**Decreased emotional reactivity after 3-month socio-affective but not
attention- or meta-cognitive-based mental training: A randomized,
controlled fMRI study**

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Abstract

Meditation-based mental training interventions show great benefits for physical and mental health. However, it remains unclear how different types of mental practice differentially affect emotion processing at both the neuronal and the behavioural level. In the context of the *ReSource* project, 332 participants underwent an fMRI scan while performing an emotion reactivity task before and after three 3-month training modules cultivating 1) attention and interoceptive awareness (*Presence*); 2) socio-affective skills, such as compassion (*Affect*); 3) socio-cognitive skills, such as theory of mind (*Perspective*). Only the *Affect* module led to a significant reduction of experienced negative affect when processing images depicting human suffering. This decrease in emotion reactivity was associated with increased activation in cognitive control and emotion-regulation regions such as lateral parietal and prefrontal brain regions. We conclude that socio-affective, but not attention- or meta-cognitive based mental training is specifically efficient to improve emotion regulation capacities when facing adversity.

Key-words: meditation, fMRI, emotion, mental training, compassion, mindfulness

1. Introduction

Meditation-based mental training programs have been developed to improve emotion regulation and to decrease symptoms of psychopathology in both clinical and non-clinical populations (Heeren and Philippot, 2011; Kuyken et al., 2016; Piet and Hougaard, 2011; Teasdale et al., 2002). Many of these programs focus on the cultivation of mindfulness (e.g. Mindfulness-Based Stress Reduction (MBSR) and the Mindfulness-Based Cognitive Therapy (MBCT) programs (Kabat-Zinn, 2003; Williams et al., 2014)) or compassion (e.g. the Mindfulness Self-Compassion Program (Neff and Germer, 2013), Compassion-Focused Therapy (Gilbert, 2009) or the Compassion Cultivation Training (Jazaieri et al., 2013)). Studies have shown beneficial effects of such mental training programs on physical health, through stress reduction (Creswell et al., 2014) or improved immune system functions (Pace et al., 2009), as well as on mental health through increasing well-being and decreasing negative emotions (Goldin and Gross, 2010; Gu et al., 2015; Sedlmeier et al., 2012; Wallace and Shapiro, 2006). However, most programs consist of a mixture of different types of mental training practices whose specific effects are still poorly understood, especially on the control of emotional reactivity and its neural correlates. Indeed, there are at least three different domains that might be targeted in these integrative practices to improve emotion regulation: attention, socio-affective and socio-cognitive skills.

The attentional skills were mostly targeted by mindfulness-based interventions (MBI), which aim to develop present-moment attention and interoceptive awareness (Kabat-Zinn, 2003), and were proposed to affect both “bottom-up” and “top-down” emotion regulation mechanisms (Chiesa et al., 2013; Guendelman et al., 2017). Previous functional magnetic resonance imaging (fMRI) studies using MBI have tested various emotion generation and regulation paradigms, such as affect labelling (Hölzel et al., 2013), face processing (Johnson et al., 2014), self-reference (Farb et al., 2007; Goldin et al., 2012) or pain regulation (Zeidan et

al., 2015) tasks (for review, see Guendelman et al., 2017; Magalhaes et al., 2018; Young et al., 2018). Among them, studies that compared expert vs. novice practitioners and used implicit emotion regulation paradigms (i.e., passive viewing of emotional stimuli) showed conflicting results (Froeliger et al., 2012; Lee et al., 2012; Taylor et al., 2011). Specifically, these studies found both increased and diminished activity of the PFC in expert compared to novice practitioners in response to negative and sad pictures (Froeliger et al., 2012; Lee et al., 2012), as well as no difference when confronted with positive, negative and neutral images (Taylor et al., 2011). In addition, two studies used a longitudinal design and failed to show significant differences between novices practitioners who underwent an MBI vs. a control group (Allen et al., 2012; Desbordes et al., 2012). However, Allen et al. (2012), found that the amount of practice predicted greater activity in fronto-insular regions in a group trained in mindfulness. Another study, using neutral and sad video clips, showed both increased and decreased activity in the PFC and increase activity of the right insula after MBI in comparison to a waitlist control group (Farb et al., 2010). Recent reviews and meta-analyses suggest that MBI more generally increases recruitment of prefrontal regions even in the absence of explicit regulation instruction, thereby allowing automatic control of emotions. They also suggest a strong involvement of the insula which could be associated with better interoceptive awareness, while the modulation of the amygdala's response after mindfulness-meditation training is not yet well understood (Guendelman et al., 2017; Magalhaes et al., 2018; Young et al., 2018).

More recently, there has also been increased interest in studying Compassion-Based Interventions (CBI) that aim to develop social emotions and motivation such as loving kindness and compassion towards the suffering of oneself and of others (Gilbert, 2009, 2017; Jazaieri et al., 2013; Neff and Germer, 2013). Pioneering investigations on the neural correlates of compassion-based meditation practices employed cross-sectional designs to compare the brains of expert long-term meditation practitioners with novice practitioners (Lutz et al., 2008; Lutz

et al., 2009). By comparing the brain responses of expert practitioners when regulating their emotions using compassion meditation and reappraisal, a “gold standard” emotion regulation technique (Ochsner and Gross, 2005), our group found that both the subjective and neural responses to these techniques were markedly different (Engen and Singer, 2015): First, in terms of subjectively experienced emotion, compassion meditation primarily increased positive emotion while reappraisal strategies decreased negative affect. Second, imaging results revealed that compassion meditation in contrast to reappraisal strategies increased activity in the ventral striatum (VS) and the medial orbito-frontal cortex (OFC), while reappraisal preferentially recruited lateral prefrontal regions. Similarly, with longitudinal mental training designs, Klimecki and colleagues found that participants who trained compassion and loving-kindness meditation reported feeling more positive emotions, which was associated with increased activity in the medial OFC, the nucleus accumbens (NAcc), the VS and midbrain areas (Klimecki et al., 2013; Klimecki et al., 2014). Thus, compassion meditation appears to both increase positive affect and recruit a set of brain areas that are known to be associated with reward, affiliation, positive social feelings and prosocial motivation (Burgdorf and Panksepp, 2006; Carter and Keverne, 2002; McCall and Singer, 2012; O’Doherty, 2004; Schultz, 2006; Singer and Klimecki, 2014) that are distinct from regions most commonly associated with cognitive emotion regulation (Buhle et al., 2014; Ochsner et al., 2002).

Importantly, emotion processing and regulation involves both socio-affective and socio-cognitive skills. The recognition that somebody is suffering, for example, is classically associated with the process of empathy, which is defined as the human capacity to share and understand other people’s emotions without confusing them with one’s own feelings (De Vignemont and Singer, 2006). Functional and structural neuroimaging studies have consistently implicated an extended cerebral network comprising the anterior insula (AI) and anterior cingulate cortex (ACC), as well as lateral prefrontal and parietal areas, such as the DLPFC,

ventrolateral PFC and supramarginal gyrus (SMG) for empathy (Bzdok et al., 2012; Fan et al., 2011; Kanske et al., 2015; Lamm et al., 2011; Singer et al., 2004). Besides the described socio-affective skills, the understanding of other people's mental states requires socio-cognitive skills, i.e., the capacity to infer thoughts, beliefs and intentions of others, which is termed mentalizing, perspective taking or Theory of Mind (ToM) (Premack and Woodruff, 1978; Saxe and Kanwisher, 2003; Singer, 2012). ToM is thought to be underpinned by a neural network including the temporoparietal junction (TPJ), superior temporal sulcus (STS), temporal pole (TP), medial prefrontal cortex (mPFC) and precuneus/posterior cingulate (PCC) (Bzdok et al., 2012; Frith and Frith, 2005; Kanske et al., 2016; Kanske et al., 2015; Saxe and Kanwisher, 2003; Schurz et al., 2014). The importance of socio-affective and socio-cognitive capacities for individual and societal welfare is incontestable, however the possibility of training these skills and the potential subsequent effects of such a training on emotion processing is not well explored.

A major obstacle to disentangling what effects meditation-based mental training has on emotion processing is that previous randomized-controlled trials (RCT) that assessed change in emotion processing and brain plasticity in healthy populations generally suffered from small sample sizes (range from 10 to 32 participants in the “active” condition) (Allen et al., 2012; Desbordes et al., 2012; Farb et al., 2010; Kral et al., 2018; Leung et al., 2018; Weng et al., 2013; Weng et al., 2018), which compromises the generalizability of the findings (Fox et al., 2016; Fox et al., 2014; Guendelman et al., 2017; Young et al., 2018). In addition, most studies focused on interventions that integrate a range of different contemplative practices and largely lacked the direct comparison with other meditation-based control conditions (Tang et al., 2015). It thus also remains unclear whether different types of mental practice, pursuing different aims, can induce selective changes in emotional reactivity (and implicit emotion regulation) at both neurofunctional and behavioural levels.

To close this gap, we enrolled 332 participants in the context of the *ReSource* Project (Singer et al., 2016), a 9-month longitudinal mental training study. Based on the considerations made above, the *ReSource* project differentiated between three distinct 3-month training modules designed to cultivate (1) present-moment focused attention and interoceptive awareness (*Presence* module); (2) socio-affective skills, such as compassion, gratitude, prosocial motivation, and dealing with difficult emotions (*Affect* module) and (3) socio-cognitive skills, such as metacognition and perspective-taking on self and others (*Perspective* module) (Figure 1a). The participants were assigned to one of the three training cohorts (TCs) who underwent the different modules in counterbalanced order or to the retest control cohort (RCC) (Figure 1b). This design allows for the comparison of differential effect of the training modules, with the training modules acting as “active” control groups for each other, and also against retest controls. We examined training-related changes of subjective and neural emotion processing when participants watched positive, negative and neutral stimuli using an emotion anticipation task (EmoAnt) (Somerville et al., 2012). In the EmoAnt, participants viewed emotional pictures that could be presented in predictable (i.e., they were preceded by a countdown) or unpredictable (i.e., preceded by a random countdown) manner, with no regulation instruction to further explore the impact of the different trainings on pre-emptive emotion control. Notably, we used emotional pictures with social content only (e.g., human suffering for negative pictures) rather than more “basic” emotions such as fear of snakes or spiders, as the modules *Affect* and *Perspective* heavily focus on training socio-affective and socio-cognitive capacities. After each block of pictures, the participants had to rate their emotions (from negative to positive) as well as their nervousness (from extremely nervous to not nervous at all) (Figure 1c). We used these assessments to measure the two core dimensions of emotions: valence and arousal (Baucom et al., 2012; Feldman Barrett and Russell, 1998; Lindquist et al., 2012).

Based on previous literature using similar tasks, we predicted that at baseline (i.e., before the mental training), participants would exhibit increased amygdala activity for emotional vs. neutral pictures (Ochsner et al., 2002; Phan et al., 2002; Phelps and LeDoux, 2005; Somerville et al., 2012). Processing of positive emotion would be also accompanied by increased activation of VS, NAcc and OFC areas, while processing of negative emotion would be associated with activation of the amygdala and lateral regions of the PFC (Kragel and LaBar, 2016; Lindquist et al., 2012; Phan et al., 2002; Preckel et al., 2019). We expected module specific effects on behaviour and brain function: Similar to previous MBI studies (Allen et al., 2012; Desbordes et al., 2012; Kral et al., 2018), the effect of the *Presence* module should be associated with an improvement of top-down emotional control, manifesting in decreased negative affective ratings and a modulation of the activation of prefronto-limbic regions; The effect of the *Affect* module should be similar to the one observed after training of loving-kindness or compassion meditation (Desbordes et al., 2012; Engen and Singer, 2015; Klimecki et al., 2014), i.e. increased positive ratings and increased activation in brain areas associated with positive affect and affiliation, such as the ventral OFC, the VS and midbrain. Finally, we did not have specific a-priori hypotheses regarding the training of socio-cognitive skills (i.e., *Perspective* module) on emotion processing due to the lack of previous intervention studies in that domain. In addition to specific effects of different modules, we explored the overall 9-months training effect, speculating in the existence of a cumulative effect of each module leading to less negative affect along with an improvement of the prefrontal control over limbic regions, as well as enhanced positive affect and increased activity in the VS, OFC and midbrain regions.

Figure 1: Design of the study. (a) Timeline of training (coloured areas) and data collection (grey areas) for the training and retest control cohorts. After baseline testing (T0), participants completed the modules in different orders. Training cohort 1 and 2 trained Presence first and then Affect and Perspective in a switched manner. Training cohort 3 trained Affect only. Retest cohorts completed the measurements without any training. They were tested in two cohorts but are analysed jointly. The full ReSource Design as shown in the figure also included follow-up assessments, but these are not included in the present study. (b) Illustration of the three

modules of the program and their core exercises: Presence (yellow), Affect (red), Perspective (green). (c) Illustration of the experimental design. In each block negative, neutral or positive pictures were presented during three seconds. The apparition of the pictures was either predictable (ordered countdown) or unpredictable (random countdown). After each block, participants rated their own affect and nervousness. Panels a) and b) were adapted from Singer et al., (2016).

2. Methods

2.1. Participants

A total of 332 healthy participants (197 females; mean age = 40.74, SD = 9.24; age range = 20-55) were recruited in the *ReSource* project. They were selected and assigned to one of the three training cohorts (TCs) or to the retest control cohort (RCC (N = 90), TC1 (N = 80), TC2 (N = 81) or TC3 (N = 81)) using a bootstrapping process which ensured that all cohorts were matched for age, gender, marital status, income, IQ, and a number of self-reported personality traits (Singer et al., 2016). The final sample size per cohort, time point and measure vary due to study dropout/exclusion, partial dropout/exclusion from MRI experiments and technical, health, or scheduling issues at individual assessments. Finally, since the behavioural analysis focused on change scores (see below), the sample of the analysis was restricted to participants and time intervals where both pre- and post-scores were available, which leads to a final sample of 285 subjects ranged between 59 to 76 participants per group and time point (see Table 1 and Table S1 in Supplemental Material for dropout details).

All participants gave informed consent prior to participation. The study was approved by the Research Ethics Committee of the University of Leipzig (number 376/12-ff) and the Research Ethics Committee of Humboldt University of Berlin (numbers 2013-02, 2013-29, and 2014-10). The study was registered with the Protocol Registration System of ClinicalTrials.gov under the title “Plasticity of the Compassionate Brain” with the ClinicalTrials.gov Identifier: NCT01833104.

Table 1. Sample description for available change scores

	T0 to T1				T1 to T2			T2 to T3		
	RCC	TC1	TC2	TC3	RCC	TC1	TC2	RCC	TC1	TC2
N	76	70	70	69	68	64	66	67	59	67
Age	39.97	40.91	41.16	39.85	39.40	40.36	40.88	39.85	40.30	40.43
	± 9.21	± 9.00	± 9.90	± 9.15	± 9.32	± 9.05	± 10.10	± 9.19	± 9.39	± 10.18
%Female	55.26	57.14	60.00	56.52	52.94	51.56	59.09	52.24	47.46	58.21

Notes: RCC = Retest Control Cohort, TC1 = Training Cohort 1, TC2 = Training Cohort 2, TC3 = Training Cohort 3.

2.2. Study design

Four cohorts were set up for the *ReSource* project. The first two training cohorts (TC1 and TC2) underwent 9-month contemplative training with three 3-month modules practiced in different order (see description below). They both started with the *Presence* module. Subsequently, TC1 completed the *Affect* module followed by the *Perspective* module and TC2 did the *Perspective* module followed by the *Affect* module. The third training cohort (TC3) only trained a 3-month *Affect* module. The retest control cohort (RCC) did not carry out any mental training but was tested at the same time intervals as the TCs (i.e., four times at three months intervals) (Figure 1b).

2.2.1. Trainings

Each of the three modules of the *ReSource* program lasts 3 months, begins with a 3-day intensive retreat, includes 13 weekly group sessions of 2h accompanied by experienced teachers, and about 30 min of daily practice. Each module has two core exercises, which participants were asked to practice five times a week.

Briefly, the *Presence* module aims at training attention, present moment awareness and interoceptive awareness. The two core exercises are “breathing meditation” and “body scan”. In the breathing meditation, participants focus their attention on their breathing and in the body

scan, participants focus on body sensations. The *Affect* module aims at cultivating an attitude of kindness and compassion toward oneself and others as well as to approach difficult emotions with acceptance, benevolence and gratitude. The core exercises are “loving-kindness meditation” and “Affect Dyads”. The loving-kindness meditation aims at developing the attitude of care and compassion. In the *Affect* dyads, participants share difficult or grateful situation with other participants, taking one after the other the role of the listener and the speaker, thus promoting socio-emotional capacities. The purpose of the *Perspective* module is to train metacognition and cognitive perspective taking on the self and others. The core exercises are “observing-thoughts meditation” and “Perspective Dyads” in which participants practice inner perspective taking (i.e., re-experiencing a recent situation from a different perspective) as well as perspective taking on others (i.e., taking the perspective of the dyadic partner). The *Perspective* module aims at training socio-cognitive abilities. Figure 1a illustrates the content of the three modules (see Singer et al., 2016 for a detailed description of the content of each module).

2.2.2. Stimuli and task

We used a modified version of the EmoAnt task developed by Somerville et al. (2012). In the original version, Somerville et al. (2012) used negative and neutral stimuli depicted both social and non-social scenes from the International Affective Picture System (IAPS) database (Lang et al., 1999). Here, we selected positive, negative and neutral stimuli with social scenes only. They were extracted from the IAPS, the Geneva Affective Picture Database (GAPED) (Dan-Glauser and Scherer, 2011) and the Emotional Picture Set (EmoPicS) (Wessa et al., 2010). Different sets of stimuli were built for each time point. Each set contained 28 positive pictures, 28 negative pictures and 28 neutral pictures with comparable valence and arousal, as defined by the norms of the databases (see supplemental material, Table S2). In each set, half of the pictures were taking place indoors and the other half outdoors.

While undergoing fMRI scanning, participants were presented with these stimuli. To ensure focused processing of the stimuli, participants judged whether each picture depicted an indoor or outdoor scene in a total of six blocks of 14 stimuli each. These blocks varied in the valence of the presented stimuli (positive, negative, neutral) and also in the predictability of stimulus presentation. To implement this, each stimulus was preceded by a 2-8 second “countdown” in which numbers were presented (length of countdown was assigned pseudorandomly). In the “predictable” condition, these numbers accurately represented the number of seconds remaining before picture onset. In the “unpredictable” condition, numbers were randomly presented, providing no predictive information regarding picture onset (Figure 1c). This resulted in six experimental conditions: ordered-positive, ordered-negative, ordered-neutral, random-positive, random-negative and random-neutral. Condition sequence was random for each participant. Half of the stimuli per valence were assigned randomly to the predictable or non-predictable condition.

Before fMRI acquisition, participants were trained to perform the task with different stimuli than those used during the experiment. Each block began with a 5 s start cue (fixation cross) followed by 3 s instructions informing participants of the forthcoming block type. Following the instructions, stimulus presentation continuously alternated between countdowns (1 s per number; jittered from 2 to 8 numbers) and picture presentation (3 s). Participants responded by using an MRI-compatible response box, using the index and middle finger on the right hand. Each block ended with a 3 s stop cue (fixation cross) followed by a rating period (5 s) in which participants used a continuous scale from none to very much (coded from 0 to 500) indicating 1) how negative to positive they felt (0 = extremely negative, 250 = neutral, 500 = extremely positive) and 2) how nervous they felt during the block (0 = not at all nervous, 500 = extremely nervous). The total duration of the experiment was 13 min 30 s.

2.3. Analysis of behavioural measures

The subjective emotional valence and nervousness ratings were considered for behavioural analyses. Data were analysed using R software (R Core Team, 2015). Following our hypotheses three separate linear mixed models (LMM) (*lme4* package (Bates et al., 2015)) analyses were performed for both measures:

Data at baseline (i.e., T0) were entered in an LMM including fixed effects for the Valence (positive, negative, neutral) and Predictability (ordered countdown, random countdown) of the stimuli and random intercepts for participants:

$$T0 \text{ Rating} = \beta_0 + \beta_1 * \text{valence} + \beta_2 * \text{predictability} + \beta_3 * (\text{valence by predictability}) + \text{random effect (participant)}$$

In order to assess the specific effect of the modules on emotion processing in the same way as in the fMRI analyses (see below), we computed two new dependent variables for each participant by subtracting average ratings for neutral pictures from those for negative and positive pictures (i.e., [negative - neutral] and [positive - neutral]). Then, for each participant and each module, we calculated a change score by subtracting individual scores before the module from the scores at the end of the module. These change scores were entered into an LMM including fixed effects for each module at a given time interval and random intercepts for participants:

$$\begin{aligned} \text{Change score} = & \beta_0 + \beta_1 * \text{Re-test2} + \beta_2 * \text{Re-test3} + \beta_3 * \text{Presence} + \beta_4 * \text{Affect1} + \beta_5 * \text{Affect2} \\ & + \beta_6 * \text{Affect3} + \beta_7 * \text{Perspective2} + \beta_8 * \text{Perspective3} + \text{random effect (participant)} \end{aligned}$$

The first retest interval (i.e., Re-test1) is the intercept of the model, so all other effects are estimated in relation to this baseline. The models allow to test the effects of the trainings by contrasting the respective parameter estimates against each other. Each module was contrasted against effects of other modules and of retest (i.e., *Presence* vs. *Re-test* (T0 to T1), *Presence* vs. *Affect* (T0 to T1), *Affect* vs. *Re-test* (all time points), *Perspective* vs. *Re-test* and *Affect* vs.

Perspective (T1 to T3), see Table S3 in the supplemental material for the description of the contrast matrix.

Similarly, to test for the overall effect of the 9-month program, data before and after the training were entered into an LMM including fixed effects for the Training (TC1 and TC2 vs. RCC) and the Timepoint (T0 vs. T3) as well as random intercepts for participants. As above, dependent variables consisted of subjective emotional valence and nervousness ratings for positive and negative as compared to neutral pictures:

$$\text{Ratings} = \beta_0 + \beta_1 * \text{training} + \beta_2 * \text{timepoint} + \beta_3 * (\text{training by timepoint}) + \text{random effect} \\ (\text{participant})$$

As an estimate of effect size, for each analysis and each contrast, we provide the models estimates (*b*).

2.4. Analysis of fMRI measures

2.4.1. MRI acquisition

MR images were acquired on a whole-body 3T Siemens Verio Scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel head-coil. Functional images were acquired with gradient-echo/T2* weighted EPI sequence (TR= 2000ms, TE= 27ms; flip angle= 77°; 37 axial slices with 1mm gap tilted ~30° from the bi-commissural plane; FOV = 210 mm; matrix size = 70 x 70; in plane voxel size = 3 x 3 mm; slice thickness = 3 mm; 405 volumes). High resolution structural images were acquired with a T1-weighted 3D-MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, TI= 900 ms, flip angle = 9°; 176 sagittal slices, FOV = 256 mm, matrix size = 240 x 256, slice thickness = 1 mm; total acquisition time = 5.10 min). We also acquired B0 field maps using a double-echo gradient-recalled sequence with matching dimensions to the EPI images (TR = 488 ms, TE = 4.49 and 6.95 ms).

2.4.2. fMRI preprocessing

Preprocessing steps were performed by using the SPM12 software package (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK), running on Matlab 8.6 (R2015b) (Mathworks, Natick, MA, USA). Functional images were first realigned (using rigid body transformations) and unwarp to additionally correct for distortion using B0 field maps and were subsequently time-corrected (slice timing). Then, the T1-weighted anatomical volume was coregistered to mean image created by the realignment procedure and was segmented. Finally, the functional images were normalized to the MNI space using DARTEL procedures (Ashburner, 2007) and smoothed using 8-mm full-Width at half maximum Gaussian.

2.4.3. First level fMRI analyses

For each participant, experimental conditions (ordered positive, ordered negative, ordered neutral, random positive, random negative, random neutral) were modelled using the General Linear Model (GLM). Movement-related parameters and outliers identified using the ART toolbox (http://nitrc.org/projects/artifact_detect/) were also included as covariate of no interest. The blood-oxygen-level dependent response for each event for the six different conditions was modelled using a canonical form of the hemodynamic response function (HRF) together with the time and dispersion derivatives. Before estimation, a high-pass filtering with a cut-off period of 128s was applied.

2.4.4. Second level fMRI analyses

We performed three separated analyses on the second level to identify: (1) the cerebral networks involved in the task before the training (i.e., at T0); (2) the specific brain plasticity induced by each module; and (3) neural modulation induced by the overall 9-month training.

1) We used a 3 x 2 repeated-measure factorial analysis using GLMflex (<http://mrtools.mgh.harvard.edu/>) to test the effect of the experimental factors at baseline (i.e.,

T0). We evaluated the main effect of the Valence, the main effect of the Predictability and the interaction Valence-by-Predictability as well as Valence specific activations (i.e., [negative vs. neutral] and [positive vs. neutral]). The results were thresholded at $p < 0.001$ (uncorrected) at the voxel level and corrected for multiple comparisons using cluster extent family-wise error rate (FWE) correction at $p < 0.05$ as implemented in the SPM toolbox, which led to an extend threshold $k > 101$ voxels.

2) We used the Sandwich Estimator (SwE) method as implemented in the SwE toolbox (<http://warwick.ac.uk/tnichols/SwE>) (Guillaume et al., 2014) to assess the effects of each modules on brain activity with the following contrasts: *Presence* vs. *Re-test*, *Presence* vs. *Affect*, *Affect* vs. *Re-test*, *Perspective* vs. *Re-test* and *Affect* vs. *Perspective* (see Table S3 in supplemental material for the description of the contrast matrix). Since no significant effect of Predictability or Predictability-by-Valence interaction was observed at T0, the analyses focused on the modules effect for [negative vs. neutral] and [positive vs. neutral] first level contrasts. Contrast maps for each subject and time points were then entered in a single model. The fitted models allow to test the above specified hypotheses by contrasting the respective parameter estimates against each other. The results were thresholded at $p < 0.001$ (uncorrected at the voxel level) and were corrected for multiple comparisons using wild bootstrap procedure (999 iterations) and cluster extent family-wise error rate (FWE) correction at $p < 0.05$ as implemented in the SwE toolbox (Guillaume et al., 2014), which led to an extend threshold $k > 98$ voxels.

Second-level functional activation maps were also overlaid with empathy and ToM networks identified in a previously published study on subsample data from the participants at baseline (i.e., the EmpaToM task) (Kanske et al., 2015). We used the EmpaToM task contrast during negative vs. neutral socio-emotional video to obtain an “empathy mask” and contrast between ToM and non-ToM questions for “ToM mask”.

3) We tested for the overall effect of the 9-month program with a 2 x 2 factorial design, including the Cohort (TC1 and TC2 vs. RCC) and the timepoint (T0 vs. T3) modelled with the SwE toolbox.

All second level analyses were constrained to voxels within a grey matter mask derived from the group DARTEL-generated template thresholded at 90% grey matter probability. Brain regions involved in different contrasts were labelled by means of macroscopic parcellation of the MNI single subject reference brain (Tzourio-Mazoyer et al., 2002)

3. Results

3.1. Behavioural results

3.1.1. Behavioural results at baseline

The analysis of subjective emotional valence ratings revealed a significant main effect of Valence [$F(2, 5659.7) = 5802.5, p < 0.001$]. As expected, the negative stimuli were judged more negative than the neutral ($z = 52.40, p < 0.001$), and the positive stimuli more positive than the neutral ($z = 22.78, p < 0.001$). However, the analysis did not reveal a significant effect of Predictability [$F(1, 5659.7) = 1.40, p = 0.24$] or a Predictability-by-Valence interaction [$F(2, 5659.7) = 1.10, p = 0.33$].

Regarding nervousness ratings, we also observed a significant main effect of Valence [$F(2, 5668.4) = 1020.82, p < 0.001$]. Participants reported to be more nervous for negative vs. neutral stimuli ($z = -26.34, p < 0.001$) as well as for neutral vs. positive stimuli ($z = -3.60, p < 0.001$). Similarly, we did not observe a significant effect of Predictability [$F(1, 5668.4) = 0.77, p = 0.38$] or a Predictability-by-Valence interaction [$F(2, 5668.4) = 0.76, p = 0.47$].

3.1.2. Behavioural change induced by the training modules

Since we did not observe significant effects of Predictability or Predictability-by-Valence interaction at T0, analyses of modules training effects focused only on the effect of the

Valence of the stimuli. To test for the specific effects of the modules, for each participant and each module, we calculated a change score by subtracting individual scores before the module from the scores at the end of the module.

Regarding subjective emotional valence ratings for [negative - neutral], from T0 to T1, effects of *Presence* was not different from retest ($b = -15.73, z = -1.39, p = 0.16$) and *Affect* ($b = 12.32, z = 1.06, p = 0.29$), however, ratings were significantly more negative after retest than after *Affect* ($b = 28.05, z = 2.13, p = 0.03$), suggesting that the *Affect* training “buffered” the increase of subjectively experienced negative affect after repeating the task a second time. Subsequent comparisons revealed an overall significant decrease in negative ratings after *Affect* from T0 to T3, which was significantly different from retest ($b = -55.13, z = 2.13, p = 0.02$) (Figure 2, Panels a and b). The model for subjective emotional valence ratings for [positive – neutral] revealed significantly increased positive ratings after *Perspective* in comparison to retest ($b = 37.29, z = 2.17, p = 0.03$).

The model for the change in nervousness rating for [negative – neutral] revealed increase nervousness from T1 to T3 after *Perspective* in comparison to both retest ($b = -72.56, z = -2.63, p = 0.009$) and *Affect* ($b = 78.98, z = 2.83, p = 0.005$) (Figure S1, Panels a and b). There was no significant differential effect of the modules on nervousness rating for [positive – neutral] ratings.

Distributions of behavioural changes after the training modules are presented in Figure S2, descriptive statistics are reported in Table S4 and detailed statistics for each contrast and measure are reported in Table S5.

Figure 2: Descriptive plots of the change in valence rating in the course of the 9-month training. (a-b)

Change in [negative – neutral] ratings. (c-d) Change in [positive – neutral] ratings. The line-graphs show ratings according to the group and time point. Values at the first measurement point are equalized representing statistical control for baseline scores. The histograms depict the estimated effect of each module (RCC = retest, PRE = Presence, AFF = Affect, PER = Perspective). To the right of the dashed lines, estimates are averaged across time intervals as it was done to test the overall effect of the modules across time points. Error bars represent 95% confidence intervals. $*p < 0.05$.

NB: as subjective valence ratings range from negative to positive (0 = extremely negative, 250 = neutral, 500 = extremely positive), for illustrative purposes, panels a and b depicted actually the difference between neutral minus negative scores.

3.1.3. Behavioural change after the overall 9-month training

We found a significant interaction between Training and Timepoint for both [negative - neutral] [$F(1, 213.26) = 4.17; p = 0.04$] and [positive - neutral] subjective valence ratings [$F(1, 211.85) = 16.91; p < 0.0001$]. Planned comparisons revealed that the ratings for [negative -

neutral] were significantly less negative from T0 to T3 for the TCs ($b = -18.53, z = -2.57, p = 0.01$), whereas there was no change for the RCC ($b = 6.43, z = 0.65, p = 0.51$) (Figure S3, Panel a). In addition, ratings for [positive - neutral] were significantly more positive from T0 to T3 for the TCs ($b = 22.37, z = 4.02, p < 0.0001$) and significantly less positive for the RCC ($b = -16.53, z = -2.16, p = 0.03$) from T0 to T3 (Figure S3, Panel b).

Regarding nervousness ratings, the interaction training-by-timepoint was only marginally significant for [negative – neutral] ratings [$F(1, 215.57) = 3.88; p = 0.05$] and not significant for [positive – neutral] ratings [$F(1, 435) = 1.22; p = 0.23$] (Figure S3, Panels c and d).

3.2. fMRI results

3.2.1. fMRI results at baseline

In comparison to neutral stimuli, negative stimuli yielded increased activation in the ventral visual pathway; i.e., in two bilateral clusters encompassing the inferior occipital, temporal and parietal gyri, as well as in the bilateral supramarginal gyrus (SMG), the right inferior frontal gyrus (IFG) and in a large cluster including left amygdala, insula and superior temporal gyrus (STG) ($p_{\text{unc(voxel)}} < 0.001, p_{\text{FWE(cluster)}} < 0.05$). For exploratory purposes, we also looked at the results with an uncorrected threshold ($p_{\text{unc(voxel)}} < 0.001, k > 10$). We observed increased activation in the superior and middle prefrontal cortex as well as in the orbitofrontal cortex, the middle insula, the middle and posterior cingulate cortex and in the right amygdala at this lower threshold (Figure 3a, Table 2). Positive stimuli induced increased activation of the ventral visual pathway and in the posterior cingulate cortex/precuneus ($p_{\text{unc(voxel)}} < 0.001, p_{\text{FWE(cluster)}} < 0.05$). Exploratory results show that the left angular gyrus, the right STS and bilateral IFG were also marginally more strongly activated in response to positive vs. neutral stimuli ($p_{\text{unc(voxel)}} < 0.001, k > 10$; Figure 3b, Table 2). We did not observe a modulation of the brain activity depending on the predictability of the stimuli and no interaction of Valence by Predictability.

Table 2. Activation peaks before the training (T0)

Lobe	Region	k	H	x	y	z	t
Negative > Neutral							
Occipital	Inferior Occipital / Temporal / Parietal Gyrus*	1729	L	-45	-64	-7	10.98
	Inferior Occipital / Temporal / Parietal Gyrus*	1370	R	48	-61	-7	10.42
Parietal	SupraMarginal Gyrus*	152	R	60	-22	32	6.00
	SupraMarginal Gyrus*	183	L	-63	-22	29	5.90
Frontal	Inferior Frontal Gyrus (orbital/triangular part)*	101	R	45	35	5	5.87
	Inferior Frontal Gyrus (triangular/opercular part)	80	R	45	11	26	5.13
	Superior/Middle Frontal Gyrus	79	L	-27	-1	47	4.89
	Superior/Middle Frontal Gyrus	77	R	33	-1	47	4.88
	Orbitofrontal cortex	20	L	-27	35	-16	4.88
	Inferior Frontal Gyrus (opercular/triangular part)	46	L	-42	5	29	4.72
	Inferior/Middle Frontal Gyrus	43	L	-48	38	11	4.70
	Orbitofrontal cortex	12	R	27	32	-19	3.88
Insula	Insula/Superior temporal gyrus	40	R	39	-4	-7	4.79
	Insula/Inferior Frontal Gyrus (orbital part)	57	L	-36	29	2	4.12
	Insula/Temporal Pole	31	L	-33	20	-19	3.92
Sub cortical grey nuclei	Thalamus*	108	R	6	-28	-4	4.75
Limbic	Amygdala/Superior Temporal Gyrus/Insula*	109	L	-36	-7	-7	5.45
	Middle Cingulate Cortex	22	R	18	-28	41	4.28

	Hippocampus/Amygdala	15	R	21	-4	-13	4.15
	Middle Cingulate cortex	20	NA	0	5	32	3.85
	Posterior Cingulate Cortex/Precuneus	46	L	-3	-52	29	3.83
	Temporal Pole: Middle/Superior temporal gyrus	32	R	48	11	-34	3.70
Positive > Neutral							
Occipital	Inferior Occipital/Temporal Gyrus*	644	R	51	-67	-4	8.56
	Inferior Occipital/Temporal Gyrus*	794	L	-48	-73	2	7.51
	Cuneus/Lingual Gyrus*	319	R	12	-82	5	6.65
Parietal	Precuneus/Posterior Cingulate Cortex*	84	NA	0	-58	35	4.21
	Angular Gyrus	27	L	-30	-67	47	3.54
Temporal	Superior Temporal Gyrus	17	R	66	-34	20	4.02
Frontal	Inferior Frontal Gyrus (opercular part)	14	R	-45	5	17	4.01
	Inferior Frontal Gyrus (triangular part)	12	L	54	35	2	3.65

*pFWEc < 0.05 cluster corrected

H = Hemisphere; R = Right; L = Left; k = number of voxels/cluster

Figure 3: Cerebral responses to emotional scenes at baseline (T0). Brain activation resulting from the contrast [negative > neutral] are represented in red-yellow scale (a) and those of the contrast [positive > neutral]

in blue-green scale (b). Findings are thresholded at $p_{\text{uncor}} < 0.001$, $k > 10$ and clusters that survived correction for multiple comparison ($p_{\text{FWEc}} < 0.05$) are surrounded with a white line.

3.2.2. Neurofunctional change induced by the training modules

In comparison to Retest, participants who trained *Affect* showed significantly increased activation in the right SMG when processing negative vs. neutral stimuli ($p_{\text{unc(voxel)}} < 0.001$, $p_{\text{FWE(cluster)}} < 0.05$). To test for wider network effects, we also investigated non-corrected trends on $p_{\text{unc(voxel)}} < 0.001$ levels, for illustrative purpose only. This revealed that participants also tended to show increased activity in several lateral prefrontal regions, comprising two clusters in the right IFG, one cluster in the left IFG, two clusters in the right middle frontal gyrus and additionally in three clusters situated in the right inferior temporal gyrus and in the bilateral occipital cortex (cuneus) ($p_{\text{unc(voxel)}} < 0.001$, $k > 10$, Figure 4, Panel a) and b); Table 3). There was no significant change in brain activity after *Affect* training for positive vs. neutral stimuli. Training *Perspective* did not lead to significant neurofunctional modulation for either [negative vs. neutral] and [positive vs. neutral] contrasts. There was no significant difference between training *Affect* and *Perspective* and between *Presence* and *Retest* for both contrasts.

To better understand our results and see if they relates to change in empathy or ToM processing, activation maps resulting from these second-level analyses were overlaid with functional activation maps from a previously published study on subsample data from the participants at baseline that aimed at measuring the cerebral correlate of empathy and ToM (i.e., the EmpaToM task) (Kanske et al., 2015). Interestingly, brain regions showing increased activation after *Affect* training overlapped partially with regulation regions of the empathy network, i.e., right SMG and right lateral prefrontal regions as reported in Kanske et al. (2015) (Figure S4a).

Exploratory analyses at an uncorrected threshold of $p_{\text{unc(voxel)}} < 0.001$, $k > 10$ revealed partial overlap between temporal regions showing increased activity after *Perspective* training

vs. Retest for the processing of positive vs. neutral stimuli and the ToM network as identified by Kanske et al. (2015) (see Figure S4b).

Table 3. Activation peaks of the change after Affect training vs. Re-test

Lobe	Region	k	H	x	y	z	Z
Negative > Neutral							
Parietal	SupraMarginal Gyrus*	140	R	45	-40	41	4.20
Temporal	Inferior Temporal Gyrus	94	R	60	-43	-13	3.86
Occipital	Lingual Gyrus	21	L	-18	-52	-1	3.86
	Cuneus/Lingual Gyrus	11	R	12	-76	32	3.44
Frontal	Inferior Frontal Gyrus (triangular part)	44	R	60	23	11	3.76
	Inferior Frontal Gyrus (triangular part)	49	L	-48	20	8	3.58
	Inferior Frontal Gyrus (triangular part)	12	L	-48	44	2	3.53
	Middle Frontal Gyrus	15	R	48	14	41	3.42
	Middle Frontal Gyrus	13	R	45	47	11	3.42

*pFWEc < 0.05 cluster corrected

H = Hemisphere; R = Right; L = Left; k = number of voxels/cluster

Figure 4: Modulation of the cerebral activity after Affect module training. Brain areas showing increase activity for the contrast [negative > neutral] after the Affect module in comparison to re-test. Findings are thresholded at $p_{\text{uncor}} < 0.001$, $k > 10$; cluster that survived $p_{\text{FWEc}} < 0.05$ correction are surrounded by a white circle.

3.2.3. Neurofunctional change after the overall 9-month training

The contrast [positive > neutral] revealed a significant Training-by-Timepoint interaction within a large cluster encompassing the left lingual gyrus and the posterior cingulate cortex ($p_{\text{unc(voxel)}} < 0.001$, $p_{\text{FWE(cluster)}} < 0.05$). For exploratory purposes, we investigated changes in brain activation after the training with non-corrected threshold ($p_{\text{unc(voxel)}} < 0.001$, $k > 10$). We additionally found increased activation within the bilateral superior temporal cortices (angular gyrus), the posterior cingulate cortex, the thalamus and the brainstem in the TCs vs. RCC (Figure S5, Table S6). The contrast [negative vs. neutral] did not show supra-threshold voxels for the interaction Training-by-Timepoint.

4. Discussion

We investigated the differential effects of three types of meditation-based mental training practices on emotional reactivity to positive and negative socio-emotional stimuli. In the context of the *ReSource* project (Singer et al., 2016), 332 participants took part in a 9-month long mental training study. They performed an emotion anticipation task (2012) while being scanned with fMRI before and after engaging in three 3-month modules focusing on improving (1) present-moment focused attention and interoceptive body awareness (*Presence*), (2) socio-affective skills, such as compassion, gratitude and coping with difficult emotions (*Affect*), or (3) socio-cognitive skills, such as perspective taking on self and others (*Perspective*). Before the training, the processing of both positive and negative vs. neutral socio-emotional stimuli elicited activation of the ventral occipito-temporal visual areas. Additional activation for negative vs. neutral stimuli was observed in lateral fronto-parietal and limbic regions, the amygdala and the insular cortex in particular. Notably, we showed that the mental training modules had differential effects on behavioural affect ratings after exposure to positive, neutral or negative pictures, as well as on underlying functional brain activation patterns. The *Affect* module led to decreased negative ratings when participants were exposed to negative pictures

compared to neutral ones and increased activity in the right SMG. Surprisingly, we did not find specific behavioural or neurofunctional changes after *Presence*. We also found that after the 9-month training, participants of the active TCs judged their affect more positively and less negatively compared to the participants of the RCC. They also revealed increased activation from baseline until the end of the 9-month training within midbrain and occipital areas when watching positive vs. neutral stimuli.

Before the training, neural activity during the task involved two different networks for positive vs. neutral and negative vs. neutral stimuli. In both emotional conditions, the ventral visual stream, mainly composed of lateral occipital and temporal cortex, as well as the amygdala, were activated. This suggests an enhancement of activation in the visual cortex when processing emotional stimuli, as ventral visual cortex responses in emotional contexts might be reinforced through feedback connections from the amygdala (Lang et al., 1998; Phan et al., 2002; Vuilleumier, 2005; Vuilleumier and Pourtois, 2007). In addition, the cerebral response to negative vs. neutral stimuli involved activation of lateral prefrontal (IFG/AI), limbic (amygdala, subcortical nuclei) and parietal regions (SMG). This pattern of results is coherent with what has been observed in other studies on processing of negative emotion (Kragel and LaBar, 2016; Lindquist et al., 2012; Phan et al., 2002; Preckel et al., 2019) or empathy (Bzdok et al., 2012; Kanske et al., 2015; Lamm et al., 2011; Singer et al., 2004). The processing of positive vs. neutral stimuli further involved midline cortical structures (ventro-medial PFC, PCC), a set of brain areas that are known to be involved in self-referential processes. We speculate that this could reflect the representation of prior experiences when faced with positive emotions of others (Buckner et al., 2008; Engen et al., 2017; Lindquist et al., 2011).

The result from the manipulation of unpredictable (i.e., random countdown) vs. predictable (i.e., ordered countdown) conditions was not conclusive, both at behavioural and neural levels. Unlike Somerville et al. (2012), we did not find a modulation of the cerebral

activity depending on the predictability of the stimuli. This could be explained by an extensive screening for anxiety, mood symptoms and personality disorders when recruiting and selecting participants for the *ReSource* project (Singer et al., 2016). Indeed, in Somerville et al. (2012) the participants covered a wide range of anxiety scores, which was also correlated with their fMRI results, especially in the unpredictable condition.

Regarding our predictions for the specific effects of the *Presence*, *Affect* and *Perspective* training modules, unlike previous studies on MBI (Fox et al., 2016; Fox et al., 2014; Tang et al., 2015; Young et al., 2018) we did not find a training-related modulation of brain activity after the *Presence* training. In previous studies, the authors claimed that present-moment focused attention helps people to better regulate their emotions via a reinforcement of the top-down cognitive control (Allen et al., 2012; Farb et al., 2012; Kral et al., 2018; Lutz et al., 2014). In our study, the training of present-moment and attention-based meditation techniques did not lead to downregulation of negative emotion either at the behavioural nor at the cerebral level. It should be noted that the *Presence* module was not exactly equivalent to the classical MBI programs (e.g., MBCT, MBSR) tested in previous RCT (Allen et al., 2012; Desbordes et al., 2012; Farb et al., 2010; Kral et al., 2018). Here, the *Presence* module focused only on attention-based mindfulness meditation, such as the body-scan or the breathing meditation, but did not include mindfulness practices focusing on acceptance, loving kindness, mindfulness on emotions or observing thoughts as in classical 8-weeks MBI. As the *ReSource* project aimed at differentiating between different types of meditation-based practices, practices explicitly associated to emotional processing were included in the *Affect* module and practices cultivating meta-cognitive capacities like observing thoughts were included in the *Perspective* module. This could explain why, unlike previous studies on mindfulness, we did not observe a modulation of emotional processing after pure attention-based practices such as implemented in the *Presence* training.

Importantly, our results revealed that, in contrast to the retest control group, after the overall 9-month training and especially after the *Affect* training, participants reported feeling less negative affect after having being exposed to negatively valenced social pictures. Moreover, between T0 and T1, negative ratings increased for the retest control participants (i.e., RCC) but not in the cohort who trained *Affect* only (i.e., TC3). Thus, for retest-control subjects, the experienced intensity of the negative images presented in this task increased when the task was repeated a second time, but for the participants who trained socio-affective skills during the *Affect* module this sensitization effect was buffered. These results suggest that already after 3 months, the compassion-based *Affect* module decreased the experience of negative affect when exposed to negative social stimuli and thus helped buffer against sensitization effects to the task when repeated a second time. After 9 months of training, the participants developed better regulation of negative emotions whenever they trained socio-affective skills, as shown by the decrease in rated negative affect after the overall training as well as after *Affect* vs. retest (averaged from T0 to T3). This significant training-related behavioural reduction of reported negative affect after compassion-based training was also reflected on a neuronal level by increased activation in the right SMG. Notably, the brain activation pattern observed after the *Affect* modules when participants are exposed to pictures depicting people suffering, partially overlaps with the empathy network defined in the same participants with another task, the so-called EmpaToM, at baseline (Kanske et al., 2015) (Figure S4a) and is consistent with findings from meta-analyses on empathy studies (Bzdok et al., 2012; Fan et al., 2011; Lamm et al., 2011). This finding is also in accordance with previous *ReSource* project related findings from our group, that demonstrated increased cortical thickness in socio-emotional networks related to empathy and compassion (mid-insula and SMG) after participants underwent the *Affect* module of the *ReSource* project (Valk et al., 2017). In the compassion network, the SMG might be important for supporting the ability to engage in self-other distinction, a process needed for

example if wanting to overcome emotional egocentric bias (Silani et al., 2013; Steinbeis et al., 2014). Indeed, studies showed that participants tended to make inaccurate empathic judgements about others when their own affective states were incongruent to the one of another and after disruption of the right SMG with transcranial magnetic stimulation (Silani et al., 2013). Furthermore, increased connectivity between the SMG and the dorso-lateral PFC in children predicted lesser egocentric bias in the affective domain (Steinbeis et al., 2014). Even though not significant after correction, the increased activation of the ventrolateral PFC is in line with this previous research and might be related to better emotion regulation after training *Affect*. Indeed, lateral regions of the PFC, are known to be involved in cognitive control, reappraisal and inhibitory processes (Aron et al., 2003; Grecucci et al., 2013; Hampshire et al., 2010).

Interestingly, and contrary to our hypotheses and previous *ReSource* project findings showing increased compassion related ratings and brain plasticity after the *Affect* module (Trautwein et al., 2020; Valk et al., 2017), we did not observe increased activation in the regions classically involved in compassion, care and gratitude, such as the OFC, the VS or the VTA (Engen and Singer, 2015; Klimecki et al., 2013; Klimecki et al., 2014) after training the *Affect* module. One explanation could be the nature of the task used here, which involved natural processing of emotion when being exposed to emotional stimuli. In contrast to some previous studies on compassion-based meditation training (Engen and Singer, 2015; Klimecki et al., 2013; Klimecki et al., 2014; Leung et al., 2018; Weng et al., 2013; Weng et al., 2018), we neither explicitly instructed the participants to use specific emotion regulation strategies, such as the generation of positive affect or loving-kindness meditation, nor asked for empathy or compassion ratings (Trautwein et al., 2020). Therefore, the participants may have used other emotion regulation capacities during the task, e.g. accepting and regulating difficult negative emotions when these arise, rather than actively generating positive affect of compassion and concern. Of note, the *Affect* module also included daily 10-minutes Dyadic practices with a

partner (Kok and Singer, 2017) where participants trained to report difficult emotions experienced during their day and to accept them without judging these. Such daily practice may have helped participants to learn acceptance and non-reactivity towards experienced negative affect.

Relative to the RCC group, we also observed increased positive ratings for positive stimuli after the overall 9-month training, which seem to be driven by the change after the *Perspective* training module (Figure 2, Panels c and d and Figure S3, Panel b). The overall increase of positive ratings after the 9-months training was associated with increased activity of occipito-temporal regions involved in the processing of positive vs. neutral stimuli at T0, the lingual region of the occipital cortex in particular. As we did not expect a change in functional activation in visual regions after the training this result is difficult to explain. However, it might be linked to increased visual processing of positively valenced stimuli, similar of that observed for negative high arousing stimuli (Lang et al., 1998; Vuilleumier, 2005; Vuilleumier and Pourtois, 2007). Positive ratings seemed to increase especially after *Perspective* training, which aims at improving metacognitive skills and perspective taking on ones' own and others' thoughts and believes. The training of socio-cognitive skills could then allow people to better understand and share positive emotions. This argument is supported by an observed trend for increased activity after *Perspective* in two regions reliably associated with ToM, the middle temporal gyrus and the dorso-medial PFC (Figure S4b). Although these results are exploratory, the location of change in brain activation partially overlaps with the ToM network identified with the EmpaToM task at baseline (Kanske et al., 2015).

The first limitation inherent to this study is that it is impossible to conduct a double-blind RCT in such mental training and meditation-based studies. Without revealing the objectives of the experimental task, the participants obviously know what type of mental training they carry out when practicing. Indeed, they have to be instructed in these practices to

be able to consciously and internally perform them later on. Thus, the instructions given during each module may have created a demand effect. However, given the implicit nature of the task used, it is unlikely that the participants were able to explicitly control their emotional and brain response to adapt to these demands. In fact, no instructions were given to the participants, so any regulation strategies employed were implicit and spontaneous, thus likely an actual outcome of the training. Furthermore, each module consisted of many different mental practices belonging to more general categories and thus it was not possible to guess which task would assess which specific effect of the respective practice in a module.

In that context, the fact that each mental training module in the *ReSource* project includes multiple exercises (such as loving-meditation and affective dyads in the *Affect* module) may also be seen as a second limitation. Indeed, it is difficult to isolate the specific effect of each exercise on emotional reactivity. However, in comparison to previous studies focusing on 8-week programs such as MBSR, MBCT and compassion-based intervention (Gilbert, 2009; Jazaieri et al., 2013; Kabat-Zinn, 2003; Neff and Germer, 2013; Williams et al., 2014), the *ReSource* project allowed a systematic comparison of classes of mental training practices, while including active control groups and large samples. A recent review on *ReSource* project findings from our group (Singer and Engert, 2019), revealed many differential effects of practice types on all levels: the level of subjective experience, behaviour, brain plasticity and stress-reduction. Accordingly, we could show here that socio-affective and compassion-based practices are specifically efficient to reduce negative emotional reactivity.

In conclusion, being confronted with the suffering of others can be a potent source of personal distress and may have deleterious mental health effects. This is seen in the high stress levels and burnout rates often reported for professionals tasked with caring for suffering individuals, such as physicians (Shanafelt et al., 2012) and nurses (Adriaenssens et al., 2015). Decreasing negative affect and increasing positive one is particularly important in clinical

settings. The applications of meditation-based mental training could thus promote resilience for exposure to others' suffering (Klimecki and Singer, 2012). Our results revealed that the 9-month mental training program of the *ReSource* project with its three 3-month training modules, and here especially the compassion-based *Affect* module lead to a decrease of experienced negative affect when confronted with emotionally distressing social stimuli and that this was associated with changes in functional plasticity in brain networks playing a key role in emotion regulation. Given the importance of affective processes on both a social and clinical level, the impact of compassion-based socio-affective mental training for a) people suffering from mental disorders, b) for health-workers such as nurses or medical doctors as well as c) for children, teachers and educators, should be further explore.

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Author contributions

T.S. initiated and developed the ReSource Project and model as well as the training protocol and secured all funding. T.S., P.K. and H.E. contributed to the present study design and development of the task. P.K. and H.E. were involved in testing and data collection. P.F. wrote the first draft and performed the data analysis and interpretation under the supervision of P.K. All authors contributed to writing up or revising the paper and approved the final version of the manuscript for submission.

Competing interests

The authors declare no competing financial interest.

Data Availability

In line with new data regulations (General Data Protection Regulation, GDPR), we regret that our data cannot be shared publicly because we did not obtain explicit participant agreement for data-sharing with parties outside the Max Planck Institute for Human Cognitive and Brain Sciences (MPI CBS). The present work is based on personal data (age, sex and medical data) that could be matched to individuals. The data is therefore pseudonymized rather than anonymized and falls under the GDPR. Data are available upon request (*contact via corresponding author email address*).

Code Availability

The code that supports the findings of this study is available from the corresponding author upon request.

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