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Meditation-induced neuroplastic changes of the prefrontal network are associated with reduced valence perception in older people

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Abstract

Background: Neuroplastic underpinnings of meditation-induced changes in affective processing are largely unclear.
Methods: We included healthy older participants in an active-controlled experiment. They were involved a meditation training or a control relaxation training of eight weeks. Associations between behavioral and neural morphometric changes induced by the training were examined.
Results: The meditation group demonstrated a change in valence perception indexed by more neutral valence ratings of positive and negative affective images. These behavioral changes were associated with synchronous structural enlargements in a prefrontal network involving the ventromedial prefrontal cortex and the inferior frontal sulcus. In addition, these neuroplastic effects were modulated by the enlargement in the inferior frontal junction. In contrast, these prefrontal enlargements were absent in the active control group, which completed a relaxation training. Supported by a path analysis, we propose a model that describes how meditation may induce a series of prefrontal neuroplastic changes related to valence perception. These brain areas showing meditation-induced structural enlargements are reduced in older people with affective dysregulations.
Conclusion: We demonstrated that a prefrontal network was enlarged after eight weeks of meditation training. Our findings yield translational insights in the endeavor to promote healthy aging by means of meditation.

Keywords

Neuroplasticity, valence, emotion, meditation, magnet resonance imaging

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Introduction

Meditation-based interventions may reduce anxiety and negative mood (Ho et al., 2015; Tang et al., 2007; Zeidan et al., 2014) and have been applied as a non-pharmaceutical approach to treat patients with mood disorders. Meditation, which originated in Sino-Hindu cultures, is a family of practices that aim to cultivate mindfulness (Lutz et al., 2008b). Different styles and traditions of meditative practice all lead to the state of quiescence and meditative equanimity. A randomised controlled trial verified that the effectiveness of meditation in preventing the recurrence of depression is comparable to drug treatment (Kuyken et al., 2015). Mood-stabilising effects of meditation may be mediated by a reduction of perceptual biases towards affective information. In line with this thought, our recent active-controlled longitudinal study revealed that healthy elderly participants exhibited more neutral responses to both positive and negative emotional pictures after an attention-based compassion meditation training (MED) of 8 weeks (Shao et al., 2016), which explicitly focuses on the non-judgemental, compassionate quality of mindful attention, 'a sense of openhearted, friendly presence and interest' (Kabat-Zinn, 2003). In the current study, we seek to link meditation-induced changes in emotion perception to neuroplastic structural changes in prefrontal brain networks.

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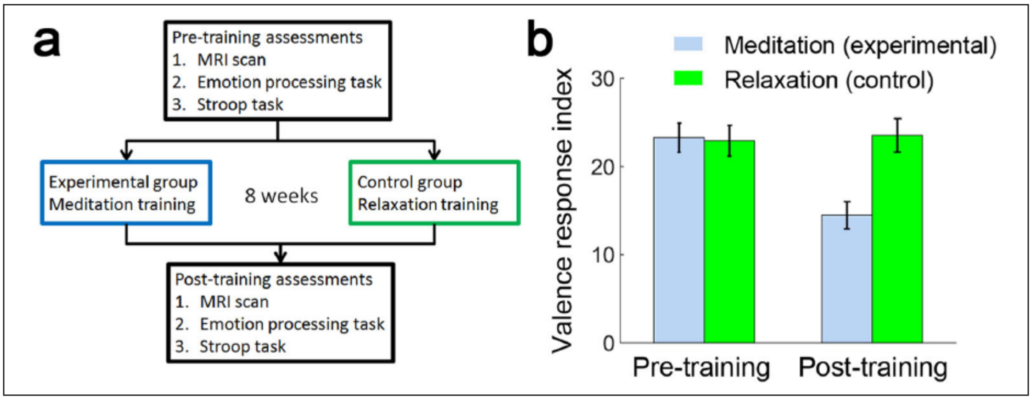

Figure 1. (a) Participants underwent meditation training (MED) or relaxation training (RLX) for 8 weeks. Structural MRI scanning, an emotion processing task and a standard Stroop colour-word task were administered before and after the trainings. (b) The valence response index (the difference between the average valence ratings of happy and sad pictures) in the MED group decreased after training, whereas it remained unchanged in the RLX group.

Longitudinal data showing causal effects of MED on structural neuroplasticity are sparse (Davidson and McEwen, 2012; Tang et al., 2015), particularly in elderly populations. However, there have been several functional magnetic resonance imaging (fMRI) studies that involved MED or comparisons of meditation experts and novices. Importantly, previous studies in other fields of research have demonstrated that brain regions undergoing functional changes are also likely to show structural changes, and vice versa. For example, changes in posterior parietal cortex after motor learning and changes in superior temporal sulcus as a function of social network size were found in both functional and structural neuroimaging data (Draganski et al., 2004; Noonan et al., 2014; Sallet et al., 2011; Sampaio-Baptista et al., 2015). Thus, it is likely that brain areas that have consistently revealed meditation-induced *functional* neuroplasticity will also be key candidates for structural changes.

Previous functional neuroimaging data as well as diffusion imaging data suggest that the ventral prefrontal cortex (PFC) could undergo structural changes after MED. Two studies that involved young adults revealed enhancements in the white matter microstructure in the anterior corona radiata after a short MED of less than 4 weeks (Tang et al., 2010, 2012). These findings led to speculations that MED may also affect structural and functional characteristics of grey matter regions adjacent to the anterior corona radiata. In line with this, the ventral PFC and striatum, which are neighbours of the anterior corona radiata, showed strong functional activity after MED. For example, after mindfulness MED, people show stronger activity in the ventromedial prefrontal cortex (vmPFC) and striatum than non-meditator controls when they are watching affective stimuli (Allen et al., 2012; Engen and Singer, 2015; Klimecki et al., 2014) or when they are in a meditation state (Holzel et al., 2007; Lutz et al., 2008a; Zeidan et al., 2014). Moreover, vmPFC is strongly connected to ventrolateral prefrontal cortex (vlPFC) during self-controlled behaviour (Hare et al., 2009, 2011) and vlPFC is active during emotion regulation (Ochsner et al., 2002; Phillips et al., 2008), which are key processes for meditation beginners (Tang et al., 2015).

Overall, these findings suggest that different prefrontal regions may guide different aspects of meditation-induced changes and may vary across different paradigms. A meta-analysis on these fMRI studies may help identifying key grey matter regions that most consistently reveal altered function following meditation. These regions might therefore be key candidates for meditation-induced prefrontal structural changes, which have previously been observed in cross-sectional studies on long-term meditators (Holzel et al., 2008; Lazar et al., 2005). Since multiple subregions in the PFC are functionally more active in meditators, it is possible that these regions would undergo neuroplastic changes in synchrony after people received an intense MED.

As degeneration in the PFC grey matter has been linked to geriatric mood disorders and ageing-related cognitive decline (Grady, 2012; Steffens and Potter, 2008), a better understanding of the meditation-induced interplay of neuroplasticity in prefrontal brain structures and its association with affective and cognitive processing may yield crucial insights in the translational endeavour to promote healthy ageing. However, it is unclear if and how meditation-induced functional changes induce structural changes in prefrontal grey matter brain networks in elderly participants.

In the current study, we addressed these issues by means of (1) a longitudinal experiment in which elderly participants underwent an 8-week MED or control RLX (Figure 1(a)), (2) a meta-analysis of previous fMRI studies for identifying the key neural correlates to the investigation of our structural magnetic resonance imaging (MRI) data, (3) a parametric voxel-based morphometry (VBM) analysis to identify neuroplastic changes that were specifically related to behavioural changes and (4) connectivity-based approaches to understand how these neuroplastic changes could happen in synchrony as an interconnected neural network.

Materials and methods

Participants

In total, 45 healthy, right-handed adults over 60 years of age with no prior MED or relaxation training (RLX) experience were recruited into this study and were assigned to participate in MED ($n=23$; 16 females; mean age = 64.78 years) or RLX ($n=22$; 14 females; mean age = 64.68 years). The groups were matched for

Table 1. Demographic data of meditation and relaxation groups.

	Meditation group (n=23)	Relaxation group (n=22)
Age	64.78	64.68
Gender	16 females	14 females
Years of education	12.17±3.21	13.73±4.12
TONI-III score	25.96±6.05	25.68±5.92
HADS-anxiety score	4.26±3.06	4.86±2.62
HADS-depression score	4.00±2.76	4.36±2.54

HADS: Hospital Anxiety and Depression Scale.

age (t_{43}=0.137, p=0.891), years of education (t_{43}=–1.414, p=0.165), non-verbal intelligence (t_{43}=0.154, p=0.879; measured by Test of Nonverbal Intelligence, Third Edition (TONI-III)) and Hospital Anxiety and Depression Scale (HADS) scores for anxiety (t_{43}=–0.707, p=0.483) and depression (t_{43}=–0.459, p=0.658). Part of the behavioural and demographic data of the same participants is reported in our recent fMRI study (Shao et al., 2016). Table 1 summarises the demographic data of our participants.

MED and RLX

Participants received either attention-based compassion MED or RLX for 8 weeks. The protocol of these trainings was also used in previous studies (Lau et al., 2015; Shao et al., 2016). RLX is a good active control for studying effects related to meditation because both RLX and MED involve similar experiences (Shao et al., 2016). Nevertheless, meditation requires additional active attention to focus on a certain mental goal, such as maintaining compassionate thoughts.

The MED was conducted by an experienced meditator with 14 years of meditation practice, including 4 years of teaching experience. Meditation participants were taught to cultivate mindfulness (Kabat-Zinn, 2003). This was achieved by (1) paying attention to the surrounding sounds and to their own breathing, feelings and sensations on the present moment; (2) applying non-judgemental and ‘acceptance’ attitudes on thoughts, feelings and sensations; (3) detaching from a self-referential framework and observing one’s own thoughts and feelings from an outsider’s perspective; and (4) cultivating compassion and kindness towards self, family members, friends, strangers and other living beings (Jain et al., 2007; Lutz et al., 2016). These strategies are interrelated and were taught in each of the meditation classes.

The RLX was conducted by a registered clinical psychologist with 4 years of teaching experience. Relaxation participants were taught to enhance body awareness and to reduce body tension (Jain et al., 2007; Ortner et al., 2007). This was achieved by teaching them diaphragmatic breathing, progressive muscle relaxation and imagery relaxation techniques.

Both types of training involved 22 classes, which were conducted by the respective trainers, at the Institute of Clinical Neuroscience at the University of Hong Kong. The classes were 1.5 h each (excluding one MED class, which lasted for 3 h). Each class began with guided meditation or relaxation practice for approximately 30 min. Didactic teaching then took place for approximately 45 min, and the class concluded with another guided practice for approximately 15 min.

All of the participants were asked to practice outside of the scheduled class time on a daily basis. They were given logbooks to record their daily self-practice, which contained daily record sheets that included the duration of their daily practice in terms of minutes and self-evaluation of that practice. Daily self-practice for at least 15 min was recommended. The total self-practice time was comparable between the MED (average 710 min, standard deviation (SD)=175.53 min) and the RLX (average 711.23 min, SD=215.27; t_{43}=–0.021, p=0.983) group.

Behavioural tasks

To evaluate changes in affective and non-affective processing, all of the participants underwent the Emotional Processing Task (EPT) and the Stroop interference task before and after they received the MED or RLX.

The EPT (Lee et al., 2012) included 20 happy, 20 sad and 20 neutral pictures from the International Affective Picture System (Lang et al., 1999). The happy and sad pictures were matched for their arousal level, and, according to the normative data, the arousal ratings for these pictures were larger than that of the neutral pictures. Pictures were presented in random order. On each trial, participants were required to subjectively rate the levels of valence and arousal by picking a point on a visual analogue scale. The valence ratings were then scaled between −37 (very unpleasant) and +37 (very pleasant), whereas the arousal ratings were scaled between 1 (not arousing) and 75 (very arousing). The scaling was not visible to participants. Participants who showed stronger affective valence ratings scored higher on happy pictures and lower on sad pictures. In our recent study, the ratings from happy and sad pictures were analysed separately (Shao et al., 2016). Here, a *valence response index* was computed to reflect the overall valence ratings of each participant by calculating the difference between the average valence rating of the happy and sad pictures; as such this index reflects how much on average the valence ratings of the happy and sad pictures deviated from the neutral valence score (i.e. a score of 0). Similarly, participants who showed stronger affective arousal perceptions would score high on both happy and sad pictures. An *arousal response index* was computed as the average arousal rating of both the happy and sad pictures (i.e. how much on average the arousal ratings deviated from the non-arousing score of 1). The same set of pictures was used during the pre- and post-training assessments.

Non-affective attentional control was assessed using a standard Stroop interference test (Lee and Chan, 2000), which involved a colour-word condition and a colour-dot condition (Supplementary Methods S1). The Stroop interference effect was calculated as the difference between the response times in the colour-word condition and the colour-dot condition.

Meta-analysis

A meta-analysis was conducted to examine the effects of MED on neural activity using an online neuroimaging database (www.neurosynth.org). Meditation-related studies were initially selected by a search using keywords ‘meditation’, ‘meditator’, ‘meditative’, ‘mindful’ and ‘compassion’ (n=44; Table S5). Fifteen studies were then excluded from the analysis because the samples were not healthy participants or experienced meditators, or the studies did not adopt an fMRI methodology. Nine studies that involved task-free fMRI data (e.g. resting state) were further excluded. Finally, a total of 20 studies were selected in the analysis. We applied automated forward inference and reverse inference procedures that were validated and explained elsewhere (Yarkoni et al., 2011) to investigate any brain regions that reliably showed stronger activity in experienced meditators. In brief, a naïve Bayesian classifier was used to make predictions of the activation pattern, and a chi-square test was performed to generate statistical maps. In the forward inference procedure, it was tested whether a voxel was consistently active across the studies that we selected. In the reverse inference procedure, a comparison was made between our selected studies with other studies in the database and then activations specific to our selected studies were identified. The results were corrected for multiple comparisons using cluster-based threshold $z>4.5$ and $p<0.01$ false discovery rate (FDR) corrected. The results of this meta-analysis allowed us to identify regions that are consistently active in meditators across studies. We then focused on these brain regions in our subsequent VBM analysis.

MRI data acquisition and preprocessing

Brain structural data were acquired on a Philips 3T MRI scanner using a T1-weighted MPRAGE sequence: $1\times1\times1\,\mathrm{mm}^3$ voxel resolution, $155\times198\times200$ grid, TR = 7 ms, TE = 3.2 ms and flip angle = 8°. The data were preprocessed following the standard FSL-VBM approach (under FSL5.0). In particular, each individual T1 image was brain extracted and segmented into grey matter, white matter and cerebrospinal fluid. A study-specific grey matter template was created using an affine registration to the GM ICBM-152 template (Andersson et al., 2007; Ashburner and Friston, 2000; Douaud et al., 2007). The final preprocessed data were smoothed with an isotropic Gaussian kernel with a sigma value of 4 mm.

MRI data analysis

Whole-brain analyses were conducted using a univariate generalised linear model (GLM) approach that involved permutation tests (5000 iterations; Winkler et al., 2014). To identify brain regions which expanded as a function of affective and attentional changes, we calculated the difference in morphometric maps between the post-training and pre-training T1 images (i.e. difference maps) and also the differences in valence response index, arousal response index and Stroop performance between the post-training and pre-training tests.

We designed a GLM that involved the following regressors to analyse the difference maps: the main effects of MED and RLX (two binary regressors), and the parametric effects of changes in valence response index, arousal response index and Stroop performance in MED and RLX separately (six parametric regressors). The two main effect regressors allowed us to estimate general changes in grey matter size after MED and RLX separately. The six behavioural regressors were normalised (z-scored) within each group so that it allowed us to estimate neural–behavioural correlations that were solely due to parametric changes in the behavioural measures after MED and RLX separately. At the contrast level, we investigated the average effects (by assigning equal weights to the MED and RLX regressors) and the differences in effects (by assigning opposite weights to the MED and RLX regressors) between the two groups. Multiple measures corrections were employed using cluster-based correction (cluster-based threshold at $z>2.3$, cluster significance threshold $p<0.05$; Worsley et al., 1992).

We conducted a novel psychomorphometric interaction (PMI) analysis, which is analogous to the psychophysiological interaction (PPI) analysis often performed on functional data (see Supplementary Methods S2 for further explanations; Friston et al., 1997; O'Reilly et al., 2012). We sought to identify structural changes at the whole-brain level that were related to changes in the valence response index (psychological regressor) and changes in the volume of a seed brain region (morphological regressor). The PPI regressor was calculated as the product of the psychological and physiological regressors. In each PMI analysis, the psychological, morphological and PMI regressors were all included in the GLM. The inferior frontal junction (IFJ) seed region was obtained from the significant cluster in Figure 3(a) that showed a significant general expansion after MED.

Path analysis was conducted using the PROCESS macro that runs in SPSS (Hayes, 2015) to examine the relationships between changes (differences between post-training and pre-training) in the valence response index and the sizes of the IFJ, inferior frontal sulcus (IFS), vmPFC and striatum (Tziortzi et al., 2014). Mediation analyses were performed using permutation tests with 1000 iterations.

Results

Behaviour

In the emotion processing task, participants were asked to rate the valence and arousal levels of a set of emotional pictures before and after the course of MED or RLX. We computed a valence response index and an arousal response index that reflected participants' overall levels in valence and arousal perception, respectively (see 'Materials and methods' section). In addition, participants were also assessed regarding their non-affective attentional control performance using a Stroop interference task.

In a two-way analysis of variance (ANOVA) testing the valence response data, there were significant main effects of group (MED or RLX; $F_{1,43}=4.127$, $p=0.048$) and time (before or after training; $F_{1,43}=13.557$, $p=0.001$). Critically, we found a significant group × time interaction effect on the valence response index ($F_{1,43}=17.969$, $p<0.001$; Figure 1(b)). A post hoc analysis showed that the valence response became weaker in MED after training ($t_{22}=-4.190$, $p<0.001$), whereas it remained unchanged in RLX ($t_{21}=1.068$, $p=0.298$).

We then applied the same two-way ANOVA model to analyse the arousal response index. We found that the main effect of group was not significant ($F_{1,43}=1.077$, $p=0.305$), the main effect of time was significant ($F_{1,43}=6.918$, $p=0.012$) and the group × time interaction was also significant ($F_{1,43}=20.860$, $p<0.001$; Figure S1). Similar to the valence response data, in a post hoc analysis, we found that the arousal response after MED became weaker ($t_{22}=-4.229$, $p<0.001$), whereas there were no significant differences before and after training after RLX ($t_{21}=1.924$, $p=0.068$).

Finally, when we analysed the Stroop interference data, the main effects of group ($F_{1,43}=2.087$, $p=0.156$) and time ($F_{1,43}=0.240$,

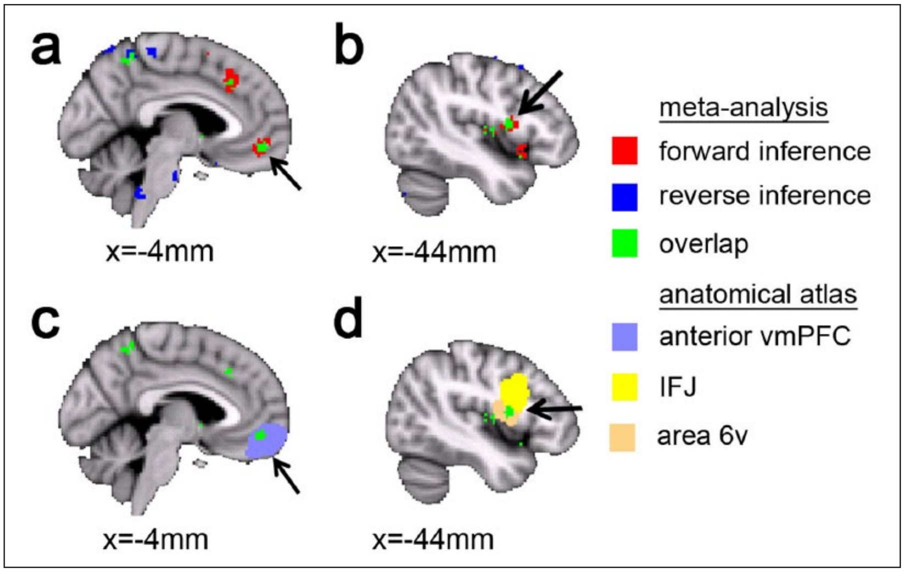

Figure 2. A meta-analysis of fMRI studies that involved meditation experts or trained meditators performing in an affective or cognitive task. (a) and (b) Forward inference (red) and reverse inference (blue) were performed. Regions including (a) vmPFC and (b) vlPFC were more active in experienced meditators in both forward and reverse inference analyses (green). By matching with neuroanatomical atlases (Neubert et al., 2014, 2015), (c) it was identified that the vmPFC lies within an anterior vmPFC region that is important for generating subjective preference of stimuli. (d) The vlPFC lies at the border between the inferior frontal junction (IFJ) and area 6v that are important for self-control and metacognition, respectively.

$p=0.627$) and the interaction effect were all insignificant ($F_{1,43}=0.730$, $p=0.397$; Figure S2).

Taken together, participants showed more neutral valence responses and weaker arousal responses to affective stimuli only after receiving the MED. Neither types of training had any impact on performance in the Stroop interference task, which involved only non-affective stimuli.

Meta-analysis of previous studies reveals stronger prefrontal activity in meditators

Before we examined the structural MRI data, we performed a meta-analysis to identify brain regions that are consistently more active in meditators. Our analysis revealed that the vmPFC (Figure 2(a)) and vlPFC (Figure 2(b)) were more active in meditators than in controls in both forward and reverse inference tests, suggesting that these regions are reliably more active in experienced meditators. We also matched the locations of these regions with neuroanatomical atlases generated via connectivity-based parcellation using resting-state fMRI data (Neubert et al., 2014, 2015). Interestingly, the identified meditation-associated vmPFC area lies within the anterior vmPFC, a region which reflects the subjective pleasantness of stimuli (Figure 2(c); McNamee et al., 2013). The vlPFC region lies at the border between IFJ and area 6v. These areas are implicated in self-control (Brass et al., 2005) and metacognition (Nelissen et al., 2005), respectively (Figure 2(d)). Based on these meta-analytic findings, we hypothesised that meditation, but not RLX, would induce neuroplastic changes in vmPFC and vlPFC in the structural MRI.

Ventral PFC enlargement after MED

We investigated the relationships between training effects, changes in task performance and brain structure using a VBM analysis. In particular, we applied a GLM that included parametric regressors that describe changes in valence response, arousal response and Stroop interference so that we could identify structural changes that were specifically associated with each type of performance change. We also included the main effects of MED and RLX in the same model.

First, we examined any general effects of MED and control RLX on grey matter that were unrelated to the behavioural changes. A contrast comparing the main effects of training between the two groups revealed that the degree of enlargement was significantly larger in MED than in RLX in the IFJ (threshold $z>2.3$, $p<0.05$, cluster-based corrected; Figure 3(a)), located just posterior to the IFS. A follow-up analysis investigating the main effects of MED and RLX independently in the IFJ showed that this significant difference was driven by the enlargement of IFJ in participants after MED but not by any changes in IFJ volume in relaxation participants (threshold $z>2.3$, $p<0.05$, cluster-based corrected; Figure 3(b)).

In addition, we also examined whether the parametric changes in behaviour were related to any general neural enlargements in both MED and RLX. The results showed that brain regions including the vmPFC (Figure 4(a)) and the IFS (Figure 4(b)), which is a subfield of the vlPFC, as well as other sensory-motor regions were negatively correlated with the ratings of the valence of the affective stimuli in both groups (threshold $z>3.7$, $p<0.05$, cluster-based corrected; Table S1). In other words, these brain regions were enlarged to a greater extent in individuals who gave more neutral ratings to the affective pictures after training. However, no region was significantly correlated with changes in arousal response or Stroop performance ($p>0.05$).

Previous studies have shown neuroplastic changes in the anterior corona radiata, which is the white matter adjacent to the vmPFC and vlPFC, after meditation (Tang et al., 2010, 2012). Given that our behavioural analysis found an overall

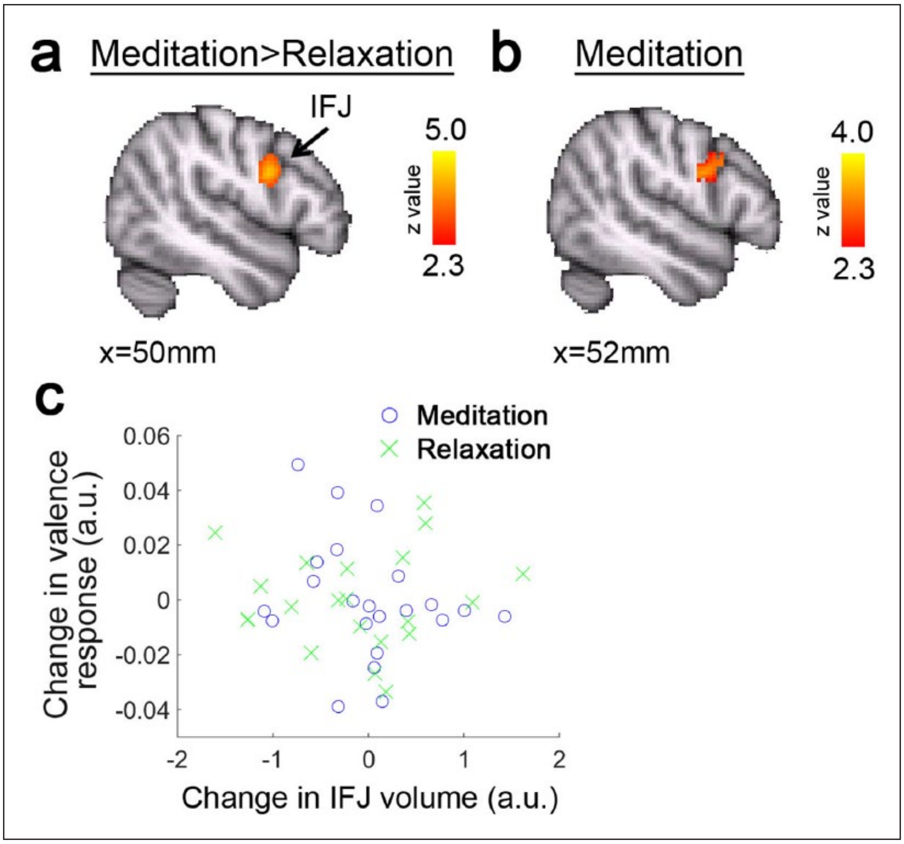

Figure 3. The IFJ was generally enlarged after training in meditators. (a) In a contrast comparing the main effects of meditation and relaxation training, the IFJ (peaked at 50,6,28) was more enlarged in MED compared with RLX. (b) The same IFJ (peaked at 52,4,26) region was significantly enlarged when data from MED were analysed independently. (c) The degree of IFJ enlargement was unrelated to the changes in valence response in both MED (blue) and RLX (green).

group change in valence response only in MED but not in RLX, in the VBM we also compared the correlation strengths between MED and RLX. This tested the possibility that the observed neural-valence correlations in ventral prefrontal regions were attributable to the MED group only. This analysis allowed us to dissociate neuroplastic effects resulting from the affective changes after MED from random emotional fluctuations following RLX. By performing a whole-brain analysis, we found that the correlations were more negative in MED than in RLX in brain regions, including the vmPFC (threshold $z > 3.7$, $p < 0.05$, cluster-based corrected; Figure 4(c)) and the IFS (Figure 4(d); Table S2). Importantly, the vmPFC region is similar to the anterior vmPFC identified in our meta-analysis of previous fMRI data (Figure 2(a)). The IFS region is also adjacent to the IFJ/area 6v region identified in the meta-analysis. To examine whether these contrast effects were related to a negative correlation after MED, a positive correlation after RLX, or both, we performed a region of interest (ROI) analysis to test these neural-valence correlations in each group independently. The vmPFC and IFS masks were defined using the clusters found in the contrast between MED and RLX presented in Figure 4(c) and (d), respectively. Similar to the whole-brain analysis, we included changes in the arousal response and Stroop performance as covariates in order to illustrate that the correlations were specific to changes in valence response. We excluded one outlier MED participant that the changes in vmPFC and vlPFC sizes were beyond 3 SDs from the group mean of the meditators, which could inflate any correlation. Our results revealed that the reduced valence response was related to the enlargement of vmPFC ($r = -0.48$, $p = 0.032$; Figure 4(e)) and IFS ($r = -0.567$, $p = 0.009$; Figure 4(f)) in MED but not in RLX (vmPFC: $r = 0.074$, $p = 0.757$; IFS: $r = -0.181$, $p = 0.458$). The correlation became even stronger in vmPFC ($r = -0.767$, $p < 0.001$; Figure S3(a)) and IFS ($r = -0.769$, $p < 0.001$; Figure S3(b)) when the outlier MED participant was added in the analysis.

Valence-related changes in meditators were moderated by the degree of IFJ enlargement

Thus far, we identified cortical regions in vmPFC and IFS that were enlarged as a function of the development of more neutral valence responses after MED. Similarly, the IFJ, which is just posterior to the IFS, was also enlarged after MED, but its degree of enlargement was unrelated to the degree of affective change. It is possible that the enlargement in IFJ in the meditators played a role in switching on a series of neuroplastic changes in the prefrontal regions that accompanied the affective change. In other words, when the IFJ was enlarged *morphologically* and the valence response became more neutral *psychologically*, neural

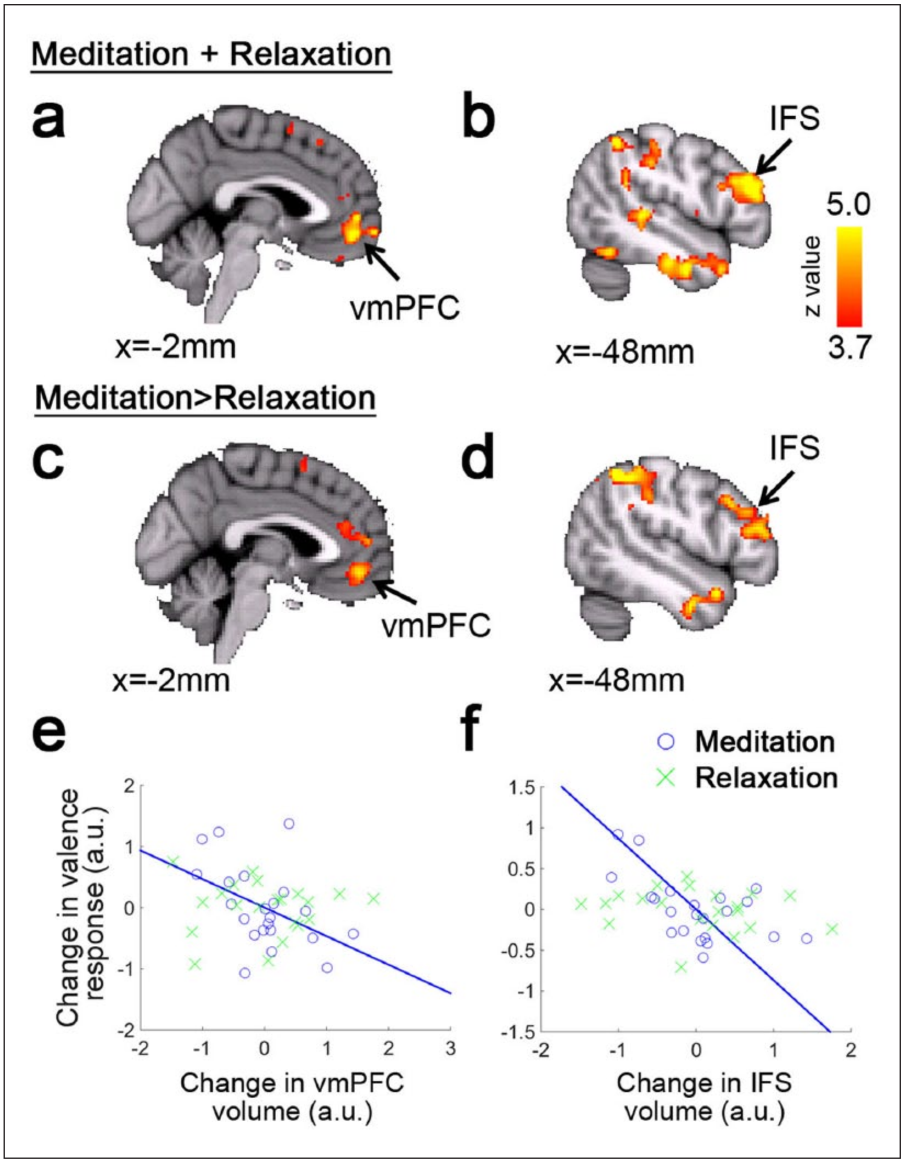

Figure 4. Reductions in valence response were related to enlargements in ventral PFC regions. More neutral valence responses were correlated with larger extents of enlargements in (a) vmPFC and (b) IFS in all participants (including MED and RLX). A follow-up analysis showed that the correlations were driven by the meditators. The degree of reduction in valence response was related to the degree of enlargement in (c, e) vmPFC and (d, f) IFS only in MED (blue), but not in RLX (green). Data of one outlier MED participant are excluded in (e) and (f). Figure S3 shows data of all participants. IFS: inferior frontal sulcus; vmPFC: ventromedial prefrontal cortex.

regions involved in the affective network may also have become larger. Therefore, we designed a novel PMI analysis, which is analogous to the PPI analysis that is often performed to analyse functional neuroimaging data (Friston et al., 1997). A seed was placed within the IFJ (Figure 5(a)) in this analysis. After MED, we found strong PMI effects in the IFS and vmPFC (threshold $z>4.7$, $p<0.05$, cluster-based corrected; Figure 5(b) and (c)), suggesting that when the IFJ was enlarged, more neutral valence responses after meditation were accompanied by enlargements in the IFS and vmPFC. Moreover, when we performed the same analysis in the control RLX participants, no significant regions were identified (threshold $z>2.3$, $p>0.05$, cluster-based corrected), suggesting that the PMI effects were specific to MED.

Fluctuations in valence responses in controls were related to subcortical changes in the striatum

In our whole-brain analysis, there were no significant effects in the striatum, which is also near to the anterior corona radiata that showed neuroplasticity after MED (Tang et al., 2010, 2012). Based on our a priori hypothesis, we employed an ROI analysis to examine whether any volumetric changes in the striatum (Figure 6(a)) were related to changes in the valence response. Intriguingly, there was no significant correlation between changes in striatal volume and valence response in MED ($r=0.250$, $p=0.287$). However, RLX participants who showed more neutral

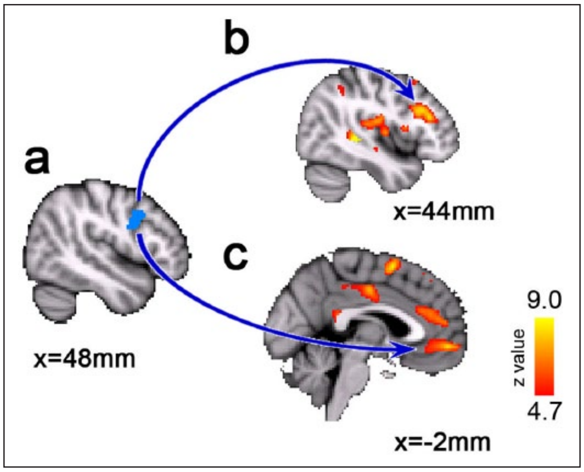

Figure 5. Psychomorphometric interaction (PMI) analysis. (a) A seed was placed at the IFJ. The results revealed that the interaction between enlargement of the IFJ and the reduction in valence response was strongly correlated with enlarged IFS (b) and vmPFC (c) in MED. In other words, changes in valence response were more strongly related to the degree of vmPFC and IFS enlargements when the IFJ was large. IFS: inferior frontal junction; IFS: inferior frontal sulcus; vmPFC: ventromedial prefrontal cortex.

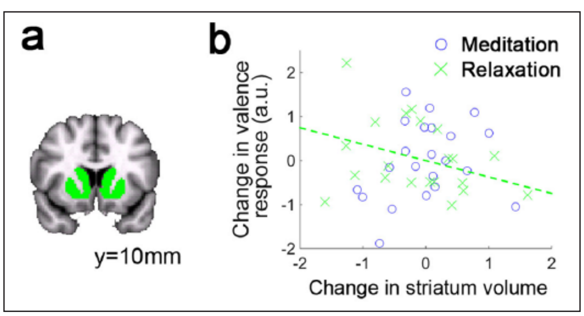

Figure 6. In control participants, changes in valence response were marginally related to changes in striatal size. (a) Changes in total striatal volume were extracted in each participant. (b) Reductions in valence response were marginally related to an increase in striatal volume only in RLX (green), but not in MED (blue).

valence responses were marginally enlarged in their striatum ($r=-0.434$, $p=0.056$, Figure 6(b)).

Meditation-induced neuroplastic changes in the prefrontal network

Results from our previous analyses showed a cortical–subcortical distinction in the valence-related neuroplastic changes after MED and RLX. After meditation, enlargement in the IFJ moderated cortical enlargements in the slightly more anterior IFS as well as the vmPFC as the valence response became more neutral. In contrast, IFJ sizes in relaxation participants were unchanged, while their random fluctuations in valence responses were related to changes in the striatal sizes of the subcortex. To test statistically whether MED and RLX were associated with different neuroplastic changes, we performed a path analysis to investigate the relationships between the type of training (MED or RLX), changes in valence response and changes in sizes of the IFJ, IFS and vmPFC.

In this analysis, we first established relationships between the changes of valence response, IFS and vmPFC. Because these changes in IFS and vmPFC were related to the changes in valence response in a very similar manner, particularly in MED (Figures 4 and 5), we hypothesised a mediation relationship between these three parameters. We found that after MED, more neutral valence responses were related to more enlarged vmPFC indirectly via the enlargement of IFS (see Supplementary Figure S4).

Finally, to address questions concerning the differential neuroplastic changes after MED and RLX, we added in factors for training type (MED or RLX) and changes in the sizes of the IFJ into the model. Based upon our previous results (Figures 2–4), training type and IFJ were assigned as moderators for the relationships of changes in valence response with IFS. The results showed that more neutral valence responses were only related to the enlargements of IFS and vmPFC when participants both received MED and exhibited an enlarged IFJ ($\beta=-0.161$, standard error (SE)$=0.097$, $p<0.05$; Figure 7(a), Table S3). In other words, changes in valence response did not have an impact upon the sizes of the IFS or the vmPFC when participants received RLX or when the change in IFJ was small in meditators ($p>0.05$; Figure 7(b), Table S3). On the other hand, we ran a similar model to test whether change in valence responses was a predictor of change in striatal volume, with training type and change in IFJ volume as moderators. The results showed that parametric fluctuations in valence responses were only related to the enlargement of striatum when participants both received RLX and exhibited a small IFJ change ($\beta=-1.227$, SE$=0.606$, $p=0.05$; Figure 7(b), Table S4). Any changes in valence response did not have an impact on the changes in striatal size in MED participants or any participants with small IFJ ($p>0.05$; Figure 7(a), Table S4).

Discussion

By means of a longitudinal active-controlled design employing behavioural and MRI measures, we examined the effects of MED on affective and cognitive processes in healthy older adults. As reported in our recent study that involved the same sample of healthy elderly participants (Shao et al., 2016), meditators exhibited more neutral valence perceptions towards the same affective stimuli (Figure 1(b)). Moreover, in the current study, we present findings from structural MRI data that revealed that after MED, the vmPFC and IFS were enlarged as a function of their changes in valence perceptions (Figure 4(c)–(f)). Subsequent analysis showed that these neuroplastic changes were modulated by a general enlargement of the IFJ (Figure 3). In contrast, the control RLX did not have an impact on the vmPFC, IFS and IFJ sizes. Instead, the natural fluctuations in the valence perceptions of relaxation participants were related to changes in the subcortical striatum but not in the cortical regions (Figures 6 and 7(b)). Our findings provide evidence that MED plays a driving effect on the development of more neutral affective perceptions and on neuroplastic changes in the form of enlargement of a prefrontal network. In contrast, random changes in affective perceptions of active-control participants were associated with striatal changes.

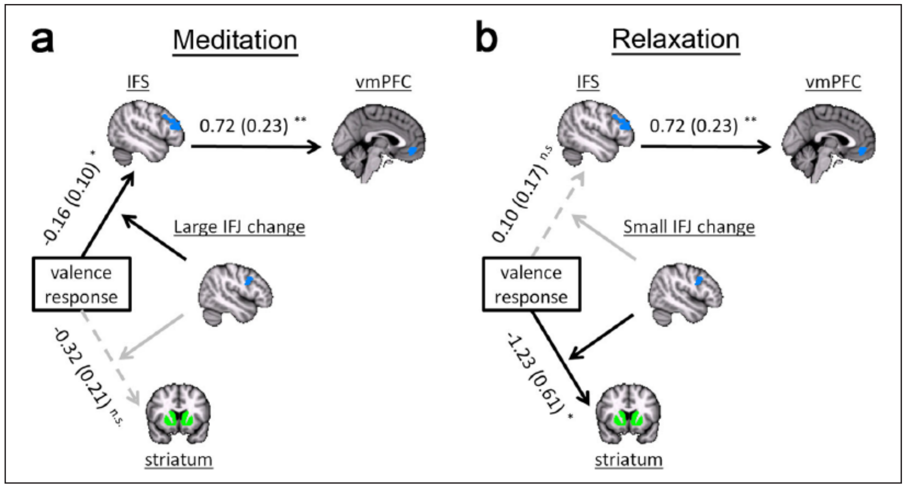

Figure 7. A path analysis shows that meditation and IFJ expansion moderated the neuroplastic changes in the ventral PFC. In a model, the change in valence response index was a predictor of the changes in vmPFC size (via changes in IFS). The change in IFJ size and the type of training were assigned as moderators. In a similar model, change in valence response index was a predictor of change in striatal size, moderated by training type and change in IFJ size. (a) After meditation training, more neutral valence responses were associated with a cascade of enlargements in the IFS and vmPFC. These prefrontal enlargements were moderated by the expanded IFJ as a mediator. There were no relationships between changes in valence response and striatal size. (b) In contrast, in RLX participants, who did not show IFJ expansion during their natural fluctuations in valence response, behavioural responses were related to their striatal sizes but not the sizes of the IFS or vmPFC. Note that no moderator was assigned between vmPFC and IFS, and hence the corresponding statistics should be the same in (a) and (b).
*$p<0.05$; **$p<0.005$.

These data suggest that the development of a meditation-based training scheme may promote neuroprotection of the PFC in older adults.

Although previous longitudinal data that examined the grey matter changes following MED in older adults are scarce, similar findings were reported in younger adults. In a cross-sectional study with long-term meditators, Holzel et al. (2008) examined whether the amount of meditation experience was related to grey matter concentration. They found that participants with longer total hours of MED were associated with larger concentration in a vmPFC region, which was similar to what is reported in the current study. Intriguingly, in a longitudinal study with naïve younger adults, there was an absence of neuroplasticity in the PFC (but expansions in areas such as temporoparietal junction and hippocampus) after 8 weeks of MED (Holzel et al., 2011a). Since younger adults have the most well-developed PFC, while PFC is susceptible to degeneration during the course of ageing, it is possible that neuroplasticity in PFC after MED is more robust in elderlies. This notion is indeed supported by an earlier cross-sectional study that compared the cortical thickness between meditators and non-meditator controls of different ages (Lazar et al., 2005). The authors reported that a lateral PFC region (BA9/10) as well as the temporoparietal junction and anterior insula were generally thicker in meditators. In addition, the controls showed age-related thinning in the lateral PFC. However, this was absent in meditators – the thickness of BA9/10 was comparable in younger and older meditators. Findings from these studies further support the notion that MED could have a neuroprotective effect on the age-related degeneration of PFC.

MED has much potential for treating mood disorders in both older and younger adults. Recently, Kuyken et al. (2015) performed a randomised controlled trial which compared the effects of meditation and antidepressant treatments on maintenance treatment in depressed patients. They found that the effects of meditation in avoiding a relapse of depression were comparable to (and even showed a trend towards outperforming) that of antidepressant treatment. Patients with mood disorders often exhibit an idiosyncratic mood-congruent attentional bias (Elliott et al., 2011; Erickson et al., 2005; Leung et al., 2009a, 2009b), in which they are more ready to process the affective content of stimuli when they match with the patients' affective state. In depressed (or manic) patients, information that is negative (or positive) in valence is perceived even more negatively (or positively). Our results showed that affective valence and arousal responses related to the same set of affective stimuli were reduced after MED (Figures 1(b) and S1). This supports the view that the antidepressant effects of meditation are mediated via a reduction in mood-congruent attentional biases. In addition, our findings provide evidence suggesting that these therapeutic effects, especially on geriatric mood disorders, could be related to enlargements in the ventral PFC, including the IFJ, IFS and vmPFC. They also provide insight into the possibility of using meditation-based interventions as a means to prevent degeneration of the PFC.

Abnormal activity in the PFC is found in patients with mood disorders. For example, Elliott et al. (2002) recorded the neural activity of depressed patients while they were performing an emotional go/no-go task. These patients showed stronger vmPFC activation response to sad stimuli than to happy stimuli, whereas the opposite pattern was found in healthy controls. Because vmPFC activity normally correlates positively with the valence or subjective preference of stimuli (Bouret and Richmond, 2010; Hare et al., 2009; Kable and Glimcher, 2007), the vmPFC of depressed patients valued sad stimuli as if they were even more appealing than happy stimuli. In contrast, when the same test was performed in manic patients, these participants showed a stronger vmPFC signal for happy stimuli than that of healthy controls (Elliott et al., 2004). These results suggest that the valence signals in the vmPFC are susceptible to mood-congruent attentional biases.

In our current study, we demonstrated that changes in valence perception in meditators were related to enlargements in the vmPFC and the IFS of the vlPFC (Figure 4(c) and (d)). Similarly, previous studies have shown that higher levels of mindfulness traits are associated with stronger functional activity in similar ventral prefrontal regions (Creswell et al., 2007). At a first glance, it might seem puzzling why the vmPFC, in which activity is susceptible to mood-congruent attentional biases and subjective preferences, would enlarge when meditators become more emotionally neutral. However, instead of considering the functional role of vmPFC alone, our hypothesis becomes more intuitive when we take a neural network perspective and consider the connectivity between vmPFC and vlPFC. Strong connectivity between these two regions is often found during the exercise of cognitive control. For example, strong functional coupling between the vlPFC and vmPFC was observed, when people had to control their desire for unhealthy but appealing food when the task required them to choose food based on its healthiness (Hare et al., 2009; Hutcherson et al., 2012; Maier et al., 2015). A similar type of vlPFC–vmPFC functional coupling has been observed when participants avoid distracting reward information (Chau et al., 2014; Walton et al., 2015). These findings suggest that this vlPFC–vmPFC connectivity plays a role in maintaining task-relevant behaviour and/or avoiding task-irrelevant behaviour. Our meditation protocol involved an intense training in maintaining compassionate thoughts and disengaging attention from any other irrelevant thoughts, a task that could require strong vlPFC–vmPFC connectivity. This demand could have led to the observed simultaneous structural enlargements in these regions in the meditation group (Figure 5). Future studies that involve functional imaging should examine the functional significance of this synchronous structural enlargement in the PFC.

In the path analysis, we suggested a model that described how the relationships between valence response and sizes of ventral prefrontal regions were modulated by the type of training. The model fitting showed that the changes in valence response were directly related to IFS enlargements and indirectly related to vmPFC enlargements. It is important to note that there was a strong correlation between changes in IFS and vmPFC sizes, and further studies will be required to confirm how they are related to changes in valence response. Nevertheless, the notion of this path analysis was to demonstrate that the MED had an impact on causing a series of neuroplastic changes in the ventral PFC.

In the current study, both MED and RLX did not show any improvement in the Stroop colour-word task that assesses non-affective attentional control. Although meditation is generally demanding for attentional control (Davidson and McEwen, 2012; Holzel et al., 2011b; Tang et al., 2015), evidence for improvements in the Stroop colour-word task performances following meditation is mixed. While some studies have revealed such effects (Chan and Woollacott, 2007; Moore and Malinowski, 2009), others failed to show an improvement (Anderson et al., 2003). It is possible that the Stroop colour-word task is not robust enough to detect specific attentional improvements caused by MED – particularly if the training is only brief as in the current study. Nevertheless, previous studies revealing improvements in a modified, affective Stroop task (instead of a non-affective Stroop colour-word task; Allen et al., 2012), as well as our current behavioural findings, highlight that MED is particularly effective in improving the regulation of affective processes. Further studies could examine the dissociable effects of meditation on affective and non-affective processes using a longer training protocol and more sensitive variants of the Stroop task, such as a computerised version that requires participants to perform in a large number of trials.

To conclude, our findings revealed that neuroplastic enlargements in the prefrontal network, including vmPFC and vlPFC, for affective valence perception were induced by MED in elderlies. By contrast, the random fluctuations of valence perception in control relaxation participants were associated with changes in striatal volume. These prefrontal regions that were enlarged after meditation were previously reported to be reduced in older people with affective dysregulations. Therefore, our findings yield translational insights in the endeavour to promote healthy ageing by means of meditation.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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