demonstrated in Panachakel et al. (2021a).

4.4. Classification strategies

The performance of mindfulness meditation state classification by deep learning methods deep and shallow ConvNets as well as traditional machine learning methods CSP and FBCSP is evaluated in four different application scenarios, each having its own practical applications on either meditation level evaluation or meditation training through neurofeedback.

For intra-subject classification, shallow ConvNet attains excellent classification performance with classification accuracy not less than 98.0% for all the five binary classification tasks, while the performance of both deep ConvNet and FBCSP is also quite promising. The intra-subject classification strategy requires the target subject to perform the whole MBSR training program first in order to use the EEG data collected at the two stages to train the meditation state classifiers. Though the trained classifier can be used to assist the practice of MBSR for the target subject subsequently, it cannot be used at the beginning of the MBSR training. In addition, the performance of subsequent application of the same target subject may still cannot be guaranteed despite the excellent intra-subject classification performance, since there may be inter-session variability that might significantly degrade or corrupt the classification ability for data from new sessions, similar to the degradation in the inter-subject classification scenario demonstrated in this study.

The mix-subject classification strategy relaxes the requirement to collect data from the target subject to data from a relatively homogeneous population covering the target subject. If this homogeneous population requirement is fulfilled, then a classifier trained from EEG data of a subset of the population can be evaluated on the training subject and applies directly to the unseen target subject from the same population, expecting similar performance as already evaluated in the mix-subject setting. The mix-subject classification performance in our study is also quite good for deep and shallow ConvNets, and therefore if we do have such kind of homogeneous population for application, then the classifier trained this way may generalize well for unseen

TABLE 6 Comparison to the literatures on mediation experience/expertise classification using meditation and resting EEG; in our study, meditation EEG and resting EEG based classifications are corresponding to MBSR1/MBSR2 and REST1/REST2, respectively; SCNN and DCNN represent shallow and deep ConvNets, respectively.

References	Meditation	Tasks	Strategy	Method	Accuracy	
					Meditation	Resting
Pandey and Miyapuram, 2021	Himalayan Yoga	Expert/non-expert/non-meditator (S/J/N)	Inter-subj	VGG16	97.27%	
				ResNet50	91.01%	
				MobNet	90.57%	
				MobNet2	88.73%	
				LightCNN	94.57%	
Lee et al., 2017	Tibetan	S/J/N	Mix-subj	ANN	99.05%	
Shaw and Routray, 2016	Kriya Yoga	Expert/novice	Mix-subj	SVM	85.54%	
				k-SVM	90.83%	
Sharma et al., 2019	Yoga and SK	Train/control	Mix-subj	ANN		87.2%
Ours	MBSR	Stage 1/Stage 2	Inter-subj	SCNN	45.14%	60.66%
				DCNN	35.90%	56.46%
				FBCSP	85.00%	78.96%
				CSP	88.66%	63.35%
			Mix-subj	SCNN	99.81%	99.88%
				DCNN	99.95%	99.78%
				FBCSP	91.16%	95.13%
				CSP	71.67%	93.98%

target subjects. As a matter of fact, in our study, for inter-subject classification, which can be regarded as an application of mix-subject classification to unseen subjects, performs poorly for the ConvNets as well as significantly inferior to mix-subject classification for CSP and FBCSP. This implies that the subjects in our study are far from homogeneous, which is true since for the 11 subjects in our study we have 6 males and 5 females, with 7 of them are Asians and 4 Caucasians.

If collecting in advance the EEG data from the target subject is either inconvenient or impractical and the requirement for mix-subject classification cannot be fulfilled, then in order to get a good classifier generalizable to unseen target subjects, the classifier should be trained and evaluated using the inter-subject classification strategy. Though in our study deep and shallow ConvNets fail for inter-subject classification, the performance of FBCSP is reasonably good for both state and stage classification tasks, especially when considering that our tasks of meditation state classification for short-term training of novices are considerably more difficult than what is reported in the literatures where expert meditators are involved and compared to non-meditator controls.

For deep learning networks, if data available for model training is not sufficiently large to guarantee effective parameters optimization, then transfer learning may get more data to improve the training. Data shortage may be a problem of intra-subject classification since only a single subject is used for training. Though both shallow and deep ConvNets in our study perform excellently for intra-subject classification since they are relatively much simpler than those popular models such as VGG16 and ResNet50, more complex deep learning models may have degraded performance due to data shortage in the intra-subject setting, and then subject-transfer learning may help improve the intra-subject classification performance. In our study, most of the intra-subject classification accuracies of deep ConvNet for the six classification tasks are indeed significantly elevated by subject-transfer learning. Subject-transfer learning may also help inter-subject classification when we use only a small part of the unlabeled EEG data of the target subject to finetune the classifier so as to reduce the effect of inter-subject variability as demonstrated in for applications using speech and electrocardiogram (ECG) signals (Xu et al., 2022).

For meditation state/experience classification, the intra-subject classification strategy has been used in Panachakel et al. (2021b), the mix-subject classification strategy has been used in Ahani et al. (2014), Khoury et al. (2015), Shaw and Routray (2016), Lee et al. (2017), Sharma et al. (2019), and Han et al. (2020), and the inter-subject classification strategy has been used in Panachakel et al. (2021a,b) and Pandey and Miyapuram (2021). The inter-subject classification strategy is most suitable for the general case but it is the most difficult due to inter-subject variation. Mix-subject classification may avoid the over-fitting problem of intra-subject classification with the use of more data for training, and it may closely approximate the inter-subject classification if the subjects are from a homogenous population. In the case of this paper, the 11 subjects are quite non-homogeneous, therefore the inter-subject classification accuracies are much lower than those of mix-subject classification. Moreover, since the early and late stage of mindfulness meditation may be different for individual subjects, that is to say, the time accumulation effect of meditation may not be the same for all subjects, making the classification of meditation experience more challenging. Though intra-subject classification may have some narrowly limited application scenario as discussed

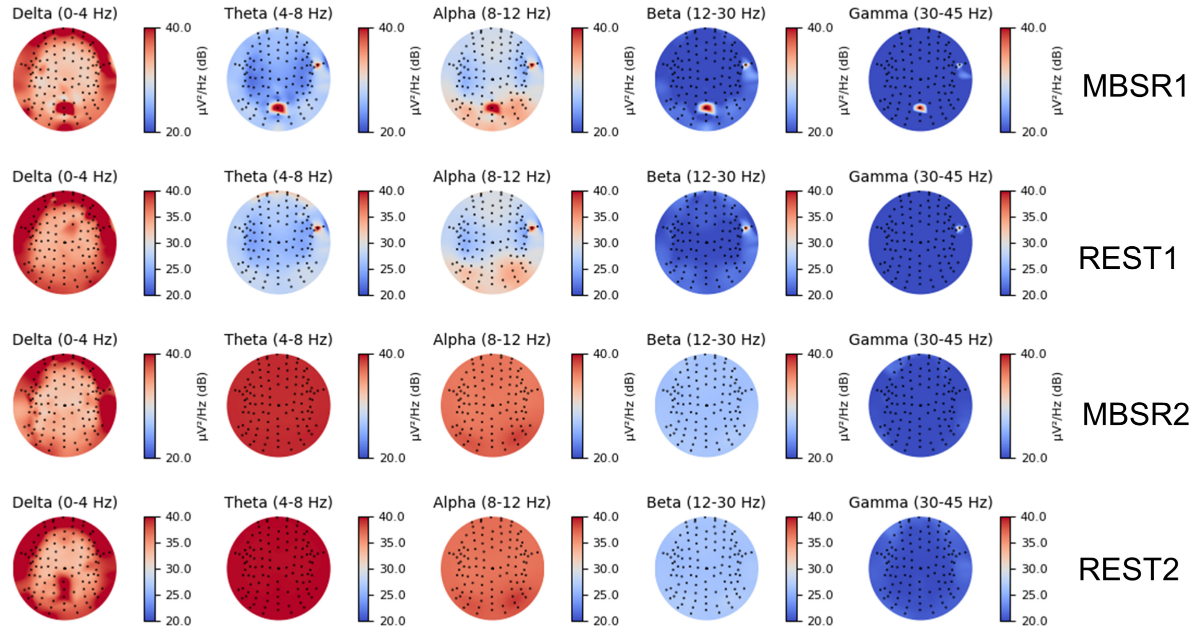

FIGURE 6
Power variation network-prediction correlation topographies of five frequency bands for deep ConvNet at the four different mental states.

above for meditation states classification, it can hardly have any practical application for meditation experience classification. Finally, the subject-transfer classification strategy combines both intra-subject and mix-subject classification strategies in order to overcome the limitations of each of the two individual strategies.

4.5. Feature analysis

To demonstrate that the CNN network is reliable for identifying meditative and resting EEG features, we visualized PSD topologies of raw EEG data in Figure 6 and reviewed the relevant literature. By referring to the results of traditional analysis methods and previous conclusions, we conduct correlation analysis between CNN network features and PSD features.

Region of Interest (ROI) were defined with the occipital lobe (channels N19, N20, N21, N41, N42, N43, N44, N45, N46, N67, N68, N69, N70, N71, N72, N96, N97, N98, N99, and N100), the middle frontal lobe (channel N53, N54, N55, N56, N57, N58, N59, N60, N61, N79, N80, N81, N82, and N83) and the middle parietal lobe (channels N48, N49, N50, N64, N65, N66, N74, N75, and N76). The selected EEG channels have been proved to be mindfulness-related (Gao et al., 2016). Alpha waves (8–12 Hz) and beta waves (12–30 Hz) are enhanced and delta waves (1–4 Hz) are decreased during mindfulness-based stress reduction exercises compared to resting states. The increase in alpha waves was significant throughout the brain, especially in the frontal and occipital lobes. The increase in beta waves is mainly concentrated in the frontal lobe. Delta waves are reduced in the centro-parietal region.

For analysis of the features learned by the CNN models and to illustrate that these features are mindfulness-related, the canonical correlation analysis (CCA) (Hardoon et al., 2004) between two feature groups including CNN-based and handcraft-based features were conducted. CNN-based features are extracted by the two CNN models from the data of each subject (also mixed subjects) at each MBSR and REST tasks, they are the output of the layer before the classification layer of the CNN networks. Handcraft-based features include the ratio of PSD value between delta and alpha bands of certain channels, also the ratio of PSD value between delta and beta bands of region of interest of the recorded EEG data.

The r-value of CCA between the CNN-based features and each sub-feature set in handcraft-based features is shown in Table 7, including two sub-tables for deep and shallow ConvNet, respectively. The first eleven columns demonstrate the correlation and significance between network feature of each subject at each task and one of the sub-feature sets of the handcraft-based features, the last column shows the correlation and significance between network feature of mixed subjects at each task and the handcraft-based features. In Table 7, the chance level is the r-value between CNN-based features and random white noise.

As we can see from Table 7, after the CCA analysis, the r-value between CNN-based features and the handcraft-based features shows a high correlation (r-value ranging from 0.54 to 0.99) and significance ($p < 0.05$), and they are all higher than the chance level, demonstrating the features learned by the CNN models are correlative to mindfulness-related features in EEG. Besides, the r-values between the CNN-based features and the handcraft-based feature at MBSR1 are around 0.82, the r-values between the CNN-based features and the handcraft-based feature at MBSR2 are around 0.95, the r-values between the CNN-based features and the handcraft-based feature at REST1 are around 0.62, the r-values between the CNN-based features and the handcraft-based feature at REST2 are around 0.72, showing that the features learned by the CNN models are MBSR tasks related features.

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TABLE 7 Correlation values (*r*) of canonical correlation analysis (CCA) between deep and shallow ConvNet derived features and handcraft-based features (band power ratios δ/α and δ/β) for each subject (also mixed subjects) at the four mental states, with * indicates significant correlation ($p < 0.05$) when compared to the corresponding chance level correlations.

Deep		1	2	3	4	5	6	7	8	9	10	11	Ave	Mix
MBSR1	δ/α	0.91*	0.82*	0.82*	0.82*	0.76*	0.77*	0.85*	0.83*	0.74*	0.8*	0.81*	0.81 ± 0.05	0.76*
	δ/β	0.88*	0.82*	0.84*	0.83*	0.8*	0.76*	0.81*	0.78*	0.88*	0.8*	0.85*	0.82 ± 0.04	0.75*
	Chance	0.14 ± 0.02	0.34 ± 0.01	0.12 ± 0.02	0.38 ± 0.01	0.35 ± 0.01	0.31 ± 0.01	0.12 ± 0.02	0.17 ± 0.02	0.38 ± 0.01	0.18 ± 0.01	0.12 ± 0.02	0.24 ± 0.11	0.24 ± 0.01
MBSR2	δ/α	0.97*	0.94*	0.94*	0.98*	0.98*	0.95*	0.77*	0.94*	0.81*	0.98*	0.99*	0.93 ± 0.07	0.95*
	δ/β	0.97*	0.98*	0.91*	0.97*	0.98*	0.92*	0.92*	0.94*	0.85*	0.98*	0.99*	0.95 ± 0.04	0.95*
	Chance	0.17 ± 0.01	0.26 ± 0.01	0.18 ± 0.02	0.15 ± 0.01	0.19 ± 0.01	0.34 ± 0.01	0.35 ± 0.01	0.14 ± 0.02	0.26 ± 0.01	0.23 ± 0.01	0.19 ± 0.01	0.22 ± 0.07	0.28 ± 0.01
REST1	δ/α	0.66*	0.68*	0.61*	0.67*	0.64*	0.66*	0.57*	0.54*	0.64*	0.61*	0.56*	0.62 ± 0.05	0.65*
	δ/β	0.68*	0.67*	0.63*	0.64*	0.6*	0.61*	0.58*	0.55*	0.67*	0.62*	0.59*	0.62 ± 0.04	0.63*
	Chance	0.15 ± 0.02	0.19 ± 0.01	0.13 ± 0.02	0.16 ± 0.02	0.38 ± 0.01	0.27 ± 0.01	0.24 ± 0.01	0.21 ± 0.01	0.32 ± 0.01	0.12 ± 0.01	0.14 ± 0.02	0.21 ± 0.08	0.25 ± 0.01
REST2	δ/α	0.74*	0.76*	0.73*	0.69*	0.72*	0.61*	0.58*	0.7*	0.73*	0.76*	0.7*	0.7 ± 0.06	0.73*
	δ/β	0.78*	0.77*	0.76*	0.7*	0.74*	0.66*	0.59*	0.71*	0.69*	0.71*	0.73*	0.71 ± 0.05	0.71*
	Chance	0.11 ± 0.03	0.26 ± 0.01	0.21 ± 0.01	0.22 ± 0.01	0.35 ± 0.01	0.22 ± 0.01	0.39 ± 0.01	0.14 ± 0.02	0.13 ± 0.02	0.15 ± 0.01	0.17 ± 0.01	0.21 ± 0.09	0.21 ± 0.01
Shallow		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Ave**	**Mix**
MBSR1	δ/α	0.82*	0.87*	0.86*	0.83*	0.81*	0.78*	0.87*	0.79*	0.84*	0.8*	0.82*	0.82 ± 0.03	0.85*
	δ/β	0.87*	0.85*	0.88*	0.84*	0.87*	0.8*	0.85*	0.8*	0.78*	0.82*	0.81*	0.83 ± 0.03	0.83*
	Chance	0.35 ± 0.01	0.12 ± 0.02	0.37 ± 0.01	0.33 ± 0.01	0.31 ± 0.01	0.14 ± 0.02	0.32 ± 0.01	0.35 ± 0.01	0.37 ± 0.01	0.17 ± 0.03	0.35 ± 0.01	0.29 ± 0.09	0.28 ± 0.01
MBSR2	δ/α	0.97*	0.97*	0.98*	0.97*	0.95*	0.89*	0.97*	0.96*	0.97*	0.95*	0.98*	0.96 ± 0.03	0.94*
	δ/β	0.98*	0.97*	0.97*	0.98*	0.96*	0.9*	0.96*	0.95*	0.95*	0.97*	0.98*	0.96 ± 0.02	0.95*
	Chance	0.24 ± 0.01	0.29 ± 0.01	0.31 ± 0.01	0.32 ± 0.01	0.2 ± 0.01	0.17 ± 0.02	0.19 ± 0.01	0.29 ± 0.01	0.32 ± 0.01	0.35 ± 0.01	0.34 ± 0.01	0.27 ± 0.06	0.26 ± 0.01
REST1	δ/α	0.63*	0.69*	0.62*	0.69*	0.69*	0.66*	0.71*	0.68*	0.67*	0.7*	0.67*	0.67 ± 0.03	0.65*
	δ/β	0.67*	0.64*	0.69*	0.63*	0.71*	0.67*	0.68*	0.65*	0.68*	0.68*	0.66*	0.67 ± 0.02	0.64*
	Chance	0.34 ± 0.01	0.12 ± 0.03	0.35 ± 0.01	0.37 ± 0.01	0.22 ± 0.01	0.11 ± 0.01	0.32 ± 0.01	0.24 ± 0.01	0.26 ± 0.01	0.32 ± 0.01	0.32 ± 0.01	0.27 ± 0.09	0.21 ± 0.01
REST2	δ/α	0.77*	0.76*	0.79*	0.77*	0.79*	0.75*	0.8*	0.77*	0.73*	0.77*	0.71*	0.76 ± 0.03	0.74*
	δ/β	0.78*	0.74*	0.71*	0.73*	0.82*	0.77*	0.74*	0.78*	0.79*	0.72*	0.75*	0.76 ± 0.03	0.78*
	Chance	0.31 ± 0.01	0.21 ± 0.01	0.36 ± 0.01	0.28 ± 0.01	0.17 ± 0.01	0.18 ± 0.02	0.19 ± 0.01	0.33 ± 0.01	0.35 ± 0.01	0.32 ± 0.01	0.35 ± 0.01	0.28 ± 0.07	0.22 ± 0.01

5. Limitations and future research

This study has some noticeable limitations. First, the study is based on a small EEG dataset of only 11 non-homogeneous subjects covering both Asians and Caucasians, resulting great inter-subject variability which is difficult to be sufficiently represented by both deep learning and traditional machine learning methods. Future studies should collect EEG data from a large number of subjects participating MBSR training with no meditation experience, and this may require a multi-center collaboration. Second, in this study for the first time we perform recognition of both state and trait effect of short term MBSR training through investigating the EEG measurements at two stages of early and late training, but only a single session of EEG measurement is performed for each stage, which limits us to investigate inter-session variability and distinguish it from trait effect of the MBSR training. In future research multi-session EEG data should be collected and utilized for classification of resting and meditation states at different stages. Finally, due to the availability of only a small dataset, we use only a very simple deep learning network of shallow ConvNet and its modification with a slightly deeper architecture, deep ConvNet. Future studies may consider more complex deep learning architectures which can cope with small data and inter-subject variability in various ways. We may use a GAN structure for intrinsic data augmentation (Fu et al., 2022), use i-vector to reduce the effect of inter-subject variability for inter-subject classification (Xu et al., 2022), and use large amount of publicly available meditation independent EEG data for self-supervised learning (SSL) to assist deep learning with small data and inter-subject variability (Rafiei et al., 2022). SSL has been demonstrated effective in speech analysis using the wave2vec (Baevski et al., 2020) architecture, which has been recently adapted as neuro2vec (Wu et al., 2022) and eeg2vec (Bethge et al., 2022) for EEG signal analysis.

6. Conclusion and implications

This study has examined the state and trait (stage) effect of short term MBSR training using CNN based deep learning methods of deep and shallow ConvNets as well as traditional machine learning methods of CSP + SVM and FBCSP + SVM, through investigating the EEG measurements of eleven MBSR practitioners during resting and meditation at early and late training stages, supporting previous findings that short-term meditation training has EEG-recognizable state (Ahani et al., 2014) and trait (Sharma et al., 2019) effects. The classifiers are trained and evaluated using inter-subject, mix-subject, intra-subject, and subject-transfer classification strategies, each according to a specific application scenario. Results show that in the intra-subject and mix-subject classification scenarios, our deep learning classifiers have classification performance superior to related EEG-based meditation state classification studies reported in the literatures for state effect classification as well as trait effect classification using EEG data during either resting or meditation, for both novice and expert meditators with a variety of meditation types including yoga, Tibetan, and mindfulness, whereas comparing to the literatures for inter-subject classification the performance of FBCSP for novice MBSR meditators is superior for state effect recognition of novice meditators and slightly inferior but still comparable for both state and trait effects recognition of expert meditators.

Studies on clinical interventions using mindfulness meditation suggest that MBSR may reduce various mental disorders such as anxiety (Beauchemin et al., 2008), depression (Hofmann et al., 2010), ADHD (Zylowska et al., 2008), and social disorder (Beauchemin et al., 2008). EEG-based mindfulness meditation state classification can serve as a quantitative evaluation of MBSR training effectiveness and level/expertise of mindfulness of the practitioner, and then can be used as online or offline feedback to assist the practitioners for improved training and practicing performance. Our study demonstrates excellent mix-subject and intra-subject classification performance as well as reasonably good inter-subject classification. When our mindfulness state classification methods are integrated with wearable EEG sensors (Anwar et al., 2018; Álvarez Casado et al., 2021) and virtual reality (Mistry et al., 2020; Viczko et al., 2021) in future research, a neurofeedback assisted MBSR training system may be developed and can help make MBSR more effective and accessible to the general populations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Hong Kong Local Institutional Review Board (IRB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CC, BS, FD, and XM conceptualized the project. CC and XM supervised the project. BS and RF performed data analysis. FD performed data pre-processing, results interpretation, and literature review. CC designed the methodology. JG and HS designed the experiments and collected the data. FD and CC drafted the manuscript. RF and CC revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

FD was employed by Deepbay Innovation Technology Corporation Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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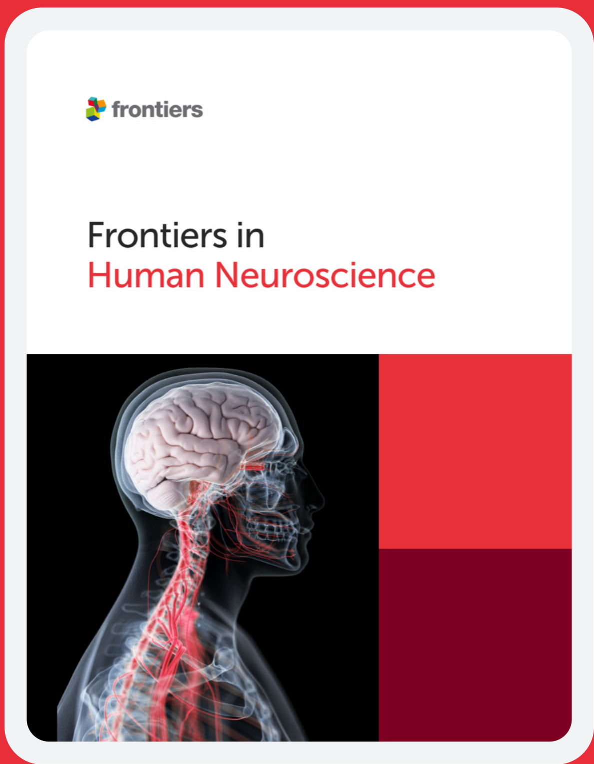

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