

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

Pauline Favre^{1,2,*}, Philipp Kanske³, Haakon Engen⁴, Tania Singer⁵

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

ARTICLE INFO

Keywords:

Meditation
fMRI
Emotion
Mental training
Compassion
Mindfulness

ABSTRACT

Meditation-based mental training interventions show physical and mental health benefits. However, it remains unclear how different types of mental practice 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 anticipation 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. In addition, after the *Affect* module, participants showed significant increased activation in the right supramarginal gyrus when confronted with negative stimuli. We conclude that socio-affective, but not attention- or meta-cognitive based mental training is specifically effective to improve emotion regulation capabilities when facing adversity.

1. Introduction

Meditation-based mental training programs are 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 Mindfulness-Based Cognitive Therapy (MBCT) programs ((Kabat-Zinn, 2003); Williams et al., 2014)) or compassion (e.g., Mindfulness Self-Compassion Program (Neff and Germer, 2013), Compassion-Focused Therapy Gilbert (2009) or Compassion Cultivation Training (Jazaieri et al., 2013)). Studies have shown benefits 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 better well-being and lower negative emotions (Goldin and Gross, 2010; Gu et al., 2015; Sedlmeier et al., 2012; Wallace and Shapiro, 2006). However, most programs consist of a mix of different types of mental training for

whom the specific effects are still poorly understood, especially on the control of emotional reactivity and its neural correlates.

Mindfulness in particular can be trained through a variety of practices. Some imply the focus of attention, e.g., on the breath or internal bodily sensations, and the re-focusing of attention when distracted. Other mindfulness practices involve the observation of one's own thoughts and feelings, without judgment. These "deconstructive" practices further engage metacognitive capacities and perspective taking on oneself and others (Dahl et al., 2015). The so-called "constructive" practices aim to generate positive emotions, loving-kindness and compassion towards oneself and others, even when facing difficult situations (Gilbert, 2009, 2017). All of these practices could contribute to better management of emotions by promoting acceptance, new appraisals and positive feelings, and by mitigating maladaptive strategies such as distraction and avoidance (Farb et al., 2014). The possibility to train these skills to better cope with or react to difficult emotions appears to be critical to psychological well-being. Consequently, there are at least three different domains that might be targeted in these integrative practices to improve emotional regulation: attention, socio-affective and socio-cognitive skills but little is known regarding their specific effects.

* Corresponding author.

E-mail address: pauline@favre-univ.fr (P. Favre).

¹ Present Address: INSERM U955, team 15 « Translational Neuro-Psychiatry », Créteil, France

² Neurospin Neuroimaging Platform, team UNIACT, CEA Paris-Saclay, Gif-sur-Yvette, France

³ Clinical Psychology and Behavioral Neuroscience, Faculty of Psychology, Technische Universität Dresden, Dresden, Germany

⁴ Department of Psychology, University of Oslo, Oslo, Norway

⁵ Social Neuroscience Lab, Max Planck Society, Berlin, Germany

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 suggested to alter 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 activity of the left superior frontal gyrus in response to negative pictures (Lee et al., 2012) and diminished activity of the right dorso-lateral PFC in response to sad pictures (Froeliger et al., 2012) in expert compared to novice practitioners, 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 activity of the ventromedial, right ventro-lateral and right superior frontal PFC, as well as of the insula and subgenual cingulate cortex and decreased activity of the left ventro-lateral PFC as well as of the left superior temporal sulcus (STS) and inferior temporal gyrus after MBI in comparison to a waitlist control group (Farb et al., 2010). The discrepancies between these previous studies might be explained by the variety of tasks and stimuli used (e.g., video clip vs. pictures or sad vs. negative images) and the variety of mindfulness practices and training programs. Indeed, in cross-sectional studies the participants were either experts in focused attention meditation (> five years) (Lee et al., 2012) or Zen meditation (>1000 hours) (Taylor et al., 2011) or Yoga (5.7 years on average) (Froeliger et al., 2012), while longitudinal studies focused on both the 8-week MBSR program (Farb et al., 2010) a 6-week customized mindfulness program including four progressive modules: focused breath awareness, body scanning, compassion, and an open-monitoring practice (Allen et al., 2012), and a 8-week adapted program from Wallace (2006) where subjects were trained in a set of meditation techniques for enhancing focused attention and mindful awareness of one’s internal state and external environment (Desbordes et al., 2012). Nonetheless, 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, but 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 positive affect and prosocial 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). Compassion can be defined as the motivation to acknowledge, alleviate and prevent suffering. It promotes social connections, benevolence, and concern for others (Gilbert, 2017; Goetz et al., 2010). While compassion includes the processes of empathy and sympathy as preliminary steps in the commitment to reduce suffering, compassion includes other factors such as care for well-being, sensitivity to the needs of others, the ability to tolerate emotional distress and acceptance without judgment Singer and Klimecki (2014). Thus, exercises in CBI aim to generate “feelings of warmth, concern and care for oneself and oth-

ers, as well as a strong motivation to improve others’ well-being”. On the neural level, compassion generation has been characterized by increased activation of the midbrain (ventral tegmental areas, substantia nigra) and the ventral striatum (VS) when untrained participants were asked to adopt a compassionate attitude toward sad faces (Kim et al., 2009) or an attitude of unconditional love toward people with disabilities (Beauregard et al., 2009). Similarly, increased activations of the VS, midbrain and subgenual ACC were found when people are making charitable donations (Harbaugh et al., 2007; Moll et al., 2006). Compassion generation may thus involve a set of brain regions 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; Vrtička et al., 2017). Regarding the neural correlates of compassion-based meditation practices, a pioneer investigation employed cross-sectional designs to compare the brains of expert long-term meditation practitioners with novice practitioners, who were briefly instructed how to generate a meditative state of loving-kindness and compassion (Lutz et al., 2008). They found increased activity of the insula, the amygdala, the temporo-parietal junction (TPJ) and STS in experts in comparison to novices when confronted with emotionally positive, neutral and negative human vocalizations. Notably, the degree of activity of the insula was positively correlated with self-reported intensity of loving-kindness and compassion in both groups (Lutz et al., 2008). In a recent study, our group sought to compare the brain responses of expert practitioners when regulating their emotions using compassion meditation and reappraisal, a “gold standard” emotion regulation technique which aims to reinterpret a situation by altering its meaning and changing its emotional impact (Engen and Singer, 2015; Ochsner and Gross, 2005). Participants were confronted with socio-affective video clips with low (everyday scenes) and high emotion intensity (people in distress) and explicitly asked to use compassion meditation, i.e., “to generate a warm feeling of positive affect and caring”, or cognitive reappraisal, i.e., “to re-interpret the film with positive emphasis”, in order to alter their emotional state. Both the subjective and neural responses to these regulation 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 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 meditation-naïve 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 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 such as reappraisal (Buhle et al., 2014; Ochsner et al., 2002).

Importantly, emotion processing and regulation involve 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) (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 TPJ, 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 undeniable, however the possibility of training these skills and the potential subsequent effects of such training on emotional processing is not well explored.

A major obstacle in disentangling what effects meditation-based mental training has on emotion processing is that previous randomized-controlled trials (RCT) that assessed changes in emotional 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 integrated 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 anticipation (and implicit emotion regulation) at both neurofunctional and behavioural levels.

To close this gap, we enrolled 332 participants in 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). Core exercises include (1) for the *Presence* module: breathing meditation and body scan; (2) for the *Affect* module: Loving-kindness meditation and *Affect* dyad; and (3) for the *Perspective* module: Observing thoughts meditation and *Perspectives* dyad (Fig. 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) (Fig. 1b). This design allows to compare differential effects 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 affective responses (i.e., valence and nervousness) and neural emotion processing using an emotion anticipation task (EmoAnt) (Somerville et al., 2012). During the task, participants watched positive, negative and neutral stimuli that were preceded by an ordered or random countdown. This task allowed to assess both the emotional reactivity linked to the processing of emotional vs. neutral pictures as well as emotional anticipation processes related to the uncertainty of the stimulation to follow. No regulation instructions were given to further explore the impact of the different trainings on pre-emptive emotion control.

Based on previous literature using similar tasks, we predicted that before the training (i.e., T0), participants' emotional reactivity would lead to 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 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). Regarding emotional anticipation, similarly to Somerville et al. (2012), we expected that participants at baseline would show increase nervousness, as well as increase activity in the insular cortex and ventral basal forebrain for unpredictable vs. predictable stimuli, especially in the negative condition.

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. As for the predictability of the stimuli, we assumed that the effect of the *Presence* module would be associated to decreased sensitivity to uncertainty as well as decreased activity in the insular cortex and the ventral basal forebrain and a greater recruitment of the ventro-medial prefrontal regions (ventral mPFC/ACC) related to emotional in response to unpredictable negative events. 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. In other words, from T0 to T1, we expected decreased negative affect (valence and nervousness) in the two cohorts who trained *Presence* (i.e., TC1 and TC2), as well as enhanced positive affect in the cohorts who trained *Affect* (i.e., TC3) in comparison to the RCC. From T1 to T2 and T2 to T3, we assumed that people who trained *Affect* (TC1 then TC2) would also show increased positive affects in comparison to both the RCC and the people who trained with the *Perspective* module (i.e., TC2 then TC1). Finally, we did not have specific a-priori hypotheses regarding the training of socio-cognitive skills (i.e., *Perspective* module) on emotional processing due to the lack of previous intervention studies in that domain. However, we speculatively assumed an enhancement of the activity of the ToM network after this socio-cognitive training.

In addition to specific effects of different modules, we explored the overall 9-months training effect (i.e., T0 vs. T3), speculating the existence of a cumulative effect of each module, leading to lower negative affects and lower sensitivity to uncertainty along with an improvement of the prefrontal control over limbic regions, as well as enhanced positive affects and increased activity in the VS, OFC and midbrain regions.

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. The recruitment and screening procedure for the *ReSource* project was a multi-step process in order to inform participants in an appropriate manner, screen for eligibility, and ensure motivation for a large-scale, one-year, longitudinal study, including extensive scientific testing (see details on the screening procedure and inclusion/exclusion criteria in Appendix I in the supplement). Demographic details of the sample are listed in Table S1 as well as in Singer et al. (2016) (Singer et al., 2016).

They were 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 partic-

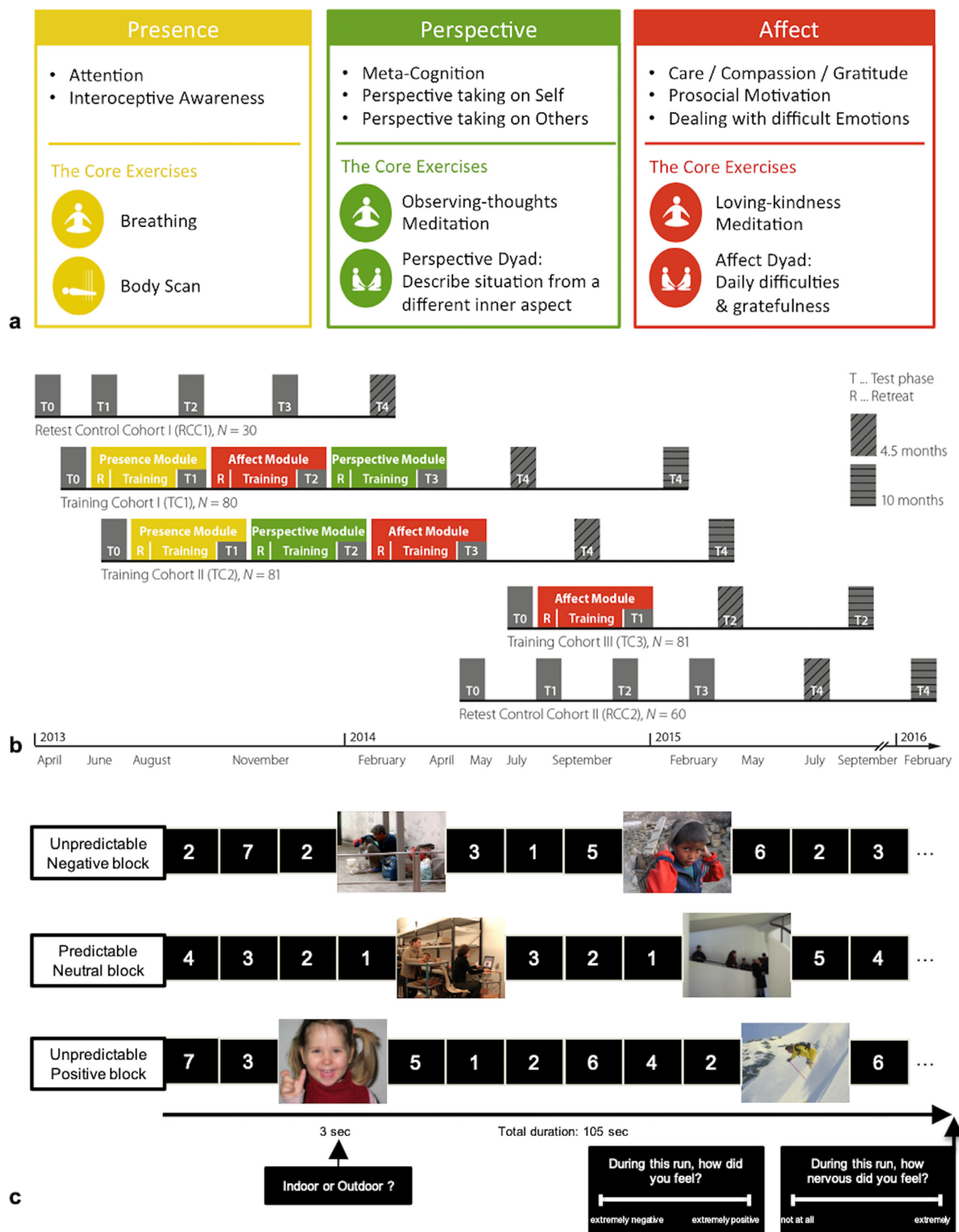


Fig. 1. Design of the study. (a) Illustration of the three modules of the program and their core exercises: Presence (yellow), Affect (red), Perspective (green). (b) Timeline of training (coloured areas) and data collection (grey areas) for the training and retest control cohorts. MRI data and behavioural ratings reported in the present study were acquired at each time point from T0 to T3. 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 counterbalanced manner. Training cohort 3 trained *Affect* only. Retest control cohorts completed the measurements without any training. They were tested in two cohorts but were 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. (c) Illustration of the experimental design. In each block negative, neutral or positive pictures were presented for three seconds. The display 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).

Table 1
Sample description for available change scores.

	T0 to T1 RCC	TC1	TC2	TC3	T1 to T2 RCC	TC1	TC2	T2 to T3 RCC	TC1	TC2
N	76	70	70	69	68	64	66	67	59	67
Age	39.97 ± 9.21	40.91 ± 9.00	41.16 ± 9.90	39.85 ± 9.15	39.40 ± 9.32	40.36 ± 9.05	40.88 ± 10.10	39.85 ± 9.19	40.30 ± 9.39	40.43 ± 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.

ipants per group and time point (see Table 1 and Table S2 in Supplemental Material for dropout details).

All participants gave informed consent prior to participation and were paid for the time spent on scientific testing. 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.

2.2. Study design

Four cohorts were set up for the *ReSource* project. The main two training cohorts (TC1 and TC2) underwent 9-month contemplative training with three 3-month modules practiced in different order to act as active control cohorts for each other (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. TC3 was included as an active control for the *Presence* module in TC1 and TC2. The retest control cohort (RCC) did not carry out any mental training but was tested at the same time intervals as the TCs. The participants from each of the four cohorts underwent an MRI scan (fMRI task with behavioural recording) before and after each module, i.e., four times for TC1, TC2 and RCC and two times for TC3 (see Fig. 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, five times a week. Compliance with daily practice was recorded using online and smartphone-based guided contemplative exercises as well as through the responses to online questions (results not detailed here, see Singer et al., 2016 and Kok and Singer, 2017). Each module has two core exercises, which participants were asked to practice five times a week. Fig. 1a illustrates the content of the three modules (see Singer et al., 2016 for a detailed description of the content of each module).

Briefly, the *Presence* module aims at training attention, present moment awareness and interoceptive awareness to prepare the participants minds for the subsequent meditative exercises. The two core exercises are “breathing meditation” and “body scan”. The breathing meditation is practiced in almost all contemplative traditions and aims at training to focus attention on the breath and to refocus on the breathing sensations when attention wanders. The body scan practice is traditional to Vipassana meditation and focuses on body sensations. Participants are train to mentally scan their body and pay attention to the sensations occurring in the various parts, thus promoting interoceptive awareness and the deliberate direction of attention.

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 (Singer and Klimecki, 2014; Vrticka et al., 2017). The core exercises are “loving-kindness meditation” and “Affect Dyad”. The loving-kindness medita-

tion is derived from the practice known as *Metta* Meditation. During this practice, participants mentally connect to intentions of love, care, and benevolence. This is enabled by some exercises, such as the visualization of smiling relatives, pleasant places, or a feeling of warmth in the body. Participants find their own way to develop this state of love, and then they are train to redirect this caring intention towards others. The *Affect* dyad is a partner-based exercise, during which participants share difficult or grateful situations with other participants, taking one after the other the role of the listener and the speaker. The speaker tries to focus on his/her own inner experience, while the listener, although listening attentively, does not respond either verbally or non-verbally. This exercise is partly based on the Vipassana traditions that emphasize the acceptance of difficult situations and emotions.

The purpose of the *Perspective* module is to train metacognition and cognitive perspective taking on the self and others (Valk et al., 2016; Molenberghs et al., 2016). The core exercises are “observing-thoughts meditation” and “Perspective Dyad”. The observing-thoughts meditation is a common practice in many contemplative traditions, which aim at developing meta-perspective on the mental contents and deidentify from them. Concretely, in the initial stages of this training, the exercise consists of the use of labels to classify the content of the incoming thoughts and, later in the program to abstain from using labels and just observe the coming and going of thoughts without getting involved in them. This practice is designed to help participants to get a meta-perspective and to gain flexibility with regards to successive thoughts, feelings and behaviours. *Perspective* dyad is also a partner-based exercise during which participants practice inner perspective taking by re-experiencing a recent situation from a different perspective, as well as perspective taking on others by taking the perspective of the dyadic partner. Precisely, the speaker and the listener alternately describe a recent situation from various inner perspectives, i.e., they take the perspective of different aspects of their personality (e.g., the inner judge, the manager or the warm-hearted mother). The listener tries to find out which of these inner personality aspects speak in a given moment and thus is, by inferring thoughts and believes of the other, training cognitive perspective taking on others (i.e., ToM).

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 (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. 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 S3). 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 six blocks constituted the six possible experimental conditions. They differed in the emotional valence of the stimuli presented in the block (positive, negative or neutral) and the predictability of the appearance of the stimuli in the block (predictable vs. unpredictable). To implement the predictability of the appearance of the stimuli, 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 (Fig. 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 (i.e., “NERVÖS” in German) they felt during the block (0 = not at all, 500 = extremely). We used these assessments to measure the task-evoked subjective emotional valence and the task-evoked anxiety, as in the original paper of Somerville et al. (2012). 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 (Core, R, 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:

$$\text{BaselineRatings} = \beta_0 + \beta_1 * \text{valence} + \beta_2 * \text{predictability} + \beta_3 * (\text{valence} * \text{predictability}) + \text{randomeffect}(\text{participant})$$

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 subjective affect ratings for neutral blocks from those for negative and positive blocks (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 (see the equation below). This analysis strategy was chosen in accordance with a similar study design of the *ReSource* project (Trautwein et al., 2020) because it allows (1) to avoid bias in the estimation of the effect of the modules when different participants before and after a module are included in the model, and (2) to include participants for whom we would not have data for all time points. In addition, change scores allow direct modelling and contrasting of module (or retest control) effects. Finally, LMMs are robust

to unbalanced and incomplete longitudinal designs and the inclusion of random effects account for potential within-subject correlations induced by repeated measurement.

$$\text{Change score} = \beta_0 + \beta_1 * \text{retest control 2} + \beta_2 * \text{retest control 3} + \beta_3 * \text{Presence} + \beta_4 * \text{Affect1} + \beta_5 * \text{Affect2} + \beta_6 * \text{Affect3} + \beta_7 * \text{Perspective2} + \beta_8 * \text{Perspective3} + \text{random effect (participant)}$$

The first retest interval (i.e., retest control 1) 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 control (i.e., *Presence* vs. *retest control* (T0 to T1), *Presence* vs. *Affect* (T0 to T1), *Affect* vs. *retest control* (all time points), *Perspective* vs. *retest control* and *Affect* vs. *Perspective* (T1 to T3), see Table S4 in the supplemental material for the description of the contrast matrix. Furthermore, as age and sex might influence emotion processing, we conducted additional sensitivity analyses including Age and Sex as covariate in the model.

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 blocks of pictures:

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

As an estimate of effect size, for each analysis and each contrast, we provide the models estimates (b). In line with previous studies of the *ReSource* project (Trautwein et al., 2020; Hildebrandt et al., 2019), we also reported the effect size of the change per module and timepoint as compared to the retest control group (dppc2: effect sizes for pretest-posttest-control group designs using pooled pretest standard deviations) (Morris, 2008). Specifically, the mean change in the retest participants was subtracted from the mean change in training participants and divided by the pooled standard deviation. These calculated effect sizes are reported and interpreted according to standard convention (i.e., small ≥ 0.20 , medium ≥ 0.50 , large ≥ 0.80).

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 = 2000 ms, TE = 27 ms; flip angle = 77°; 37 axial slices with 1mm gap tilted ~30° from the bi-commissural plane; FOV = 210 mm; matrix size = 70×70; in plane voxel size = 3 × 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 × 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, at each time point, the six 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://nirx.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 3×2 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 S4 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 at the cluster level using FWE correction ($p_{FWE} < 0.05$) through the wild bootstrap procedure (999 iterations) implemented in the SwE toolbox (Guillaume et al., 2014; Guillaume and Nichols, 2015), which led to an extend threshold $k > 98$ voxels. Since the FWE correction might lead to type II error (i.e., non-rejection of the null hypothesis) Lieberman and Cunningham (2009), exploratory analyses were performed at the marginal threshold of $p < 0.001$ (uncorrected at the voxel level); $k > 10$. These exploratory analyses were only performed to inform future studies and will not be interpreted in the current manuscript.
- 3) We tested for the overall effect of the 9-month program with a 2×2 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 (i.e., an explicit mask) derived from the group DARTel-generated template thresholded at 90% grey matter probability. This mask was carefully visually inspected to ensure proper overlapping with the grey matter. 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 the emotional anticipation manipulation did not have an effect at baseline (i.e., we did not find significant effects of Predictability or Predictability-by-Valence interaction at T0), subsequent analyses on the training modules effects focused only on emotional reactivity, i.e., 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 control ($b = -15.73, z = -1.39, p = 0.16$) and *Affect* ($b = 12.32, z = 1.06, p = 0.29$), however, ratings were significantly more negative after retest control 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 control ($b = -55.13, z = 2.13, p = 0.02$) (Fig. 2, Panels a and b). Effect sizes for the *Affect* effect controlling for retest control effect were medium at T0 to T1 and T2 to T3, but negligible at T1 to T2 (Table S7). The effect of *Perspective* was not significantly different from retest control ($b = -0.55, z = -0.03, p = 0.98$) and *Affect* ($b = -26.53, z = -1.34, p = 0.18$), but ratings were significantly less negative after *Perspective* vs. *Presence* ($b = -41.34, z = -2.12, p = 0.03$). The model for subjective emotional valence ratings for [positive - neutral] revealed significantly increased positive ratings after *Perspective* in comparison to retest control ($b = 37.29, z = 2.17, p = 0.03$). The effect sizes for the *Perspective* effect relatively to retest control were medium at T1 to T2 and negligible at T2 to T3 (Table S7). Other comparisons between modules were not significant.

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 control ($b = -72.56, z = -2.63, p = 0.009$) and *Affect* ($b = 78.98, z = 2.83, p = 0.005$) (Fig. S1, Panels a and b). The effect sizes for the *Perspective* effect controlling for retest were medium at T1 to T2 and large at T2 to T3 (Table S7). There was no other significant differential effect of the modules on nervousness rating for [negative - neutral] or for [positive - neutral] rating.

Distributions of behavioural changes after the training modules are presented in Fig. S2, descriptive statistics are reported in Table S5 and detailed statistics for each contrast and measure are reported in Table S6. Sensitivity analyses revealed no main effects of Age and Sex and no significant interaction with the effect of the training effects, except for the nervousness rating for [positive - neutral] where we found a significant interaction between Age and Training (Table S8).

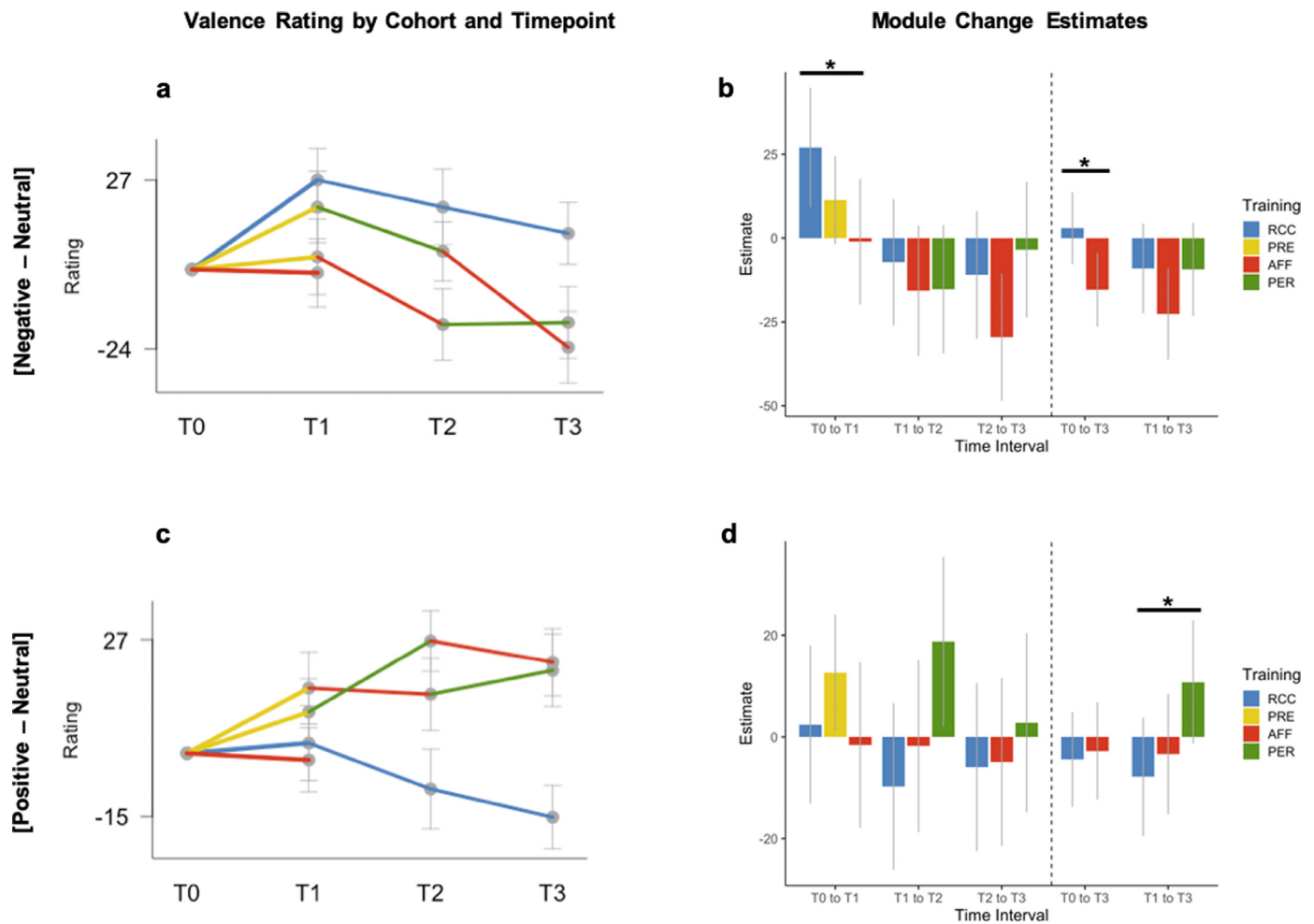


Fig. 2. Descriptive plots of the change in valence rating in the course of the 9-month training. (a-b) Change in [negative - neutral] ratings. (c-d) Change in [positive - neutral] ratings. The line-graphs show ratings according to the group and time point. Values at the first measurement point are equalized representing statistical control for baseline scores. The histograms depict the estimated effect of each module (RCC = retest control cohort, 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 ($b = 6.43$, $z = 0.65$, $p = 0.51$) (Fig. 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 (Fig. 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 [$F(1, 435) = 1.22$; $p = 0.23$] (Fig. 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 SMG, the right 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 (Fig. 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 ($p_{\text{unc(voxel)}} < 0.001$, $k > 10$; Fig. 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.

3.2.2. Neurofunctional change induced by the training modules

In comparison to retest control, 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 inves-

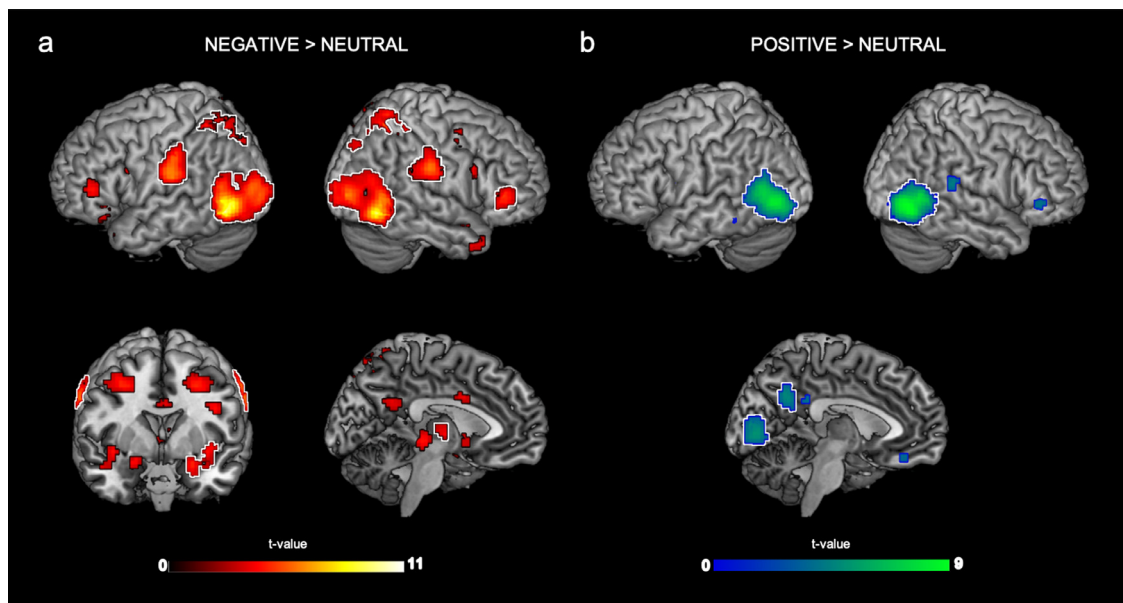


Fig. 3. Cerebral responses to emotional scenes at baseline (T0). Brain activation resulting from the contrast [negative > neutral] are represented in red-yellow scale (a) and those of the contrast [positive > neutral] in blue-green scale (b). Findings are thresholded at $p_{\text{uncor}} < 0.001$, $k > 10$ and clusters that survived correction for multiple comparison ($p_{\text{FWEc}} < 0.05$) are surrounded with a white line.

Table 2

Activation peaks before the training (T0).

Lobe	Region	BA	k	H	x	y	z	t
Negative > Neutral								
Occipital	Inferior Occipital / Temporal / Parietal Gyrus*	7/18/19/38/39	1729	L	-45	-64	-7	10.98
	Inferior Occipital / Temporal / Parietal Gyrus*	7/18/19/38/39	1370	R	48	-61	-7	10.42
Parietal	SupraMarginal Gyrus*	40	152	R	60	-22	32	6.00
	SupraMarginal Gyrus*	40	183	L	-63	-22	29	5.90
Frontal	Inferior Frontal Gyrus (orbital/triangular part)*	45/46/47	101	R	45	35	5	5.87
	Inferior Frontal Gyrus (triangular/opercular part)	46	80	R	45	11	26	5.13
	Superior/Middle Frontal Gyrus	6	79	L	-27	-1	47	4.89
	Superior/Middle Frontal Gyrus	6	77	R	33	-1	47	4.88
	Orbitofrontal cortex	11	20	L	-27	35	-16	4.88
	Inferior Frontal Gyrus (opercular/triangular part)	9	46	L	-42	5	29	4.72
	Inferior/Middle Frontal Gyrus	46	43	L	-48	38	11	4.70
	Orbitofrontal cortex	11	12	R	27	32	-19	3.88
	Insula/Superior temporal gyrus	13	40	R	39	-4	-7	4.79
	Insula/Inferior Frontal Gyrus (orbital part)	47	57	L	-36	29	2	4.12
Insula	Insula/Temporal Pole	47/13	31	L	-33	20	-19	3.92
	Thalamus*	NA	108	R	6	-28	-4	4.75
	Sub cortical grey nuclei							
Limbic	Amygdala/Superior Temporal Gyrus/Insula*	13/21/28	109	L	-36	-7	-7	5.45
	Middle Cingulate Cortex	31	22	R	18	-28	41	4.28
	Hippocampus/Amygdala	34	15	R	21	-4	-13	4.15
	Middle Cingulate cortex	24	20	NA	0	5	32	3.85
	Posterior Cingulate Cortex/Precuneus	31	46	L	-3	-52	29	3.83
	Temporal Pole: Middle/Superior temporal gyrus	38	32	R	48	11	-34	3.70
Positive > Neutral								
Occipital	Inferior Occipital/Temporal Gyrus*	19/37/39	644	R	51	-67	-4	8.56
	Inferior Occipital/Temporal Gyrus*	19/37/39	794	L	-48	-73	2	7.51
	Cuneus/Lingual Gyrus*	17/18	319	R	12	-82	5	6.65
Parietal	Precuneus/Posterior Cingulate Cortex*	7/31	84	NA	0	-58	35	4.21
Temporal	Superior Temporal Gyrus	40/42	17	R	66	-34	20	4.02
Frontal	Inferior Frontal Gyrus (opercular part)	44/45	14	R	-45	5	17	4.01
	Inferior Frontal Gyrus (triangular part)	45/47	12	L	54	35	2	3.65

* $p_{\text{FWEc}} < 0.05$ cluster corrected

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

tigated 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) ($p_{\text{unc(voxel)}} < 0.001$, $k > 10$, Fig. 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 be-

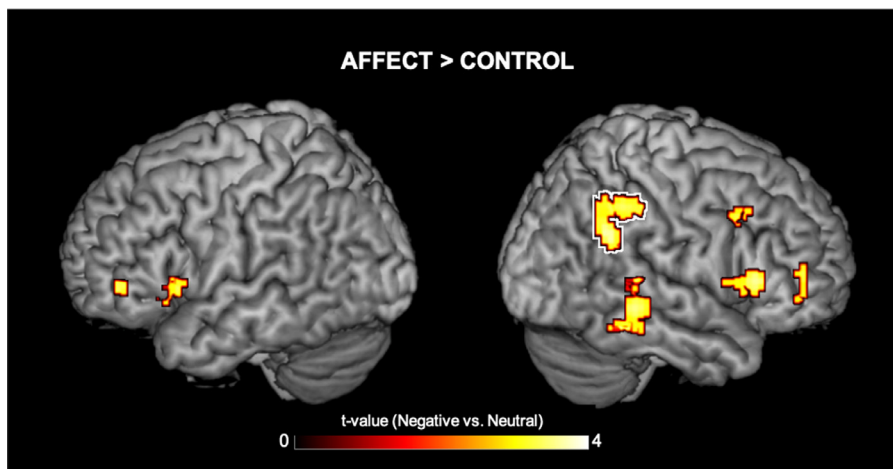


Fig. 4. Modulation of the cerebral activity after Affect module training. Brain areas showing increase activity for the contrast [negative > neutral] after the Affect module in comparison to retest control. Findings are thresholded at $p_{\text{uncor}} < 0.001$, $k > 10$; cluster that survived $p_{\text{FWEc}}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

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

Lobe	Region	BA	k	H	x	y	z	Z
Negative > Neutral								
Parietal	SupraMarginal Gyrus*	40	140	R	45	-40	41	4.20
Temporal	Inferior Temporal Gyrus	21/22	94	R	60	-43	-13	3.86
Occipital	Lingual Gyrus	19/30	21	L	-18	-52	-1	3.86
	Cuneus/Lingual Gyrus	7	11	R	12	-76	32	3.44
Frontal	Inferior Frontal Gyrus (triangular part)	44/45	44	R	60	23	11	3.76
	Inferior Frontal Gyrus (triangular part)	45/47	49	L	-48	20	8	3.58
	Inferior Frontal Gyrus (triangular part)	46/47	12	L	-48	44	2	3.53
	Middle Frontal Gyrus	8/9	15	R	48	14	41	3.42
	Middle Frontal Gyrus	46	13	R	45	47	11	3.42

*pFWEc < 0.05 cluster corrected

BA = Brodmann area, H = Hemisphere; R = Right; L = Left; k = number of voxels/cluster

tween training *Affect* and *Perspective*, between *Presence* and retest control, as well as between *Presence* and *Affect* (T1) for both contrasts.

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 (Fig. S4, Table S9). 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 processing of 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 fMRI task allowing to assess both emotional anticipation and reactivity processes (Somerville et al., 2012) before and after engaging in three 3-month training modules. The training modules focused 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, emotional reactivity (positive and negative vs. neutral) towards 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 subjective 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 subjective negative affect ratings and increased activity in the right SMG after participants were exposed to negative pictures compared to neutral ones. After the *Perspective* module, participants rated the positive vs. neutral pictures more positively, but did not show significant changes in brain activity. 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 presented 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 related to emotional reactivity 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 were activated, as well as the left amygdala for the negative vs. neutral contrast. 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 (ventromedial 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).

Regarding the evaluation of processes related to emotional anticipation, 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. We were thus unable to measure changes in emotional anticipation processes following the different training modules.

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 neither 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 being exposed to negative 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 three 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 nine 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 control (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. To help the interpretation of our findings, activation maps resulting from the 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 correlates of empathy and theory of mind (Kanske et al., 2015). Notably, the brain activation pattern observed after the *Affect* modules when participants are exposed to pictures depicting people suffering, partially overlaps with regulation regions of the empathy network (i.e., right SMG and right lateral prefrontal regions) defined in the same participants at baseline (Kanske et al., 2015) (Figure S5) 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 judgments 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).

From another perspective, we can ask ourselves whether it is beneficial for people to reduce their negative emotions in response to witnessing the suffering of others. It can be argued that sharing the suffering with others reflects an empathic response. However, empathic responses can also easily lead to so-called empathic or personal distress (Singer and Klimecki, 2014), i.e., an aversive and self-oriented emotional response to the suffering of others. Such non-adaptive response can be very damaging for people frequently confronted with others' suffering and distress. This is the case, for example, for caregivers whose risk of developing burnout is significant if they fail to manage their initial empathic response and turn it into a healthy compassionate response. Thus, in contrast to empathic distress, compassion is associated to concern, positive affect and is a resilient coping strategy (Klimecki et al., 2013; Klimecki et al., 2014). One aim of the *Affect* module was precisely to train participants in recognizing a healthy empathic response and turn it into compassion to avoid ending up in empathic distress. This was indeed demonstrated by Trautwein et al. (2020) (Trautwein et al., 2020) with evidence for increased training-related compassion after the *Affect* module. 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 that after the overall 9-month training participants rated their subjective affect more positively after being exposed to positive pictures, which seem to be driven by the change after the *Perspective* training module ([Fig. 2](#), Panels c and d and [Fig. 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 positive 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.

Although we found significant change in subjective affect rating and in brain activity after the *Affect* and *Perspective* module in comparison to re-test, we cannot conclude as to the specificity of the observed effects. Indeed, at both behavioural and neural levels, we did not show significant relative difference between *Presence*, *Affect* and *Perspective*, so it is possible that the positive effects of the program have accumulated over the different training modules. Notably, we found an overall change in positive and negative rating over the 9-months training program for the two active cohorts relative to the re-test cohort. This overall change could be related to previous results of our group showing improved heart beat perception and decrease alexithymia after the 9-month training but no specific modules effect [Bornemann and Singer \(2017\)](#). This study shows better interoceptive skills and improved emotion recognition in the two training cohorts but no change in the retest control cohort which may be related to improve emotion regulation skills ([Dunn et al., 2010](#); [Wiens et al., 2000](#)).

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 dyad in the *Affect* module) may also be seen as a second limitation. Indeed, 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.

Last, for practical reasons, we could neither include another active training cohort that focused only on *Perspective* training in the first 3 months (i.e., similar to TC3), nor another active training cohort that would have followed another kind the 9-month training. Indeed, the main purpose of the *ReSource* project was to disentangle the specific effects of different types of mental training practices (attention-based, socio-emotional and socio-cognitive) and the design was developed for that purpose, i.e., to enable the different training modules to be used as active controls for each other.

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 by healthcare professionals, 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 to the 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 especially the compassion-based *Affect* module, lead to a decrease of experienced negative affect when confronted with emotionally distressing social stimuli. This decrease was associated with changes in functional plasticity in brain networks playing a key role in emotional regulation. Given the importance of affective processes on both social and clinical levels, 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 explored.

Author contributions

Pauline Favre: Methodology, Formal analysis, Writing - Original Draft, Visualization. Philipp Kanske: Conceptualization, Investigation, Writing - Review and Editing, Supervision. Haakon Engen: Conceptualization, Investigation, Writing - Review and Editing. Tania Singer: Conceptualization, Writing - Review and Editing, Supervision, Funding Acquisition.

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.

Declaration of Competing Interest

The authors declare no competing financial interest.

Acknowledgments

This study forms part of the *ReSource* Project headed by Tania Singer. Data for this project were collected between 2013 and 2016 at

the former department of Social Neuroscience at the Max Planck Institute for Human Cognitive and Brain Sciences Leipzig. Tania Singer (Principal Investigator) received funding for the ReSource Project from the European Research Council under the European Community's Seventh Framework Program (FP7/2007-2013) ERC Grant Agreement Number 205557.

We are thankful to the members of the Social Neuroscience Department involved in the ReSource Project over many years, in particular to the teachers of the ReSource intervention program, to Astrid Ackermann, Christina Bochow, Matthias Bolz and Sandra Zurborg for managing the large-scale longitudinal study, to Elisabeth Murzik, Sylvia Tydecks, Kerstin Träger, and Nadine Otto for help with recruiting and data archiving, to Henrik Grunert for technical assistance, to Manuela Hofmann, Sylvie Neubert, and Nicole Pampus for help with data collection, and to Hannes Niederhausen and Torsten Kästner for data management.

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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.neuroimage.2021.118132](https://doi.org/10.1016/j.neuroimage.2021.118132).

References

- Adriaenssens, J., De Gucht, V., Maes, S., 2015. Causes and consequences of occupational stress in emergency nurses, a longitudinal study. *J. Nurs. Manage.* 23, 346–358.
- Allen, M., Dietz, M., Blair, K.S., van Beek, M., Rees, G., Vestergaard-Poulsen, P., Lutz, A., Roepstorff, A., 2012. Cognitive-affective neural plasticity following active-controlled mindfulness intervention. *J. Neurosci.* 32, 15601–15610.
- Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. *Neuroimage* 38, 95–113.
- Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4. *J. Stat. Software* 67.
- Beauregard, M., Courtemanche, J., Paquette, V., St-Pierre, É.L., 2009. The neural basis of unconditional love. *Psychiatry Res.* 172, 93–98.
- Bormann, B., Singer, T., 2017. Taking time to feel our body: Steady increases in heart-beat perception accuracy and decreases in alexithymia over 9 months of contemplative mental training. *Psychophysiology* 54, 469–482.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38.
- Buhle, J.T., Silvers, J.A., Wager, T.D., Lopez, R., Onyemkwo, C., Kober, H., Weber, J., Ochsner, K.N., 2014. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cereb. Cortex* 24, 2981–2990.
- Burgdorf, J., Panksepp, J., 2006. The neurobiology of positive emotions. *Neurosci. Biobehav. Rev.* 30, 173–187.
- Bzdok, D., Schilbach, L., Vogeley, K., Schneider, K., Laird, A.R., Langner, R., Eickhoff, S.B., 2012. Parsing the neural correlates of moral cognition: ALE meta-analysis on morality, theory of mind, and empathy. *Brain Struct. Funct.* 217, 783–796.
- Carter, C., Keverne, E.B., 2002. The Neurobiology of Social Affiliation and Pair Bonding. *Hormones, Brain and Behavior*. Elsevier, pp. 299–337.
- Chiesa, A., Serretti, A., Jakobsen, J.C., 2013. Mindfulness: top-down or bottom-up emotion regulation strategy? *Clin. Psychol. Rev.* 33, 82–96.
- Core, R., 2015. Team. R: a language and environment for statistical computing 3 (2).
- Creswell, J.D., Pacilio, L.E., Lindsay, E.K., Brown, K.W., 2014. Brief mindfulness meditation training alters psychological and neuroendocrine responses to social evaluative stress. *Psychoneuroendocrinology* 44, 1–12.
- Dahl, C.J., Lutz, A., Davidson, R.J., 2015. Reconstructing and deconstructing the self: cognitive mechanisms in meditation practice. *Trends Cogn. Sci.* 19, 515–523.
- Dan-Glauser, E.S., Scherer, K.R., 2011. The Geneva affective picture database (GAPED): a new 730-picture database focusing on valence and normative significance. *Behavior Res. Methods* 43, 468.
- De Vignemont, F., Singer, T., 2006. The empathic brain: how, when and why? *Trends Cogn. Sci.* 10, 435–441.
- Desbordes, G., Negi, L.T., Pace, T.W., Wallace, B.A., Raision, C.L., Schwartz, E.L., 2012. Effects of mindful-attention and compassion meditation training on amygdala response to emotional stimuli in an ordinary, non-meditative state. *Front. Hum. Neurosci.* 6, 292.
- Dunn, B.D., Galton, H.C., Morgan, R., Evans, D., Oliver, C., Meyer, M., Cusack, R., Lawrence, A.D., Dalgleish, T., 2010. Listening to your heart: How interoception shapes emotion experience and intuitive decision making. *Psychol. Sci.* 21, 1835–1844.
- Engen, H.G., Kanske, P., Singer, T., 2017. The neural component-process architecture of endogenously generated emotion. *Soc. Cogn. Affect. Neurosci.* 12, 197–211.
- Engen, H.G., Singer, T., 2015. Compassion-based emotion regulation up-regulates experienced positive affect and associated neural networks. *Soc. Cogn. Affect. Neurosci.* 10, 1291–1301.
- Fan, Y., Duncan, N.W., de Greck, M., Northoff, G., 2011. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neurosci. Biobehav. Rev.* 35, 903–911.
- Farb, N.A., Anderson, A.K., Irving, J.A., Segal, Z., 2014. Mindfulness interventions and emotion regulation. *Handbook Emotion Regulation* 548–567.
- Farb, N.A., Anderson, A.K., Mayberg, H., Bean, J., McKeon, D., Segal, Z.V., 2010. Minding one's emotions: mindfulness training alters the neural expression of sadness. *Emotion* 10, 25–33.
- Farb, N.A., Anderson, A.K., Segal, Z.V., 2012. The mindful brain and emotion regulation in mood disorders. *Canadian J. Psychiatry* 57, 70–77.
- Farb, N.A., Segal, Z.V., Mayberg, H., Bean, J., McKeon, D., Fatima, Z., Anderson, A.K., 2007. Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *Soc. Cogn. Affect. Neurosci.* 2, 313–322.
- Fox, K.C., Dixon, M.L., Nijeboer, S., Girn, M., Floman, J.L., Lifshitz, M., Ellamil, M., Sedlmeier, P., Christoff, K., 2016. Functional neuroanatomy of meditation: A review and meta-analysis of 78 functional neuroimaging investigations. *Neurosci. Biobehav. Rev.* 65, 208–228.
- Fox, K.C., Nijeboer, S., Dixon, M.L., Floman, J.L., Ellamil, M., Rumak, S.P., Sedlmeier, P., Christoff, K., 2014. Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. *Neurosci. Biobehav. Reviews* 43, 48–73.
- Frith, C., Frith, U., 2005. Theory of mind. *Curr. Biol.* 15, R644–R645.
- Froeliger, B., Garland, E.L., Modlin, L.A., McClernon, F.J., 2012. Neurocognitive correlates of the effects of yoga meditation practice on emotion and cognition: a pilot study. *Front. Integr. Neurosci.* 6, 48.
- Gilbert, P., 2009. Introducing compassion-focused therapy. *Adv. Psychiatric Treat.* 15, 199–208.
- Gilbert, P., 2017. *Compassion: Concepts, Research and Applications*. Taylor & Francis.
- Goetz, J.L., Keltner, D., Simon-Thomas, E., 2010. Compassion: an evolutionary analysis and empirical review. *Psychol. Bull.* 136, 351.
- Goldin, P., Ziv, M., Jazaieri, H., Gross, J., 2012. Randomized controlled trial of mindfulness-based stress reduction versus aerobic exercise: effects on the self-referential brain network in social anxiety disorder. *Front. Human Neurosci.* 6, 295.
- Goldin, P.R., Gross, J.J., 2010. Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion* 10, 83.
- Gu, J., Strauss, C., Bond, R., Cavanagh, K., 2015. How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clin. Psychol. Rev.* 37, 1–12.
- Guendelman, S., Medeiros, S., Rampes, H., 2017. Mindfulness and emotion regulation: insights from neurobiological, psychological, and clinical studies. *Front. Psychol.* 8, 220.
- Guillaume, B., Hua, X., Thompson, P.M., Waldorp, L., Nichols, T.E., Initiative, A.S.D.N., 2014. Fast and accurate modelling of longitudinal and repeated measures neuroimaging data. *Neuroimage* 94, 287–302.
- Guillaume, B., Nichols, T., 2015. Non-parametric inference for longitudinal and repeated-measures neuroimaging data with the wild bootstrap. In: Poster Presented at the Organization for Human Brain Mapping (OHBM) in Hawaii, pp. 14–18.
- Harbaugh, W.T., Mayr, U., Burghart, D.R., 2007. Neural responses to taxation and voluntary giving reveal motives for charitable donations. *Science* 316, 1622–1625.
- Heeren, A., Philippot, P., 2011. Changes in ruminative thinking mediate the clinical benefits of mindfulness: Preliminary findings. *Mindfulness* 2, 8–13.
- Hildebrandt, L.K., McCall, C., Singer, T., 2019. Socioaffective versus sociocognitive mental trainings differentially affect emotion regulation strategies. *Emotion* 19, 1329.
- Hölzel, B.K., Hoge, E.A., Greve, D.N., Gard, T., Creswell, J.D., Brown, K.W., Barrett, L.F., Schwartz, C., Vaitl, D., Lazar, S.W., 2013. Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. *NeuroImage* 2, 448–458.
- Jazaieri, H., Jinpa, G.T., McGonigal, K., Rosenberg, E.L., Finkelstein, J., Simon-Thomas, E., Cullen, M., Doty, J.R., Gross, J.J., Goldin, P.R., 2013. Enhancing compassion: a randomized controlled trial of a compassion cultivation training program. *J. Happiness Studies* 14, 1113–1126.
- Johnson, D.C., Thom, N.J., Stanley, E.A., Haase, L., Simmons, A.N., Shih, P.-a.B., Thompson, W.K., Poterat, E.G., Minor, T.R., Paulus, M.P., 2014. Modifying resilience mechanisms in at-risk individuals: a controlled study of mindfulness training in Marines preparing for deployment. *Am. J. Psychiatry* 171, 844–853.
- Kabat-Zinn, J., 2003. Mindfulness-based interventions in context: past, present, and future. *Clinical Psychol.* 10, 144–156.
- Kanske, P., Böckler, A., Trautwein, F.-M., Parianen Lesemann, F.H., Singer, T., 2016. Are strong empathizers better mentalizers? Evidence for independence and interaction between the routes of social cognition. *Soc. Cogn. Affect. Neurosci.* 11, 1383–1392.
- Kanske, P., Böckler, A., Trautwein, F.-M., Singer, T., 2015. Dissecting the social brain: Introducing the EmpaToM to reveal distinct neural networks and brain-behavior relations for empathy and Theory of Mind. *Neuroimage* 122, 6–19.
- Kim, J.-W., Kim, S.-E., Kim, J.-J., Jeong, B., Park, C.-H., Son, A.R., Song, J.E., Ki, S.W., 2009. Compassionate attitude towards others' suffering activates the mesolimbic neural system. *Neuropsychologia* 47, 2073–2081.
- Klimecki, O., Singer, T., 2012. Empathic distress fatigue rather than compassion fatigue?

- In: Integrating Findings from Empathy Research in Psychology and Social Neuroscience. Pathological altruism, pp. 368–383.
- Klimecki, O.M., Leiberg, S., Lamm, C., Singer, T., 2013. Functional neural plasticity and associated changes in positive affect after compassion training. *Cereb. Cortex* 23, 1552–1561.
- Klimecki, O.M., Leiberg, S., Ricard, M., Singer, T., 2014. Differential pattern of functional brain plasticity after compassion and empathy training. *Soc. Cogn. Affect. Neurosci.* 9, 873–879.
- Kok, B.E., Singer, T., 2017. Effects of contemplative dyads on engagement and perceived social connectedness over 9 months of mental training: a randomized clinical trial. *JAMA Psychiatry* 74, 126–134.
- Kragel, P.A., LaBar, K.S., 2016. Decoding the nature of emotion in the brain. *Trends Cogn. Sci.* 20, 444–455.
- Kral, T.R., Schuyler, B.S., Mumford, J.A., Rosenkranz, M.A., Lutz, A., Davidson, R.J., 2018. Impact of short-and long-term mindfulness meditation training on amygdala reactivity to emotional stimuli. *Neuroimage* 181, 301–313.
- Kuyken, W., Warren, F.C., Taylor, R.S., Whalley, B., Crane, C., Bondolfi, G., Hayes, R., Huijbers, M., Ma, H., Schweizer, S., 2016. Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: an individual patient data meta-analysis from randomized trials. *JAMA Psychiatry* 73, 565–574.
- Lamm, C., Decety, J., Singer, T., 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage* 54, 2492–2502.
- Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1999. International Affective Picture System (IAPS): Technical Manual and Affective Ratings. The Center for Research in Psychophysiology, University of Florida, Gainesville, FL.
- Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B., Nangia, V., 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology* 35, 199–210.
- Lee, T.M., Leung, M.-K., Hou, W.-K., Tang, J.C., Yin, J., So, K.-F., Lee, C.-F., Chan, C.C., 2012. Distinct neural activity associated with focused-attention meditation and loving-kindness meditation. *PLoS One* 7.
- Leung, M.-K., Lau, W.K., Chan, C.C., Wong, S.S., Fung, A.L., Lee, T.M., 2018. Meditation-induced neuroplastic changes in amygdala activity during negative affective processing. *Soc. Neurosci.* 13, 277–288.
- Lieberman, M.D., Cunningham, W.A., 2009. Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc. Cogn. Affect. Neurosci.* 4, 423–428.
- Lindquist, K.A., Wager, T.D., Kober, H., Bliss-Moreau, E., Barrett, L.F., 2011. The brain basis of emotion: a meta-analytic review. *Behav. Brain Sci.* 173, 1–86.
- Lindquist, K.A., Wager, T.D., Kober, H., Bliss-Moreau, E., Barrett, L.F., 2012. The brain basis of emotion: a meta-analytic review. *Behav. Brain Sci.* 35, 121.
- Lutz, A., Brefczynski-Lewis, J., Johnstone, T., Davidson, R.J., 2008. Regulation of the neural circuitry of emotion by compassion meditation: effects of meditative expertise. *PLoS One* 3, e1897.
- Lutz, J., Herwig, U., Opialla, S., Hittmeyer, A., Jäncke, L., Rufer, M., Holtforth, M.G., Brühl, A.B., 2014. Mindfulness and emotion regulation—an fMRI study. *Soc. Cogn. Affect. Neurosci.* 9, 776–785.
- Magalhaes, A.A., Oliveira, L., Pereira, M.G., Menezes, C.B., 2018. Does meditation alter brain responses to negative stimuli? a systematic review. *Front. Human Neurosci.* 12, 448.
- McCall, C., Singer, T., 2012. The animal and human neuroendocrinology of social cognition, motivation and behavior. *Nat. Neurosci.* 15, 681–688.
- Molenberghs, P., Trautwein, F.-M., Böckler, A., Singer, T., Kanske, P., 2016. Neural correlates of metacognitive ability and of feeling confident: a large-scale fMRI study. *Soc. Cogn. Affect. Neurosci.* 11, 1942–1951.
- Moll, J., Krueger, F., Zahn, R., Pardini, M., de Oliveira-Souza, R., Grafman, J., 2006. Human fronto-mesolimbic networks guide decisions about charitable donation. *Proc. Natl. Acad. Sci.* 103, 15623–15628.
- Morris, S.B., 2008. Estimating effect sizes from pretest-posttest-control group designs. *Org. Res. Methods* 11, 364–386.
- Neff, K.D., Germer, C.K., 2013. A pilot study and randomized controlled trial of the mindful self-compassion program. *J. Clin. Psychol.* 69, 28–44.
- O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr. Opin. Neurobiol.* 14, 769–776.
- Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D.E., 2002. Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *J. Cogn. Neurosci.* 14, 1215–1229.
- Ochsner, K.N., Gross, J.J., 2005. The cognitive control of emotion. *Trends Cogn. Sci.* 9, 242–249.
- Pace, T.W., Negi, L.T., Adame, D.D., Cole, S.P., Sivilli, T.I., Brown, T.D., Issa, M.J., Raision, C.L., 2009. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology* 34, 87–98.
- Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16, 331–348.
- Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* 48, 175–187.
- Piet, J., Hougaard, E., 2011. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clin. Psychol. Rev.* 31, 1032–1040.
- Preckel, K., Trautwein, F.-M., Paulus, F.M., Kirsch, P., Krach, S., Singer, T., Kanske, P., 2019. Neural mechanisms of affective matching across faces and scenes. *Sci. Rep.* 9, 1–10.
- Premack, D., Woodruff, G., 1978. Does the chimpanzee have a theory of mind? *Behav. Brain Sci.* 1, 515–526.
- Saxe, R., Kanwisher, N., 2003. People thinking about thinking people: the role of the temporo-parietal junction in “theory of mind. *Neuroimage* 19, 1835–1842.
- Schultz, W., 2006. Behavioral theories and the neurophysiology of reward. *Ann. Rev. Psychol.* 57, 87–115.
- Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J., 2014. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neurosci. Biobehav. Rev.* 42, 9–34.
- Sedlmeier, P., Eberth, J., Schwarz, M., Zimmermann, D., Haarig, F., Jaeger, S., Kunze, S., 2012. The psychological effects of meditation: a meta-analysis. *Psychol. Bull.* 138, 1139.
- Shanafelt, T.D., Boone, S., Tan, L., Dyrbye, L.N., Sotile, W., Satele, D., West, C.P., Sloan, J., Oreskovich, M.R., 2012. Burnout and satisfaction with work-life balance among US physicians relative to the general US population. *Arch. Intern. Med.* 172, 1377–1385.
- Silani, G., Lamm, C., Ruff, C.C., Singer, T., 2013. Right supramarginal gyrus is crucial to overcome emotional egocentricity bias in social judgments. *J. Neurosci.* 33, 15466–15476.
- Singer, T., 2012. The past, present and future of social neuroscience: a European perspective. *Neuroimage* 61, 437–449.
- Singer, T., Engert, V., 2019. It matters what you practice: Differential training effects on subjective experience, behavior, brain and body in the ReSource Project. *Curr. Opin. Psychol.* 28, 151–158.
- Singer, T., Klimecki, O.M., 2014. Empathy and compassion. *Curr. Biol.* 24, R875–R878.
- Singer, T., Kok, B.E., Bornemann, B., Zurborg, S., Bolz, M., Bochow, C., 2016. The ReSource Project: Background, Design, Samples, and Measurements, 2nd ed. Max Planck Institute for Human Cognition and Brain Science, Leipzig, Germany.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. *Science* 303, 1157–1162.
- Somerville, L.H., Wagner, D.D., Wig, G.S., Moran, J.M., Whalen, P.J., Kelley, W.M., 2012. Interactions between transient and sustained neural signals support the generation and regulation of anxious emotion. *Cereb. Cortex* 23, 49–60.
- Steinbeis, N., Bernhardt, B.C., Singer, T., 2014. Age-related differences in function and structure of rSMG and reduced functional connectivity with DLPFC explains heightened emotional egocentricity bias in childhood. *Soc. Cogn. Affect. Neurosci.* 10, 302–310.
- Tang, Y.-Y., Hölzel, B.K., Posner, M.I., 2015. The neuroscience of mindfulness meditation. *Nat. Rev. Neurosci.* 16, 213–225.
- Taylor, V.A., Grant, J., Daneault, V., Scavone, G., Breton, E., Roffe-Vidal, S., Courtemanche, J., Lavarenne, A.S., Beaugard, M., 2011. Impact of mindfulness on the neural responses to emotional pictures in experienced and beginner meditators. *Neuroimage* 57, 1524–1533.
- Teasdale, J.D., Moore, R.G., Hayhurst, H., Pope, M., Williams, S., Segal, Z.V., 2002. Metacognitive awareness and prevention of relapse in depression: empirical evidence. *J. Consult. Clin. Psychol.* 70, 275.
- Trautwein, F.-M., Kanske, P., Böckler, A., Singer, T., 2020. Differential benefits of mental training types for attention, compassion, and theory of mind. *Cognition* 194, 104039.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289.
- Valk, S.L., Bernhardt, B.C., Boeckler, A., Kanske, P., Singer, T., 2016. Substrates of metacognition on perception and metacognition on higher-order cognition relate to different subsystems of the mentalizing network. *Hum. Brain Mapp.* 37, 3388–3399.
- Valk, S.L., Bernhardt, B.C., Trautwein, F.-M., Böckler, A., Kanske, P., Guizard, N., Collins, D.L., Singer, T., 2017. Structural plasticity of the social brain: Differential change after socio-affective and cognitive mental training. *Sci. Adv.* 3, e1700489.
- Vrtička, P., Favre, P., Singer, T., 2017. Compassion and the brain. *Compassion. Routledge* 135–150.
- Vuilleumier, P., 2005. How brains beware: neural mechanisms of emotional attention. *Trends Cogn. Sci.* 9, 585–594.
- Vuilleumier, P., Pourtois, G., 2007. Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia* 45, 174–194.
- Wallace, B.A., 2006. The Attention Revolution: Unlocking the Power of the Focused Mind. Simon and Schuster.
- Wallace, B.A., Shapiro, S.L., 2006. Mental balance and well-being: building bridges between Buddhism and Western psychology. *Am. Psychol.* 61, 690.
- Weng, H.Y., Fox, A.S., Shackman, A.J., Stodola, D.E., Caldwell, J.Z., Olson, M.C., Rogers, G.M., Davidson, R.J., 2013. Compassion training alters altruism and neural responses to suffering. *Psychol. Sci.* 24, 1171–1180.
- Weng, H.Y., Lapate, R.C., Stodola, D.E., Rogers, G.M., Davidson, R.J., 2018. Visual attention to suffering after compassion training is associated with decreased amygdala responses. *Front. Psychol.* 9, 771.
- Wessa, M., Kanske, P., Neumeister, P., Bode, K., Heissler, J., Schönfelder, S., 2010. EmoPicS: subjective and psychophysiological evaluation of new imagery for clinical biopsychological research. *Z. Klin. Psychol. Psychother. Suppl* 1, 11–77.
- Wiens, S., Mezzacappa, E.S., Katkin, E.S., 2000. Heartbeat detection and the experience of emotions. *Cogn. Emotion* 14, 417–427.
- Williams, J.M.G., Crane, C., Barnhofer, T., Brennan, K., Duggan, D.S., Fennell, M.J., Hackmann, A., Krusche, A., Muse, K., Von Rohr, I.R., 2014. Mindfulness-based cognitive therapy for preventing relapse in recurrent depression: a randomized dismantling trial. *J. Consult. Clin. Psychol.* 82, 275.

Young, K.S., van der Velden, A.M., Craske, M.G., Pallesen, K.J., Fjorback, L., Roepstorff, A., Parsons, C.E., 2018. The impact of mindfulness-based interventions on brain activity: a systematic review of functional magnetic resonance imaging studies. *Neurosci. Biobehav. Reviews* 84, 424–433.

Zeidan, F., Emerson, N.M., Farris, S.R., Ray, J.N., Jung, Y., McHaffie, J.G., Coghill, R.C., 2015. Mindfulness meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness meditation-induced analgesia. *J. Neurosci.* 35, 15307–15325.