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

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1. 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 behavioral 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.

Key-words: meditation, fMRI, emotion, mental training, compassion, mindfulness
I. 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 (Bosson and Philippot, 2011; Kuyken et al., 2016; Paik and Hongaard, 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 (Ferrari 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 (Dahl et al., 2008, 2017). All of these practices could contribute to better management of emotional reactivity by promoting acceptance, new appraisals and positive feelings, and by reducing 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.

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., 2011), face processing (Johnson et al., 2014), self-reference (Farb et al., 2007; Goldin et al., 2012) or pain regulation (Goldin 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 novice 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
ventro-medial, 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 inferior temporal cortex (ITC) and inferior temporal gyri 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 (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 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 others (Gilbert, 2009, 2017; Jazaieri et al., 2013; Neff and Goosen, 2011). 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 others, 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 (Kens et al., 2009) or an attitude of unconditional love toward people with disabilities (Reinhard et al., 2009). Similarly, increased activations of the VS, midbrain and subgenual ACC were found when people are making charitable donations (Shipherd et al., 2007; Mehl et al., 2006). Compassion generation may thus involve a set of brain regions associated with reward, affiliation, positive social feelings and prosocial motivation (Barch and Dosenbach, 2008; Carter and Koenig, 2002; McCull and Singer, 2012; O’Donovan, 2004; Schubart, 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 (Zak 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. Moreover, 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; Gehman and Gross, 2009). 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 emotions, 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-naive 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 (Bargh et al. and Panksepp, 2006; Carter and Koenigs, 2002; McCullum and Singer, 2012; O’Doherty, 2004; Schulte, 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 (Decety 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; Kaneko et al., 2015; Lamm et al., 2011; Singer et al., 2006). 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, 2000; Singer, 2012). ToM is thought to be underpinned by a neural network including the TPJ, STS, temporal poles (TP), medial prefrontal cortex (mPFC) and precuneus/posterior cingulate (PCC) (Bzdok et al., 2012; Frith and Frith, 2005; Kaneko et al., 2016; Kaneko et al., 2015; Saxe and Kanwisher, 2003; Saxe et al., 2016). 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; Keel et al., 2018; Lam et al., 2018; Wang et al., 2013; Wang 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 behavioral 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 (Figure 1a).

The participants were assigned to one of the three training cohorts (TCs) who underwent the different modules in counterbalanced order or to the retest control cohort (RCC) (Figure 1b). This design allows 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 us to assess both the initial neural activity linked to the processing of emotional vs. neutral stimuli 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, 2009; Somerville et al., 2012). Processing of positive emotion would be accompanied by increased activation of VL, NAcc and OFC areas, while processing of negative emotion would be associated with activations of the amygdala and lateral regions of the PFC (Kragel and LaBar, 2010; Lindquist et al., 2012; Phan et al., 2002; Preckel et al., 2019). Regarding emotional anticipation, similarly to Sommerville et al. (2012), we expected that participants at baseline would show increased nervousness, as well as increased 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 increased 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., TC3 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-month 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.
Figure 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 retest phases (grey areas) for the training and 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), the groups 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
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 1 in the supplementary). Demographic details of the sample are listed in Table S1 as well as in 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/inclusion, partial dropout/inclusion from MRI experiments and technical, health, or scheduling issues at individual assessments. Finally, since the behavioral 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 203 subjects ranging between 59 to 76 participants 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 376/12-0) and the Research Ethics Committee of Humboldt University of Berlin (numbers 2013-02, 2013-29, and 2014-01). The study was registered with the Protocol Registration System of ClinicalTrials.gov under the title “Plasticity of the Compassionate Brain” with the ClinicalTrials.gov Identifier: NCT01833104.

Table 1. Sample description for available change scores

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<th>T2-T3</th>
<th>RCC T0-T3</th>
<th>TC1 T0-T3</th>
<th>TC2 T0-T3</th>
<th>TC3 T0-T3</th>
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<tr>
<td>Age</td>
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<td>40.91</td>
<td>41.16</td>
<td>40.85</td>
<td>40.91</td>
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<td>40.91</td>
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<td>±</td>
<td>9.21</td>
<td>9.00</td>
<td>9.90</td>
<td>9.15</td>
<td>9.32</td>
<td>10.10</td>
<td>±9.21</td>
<td>±9.32</td>
<td>±10.10</td>
<td>±9.21</td>
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<tr>
<td>Female</td>
<td>55.26</td>
<td>57.14</td>
<td>60.00</td>
<td>56.52</td>
<td>52.94</td>
<td>51.56</td>
<td>59.09</td>
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Notes: RCC = Retest Control Cohort, TC1 = Training Cohort 1, TC2 = Training Cohort 2, TC3 = Training Cohort 3.

2.2. Study design

Four cohorts were set up for the ReSource project. The 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 pure 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 Figure 1b).

### 2.2.1. Trainings

Each of the three modules of the ReSoUrce program lasts 3 months, begins with a 3-day intensive retreat, includes 13 weekly group sessions of 2h accompanied by experienced teachers, and about 90 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 Kirk and Singer, 2017). Each module has two core exercises, which participants were asked to practice five times a week. Figure 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 trained in 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, benediction and gratitude (Singer and Klimecki, 2014; Vertes et al., 2017). The core exercises include “loving-kindness meditation” and “Affec Dyad”. The loving-kindness meditation 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 trained 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 behaviors. Perspective dyad is also a partner-based exercise during which participants practice inner perspective taking by re-experiencing a recent situation from different perspectives, as well as perspective taking on others by taking the perspective of the dyadic partner. Precisely, the speaker and the listener separately describe a recent situation from various inner perspectives, i.e., they take the perspectives 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 situation.
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 taken 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 seconds “countdown” in which numbers were presented (length of countdown was assigned pseudorandomly). In the “predictable” condition, these numbers accurately represented the
number of seconds remaining before picture onset. In the “unpredictable” condition, numbers were randomly presented, providing no predictive information regarding picture onset (Figure 1c). This resulted in six experimental conditions: ordered-positive, ordered-negative, ordered-neutral, random-positive, random-negative and random-neutral. Condition sequence was random for each participant. Half of the stimuli per valence were assigned randomly to the predictable or non-predictable condition.

Before fMRI acquisition, participants were trained to perform the task with different stimuli than those used during the experiment. Each block began with a 5 s start cue (fixation cross) followed by 3 s instructions informing participants of the forthcoming block type. Following the instructions, stimulus presentation continuously alternated between countdowns (1 s per number; jittered from 2 to 8 numbers) and picture presentation (3 s). Participants responded by using an MRI-compatible response box, using the index and middle finger on the right hand. Each block ended with a 3 s stop cue (fixation cross) followed by a rating period (5 s) in which participants used a continuous scale from none to very much (coded from 0 to 500) indicating 1) how negative to positive they felt (0 = extremely negative, 250 = neutral, 500 = extremely positive) and 2) how nervous (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 Sommerville et al. (2012). The total duration of the experiment was 13 min 30 s.

2.3. Analysis of behavioral measures

The subjective emotional valence and nervousness ratings were analysed for behavioral analyses. Data were analyzed using R software (R Core Team, 2015). Following our hypotheses, three separate linear mixed models (LMMs) (lme4 package (Bates et al., 2015)) analyses were performed for both measures:
Data at baseline (i.e., T0) were entered in an LMM including fixed effects for the Valence (positive, negative, neutral) and Predictability (ordered countdown, random countdown) of the stimuli and random intercepts for participants:

\[ T0 \text{ Rating} = \beta_0 + \beta_1 \text{Valence} + \beta_2 \text{Predictability} + \beta_3 \text{(Valence by Predictability)} + \text{random effect (participant)} \]

In order to assess the specific effect of the modules on emotion processing in the same way as in the fMRI analyses (see below), we computed two new dependent variables for each participant by subtracting average 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 measurements.

\[ \text{Change score} = \beta_0 + \beta_1 \text{retest control}_1 + \beta_2 \text{retest control}_2 + \beta_3 \text{Presence} + \beta_4 \text{Affect}_1 + \beta_5 \text{Affect}_2 + \beta_6 \text{Affect}_3 + \beta_7 \text{Perspective}_1 + \beta_8 \text{Perspective}_2 + \beta_9 \text{Perspective}_3 + \text{random effect (participant)} \]

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 T2), 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:

Ratings = β0 + β1*training + β2*timepoint + β3*(training by timepoint) + random effect (participant)

As an estimate of effect size, for each analysis and each contrast, we provide the models estimates (β). In line with previous studies of the ReSource project (Traweck 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 et al., 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= 2000ms, TE= 27ms; flip angles 77°; 37 axial slices with inner gap tilted ~30° from the bi-commissural plane; FOV = 210 mm; matrix size = 70 x 70; in-plane voxel size = 3 x 3 mm; slice thickness = 3 mm; 405 volumes). High-resolution structural images were acquired with a T1-weighted 3D-MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, TI= 900 ms, flip angle = 9°; 176 sagittal slices; FOV = 256 mm; matrix size = 240 x 256, slice thickness = 1 mm, total acquisition time = 5.10 min). We also acquired B0 field maps using a double-echo gradient-recalled sequence with matching dimensions to the EPI images (TR = 200 ms; TE = 4.49 and 6.95 ms).

2.4.2. fMRI preprocessing

Preprocessing steps were performed by using the SPM12 software package (Welcome Department of Imaging Neuroscience, Institute of Neurology, London, UK), running on Matlab 8.6 (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 co-registered 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 a 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.
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 sequential analyses on the second level to identify: (1) the cerebral networks involved in the task before the training (i.e., at T0); (2) the specific brain plasticity induced by each module; and (3) neural modulation induced by the overall 9-month training.

1) We used a 3 x 2 repeated-measure factorial analysis using GLMflex (http://mrtools.mgh.harvard.edu/) to test the effect of the experimental factors at baseline (i.e., T0). We evaluated the main effect of the Valence, the main effect of the Predictability and the interaction Valence-by-Predictability as well as Valence specific activations (i.e., [negative vs. neutral] and [positive vs. neutral]). The results were thresholded at \( p < 0.001 \) (uncorrected) at the voxel level and corrected for multiple comparisons using cluster extent family-wise error rate (FWE) correction at \( p < 0.05 \) as implemented in the SPM toolbox, which led to an extend threshold \( k > 101 \) voxels.

2) We used the Sandwich Estimator (SwE) method as implemented in the SwE toolbox (http://warwick.ac.uk/tnichols/SwE) (Guillaume et al., 2014) to assess the effects of each module 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 supplementary 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 median 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, 2013), which led to an extended 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.

We tested for the overall effect of the 9-month program with a 2 x 2 factorial design, including the Cohort (TC1 vs TC2 vs. REC) 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 \( [F(2, 5659.7) = 5802.5, p<0.001] \). An 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 ($F(1, 5697.7) = 1.40, p=0.24$) or a Predictability-by-Valence interaction ($F(2, 5697.7) = 1.10, p=0.35$).

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. Behavioral 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 ‘off-task’ 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 ($b = -55.13, z = 2.13, p=0.04$) (Figure 2, Panels a and b). Further tests for the Affect effect controlling for retest control effect were as in 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 increased nervousness from T1 to T3 after Perspective in comparison to both retest control ($b = -72.56$, $z = -2.63$, $p = 0.009$) and Affect ($b = 78.98$, $z = 2.83$, $p = 0.005$) (Figure 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 behavioral changes after the training modules are presented in Figure 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).
Figure 2: Descriptive plots of the change in valence rating in the course of the 9-month training. (a-b) Change in \([-\text{negative} - \text{neutral}]\) ratings. 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 cohort, AFF = Affect, PER = Perspective). To the right of the dashed lines, estimates are averaged across intervention points 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 (0 = extremely negative) to positive (250 = neutral, 500 = extremely positive), for illustrative purposes, panels a and b depict 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 \([-\text{negative} - \text{neutral}]\) \(F(1, 213.26) = 4.17; p = 0.04\) and \([\text{positive} - \text{neutral}]\) subjective valence ratings \(F(1, 211.85) = 16.91; p < 0.0001\). Planned comparisons revealed that the ratings for \([-\text{negative} - \text{neutral}]\) were significantly less negative from T0 to T3 for the TCs \(b = -18.53, z = 26\).
2.57, \( p = 0.01 \)), whereas there was no change for the RCC (\( b = 6.43, \ z = 0.65, \ p = 0.51 \)) (Figure S3, Panel a). In addition, ratings for [positive – neutral] were significantly more positive from T0 to T3 for the TCs (\( b = 22.57, \ z = 4.62, \ p < 0.0001 \)) and significantly less positive for the RCC (\( b = -16.53, \ z = -2.16, \ p = 0.03 \)) from T0 to T3 (Figure S3, Panel b).

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

3.2. fMRI results

3.2.1. fMRI results at baseline

In comparison to neutral stimuli, negative stimuli yielded increased activation in the ventral visual pathway, i.e., in two bilateral clusters encompassing the inferior occipital, temporal and parietal gyri, as well as in the bilateral SMG, the right IFG and in a large cluster including left amygdala, insula and superior temporal gyrus (STG) \( (p_{\text{min-corr}} < 0.001, \ p_{\text{FWE}} < 0.05) \). For exploratory purposes, we also looked at the results with an uncorrected threshold \( (p_{\text{min-corr}} < 0.001, \ k > 10) \). We observed increased activation in the superior and middle prefrontal cortex as well as in the orbitofrontal cortex, the middle insula, the middle and posterior cingulate cortex and in the right amygdala at this lower threshold (Figure 3a, Table 2). Positive stimuli induced increased activation of the ventral visual pathway and in the posterior cingulate cortex/precuneus \( (p_{\text{min-corr}} < 0.001, \ p_{\text{FWE}} < 0.05) \). 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 \( (p_{\text{min-corr}} < 0.001, \ k > 10) \) (Figure 3b, Table 2). We did not observe a modulation of the brain activity depending on the predictability of the stimuli and no interaction of Valence by Predictability.
Table 2. Activation peaks before the training (T0)

<table>
<thead>
<tr>
<th>Lobe Region</th>
<th>BA</th>
<th>k</th>
<th>H</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative &gt; Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>Inferior Occipital / Temporal / Parietal Gyrus*</td>
<td>7/18/19/38/39</td>
<td>172</td>
<td>9</td>
<td>-45</td>
<td>-64</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Inferior Occipital / Temporal / Parietal Gyrus*</td>
<td>7/18/19/38/39</td>
<td>137</td>
<td>0</td>
<td>48</td>
<td>-61</td>
<td>-7</td>
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<td>Parietal</td>
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<td>152</td>
<td>R</td>
<td>60</td>
<td>-22</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>SupraMarginal Gyrus*</td>
<td>40</td>
<td>183</td>
<td>L</td>
<td>-63</td>
<td>-22</td>
<td>29</td>
</tr>
<tr>
<td>Frontal</td>
<td>Inferior Frontal Gyrus (orbital/triangular part)*</td>
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<td>101</td>
<td>R</td>
<td>45</td>
<td>35</td>
<td>5</td>
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<tr>
<td></td>
<td>Inferior Frontal Gyrus (triangular/opercular part)</td>
<td>46</td>
<td>80</td>
<td>R</td>
<td>45</td>
<td>11</td>
<td>26</td>
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<td></td>
<td>Superior/Middle Frontal Gyrus</td>
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<td>47</td>
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<tr>
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<td>R</td>
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<td>47</td>
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<tr>
<td></td>
<td>Orbitofrontal cortex</td>
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<td>20</td>
<td>L</td>
<td>-27</td>
<td>-15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Superior/Middle Frontal Gyrus (opercular/triangular part)</td>
<td>9</td>
<td>64</td>
<td>R</td>
<td>-2</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Orbitofrontal cortex</td>
<td>11</td>
<td>12</td>
<td>R</td>
<td>27</td>
<td>52</td>
<td>19</td>
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<tr>
<td></td>
<td>Insular cortex</td>
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<td>15</td>
<td>L</td>
<td>-32</td>
<td>7</td>
<td>1</td>
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<tr>
<td></td>
<td>Insular cortex</td>
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<td>22</td>
<td>R</td>
<td>28</td>
<td>-2</td>
<td>7</td>
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<tr>
<td></td>
<td>Subcortical grey nuclei</td>
<td>Thalamus*</td>
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<td>108</td>
<td>R</td>
<td>6</td>
<td>28</td>
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<tr>
<td></td>
<td></td>
<td>Hippocampus/Amygdala</td>
<td>34</td>
<td>15</td>
<td>R</td>
<td>21</td>
<td>-4</td>
</tr>
<tr>
<td>Region</td>
<td>Brodmann Area</td>
<td>Hemisphere</td>
<td>MNI Coordinates</td>
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<td>z-Value</td>
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<tr>
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<td>-45</td>
<td>17</td>
<td>4.00</td>
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<tr>
<td>Superior Frontal Gyrus (opercular part)</td>
<td>47</td>
<td>L</td>
<td>54</td>
<td>-34</td>
<td>20</td>
<td>3.65</td>
<td></td>
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*pFWEc < 0.05 cluster corrected

BA = Brodmann Area; H = Hemisphere; R = Right; L = Left; k = number of voxels/cluster
Figure 3: Cerebral responses to emotional scenes at baseline (T0). Brain activation resulting from the contrast [negative > neutral] are represented in red-yellow scale (a) and those of the contrast [positive > neutral] in blue-green scale (b). Findings are thresholded at $p_{\text{unc}}<0.001$, $k>10$ and clusters that survived correction for multiple comparisons ($p_{\text{FWE}}<0.05$) are surrounded with a white line.

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 ($p_{\text{unc}}<0.001$, $p_{\text{FWE}}<0.05$). To test for wider network effects, we also investigated non-corrected trends on $p_{\text{unc}}<0.001$ 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 gyri and in the bilateral occipital cortex (cuneus) ($p_{\text{unc}}<0.001$, $k>10$, Figure 3, Panel a) and b); Table 3). There was no significant change in brain activity after Affect training for positive vs. neutral stimuli. Training Perspective did not lead to significant neurofunctional modulation for either [negative vs. neutral] and [positive vs. neutral] contrasts. There was no
significant difference between training Affect and Perspective, between Presence and retest control, as well as between Presence and Affect (T1) for both contrasts.

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

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Region</th>
<th>BA</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z</th>
</tr>
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<td>45</td>
<td>-40</td>
<td>41</td>
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<td>Inferior Temporal Gyrus</td>
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<td>-43</td>
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<td>3.86</td>
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<td>-52</td>
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<td>Cuneus/Lingual Gyrus</td>
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<td>12</td>
<td>-76</td>
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<td>3.44</td>
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<td>Frontal</td>
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<td>44</td>
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<td>23</td>
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<td>20</td>
<td>8</td>
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<td>44</td>
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<tr>
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<td>-38</td>
<td>14</td>
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<td>33</td>
<td>15</td>
<td>47</td>
<td>11</td>
<td>3.42</td>
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*pFWEc < 0.05 cluster corrected

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

Figure 4: Modulation of the cerebral activity after Affect module training. Brain areas showing increased activity for the contrast [negative > neutral] after the Affect module in comparison to retest control. Findings are thresholded at *puncor < 0.001, k>10; cluster that survived *pFWEc <0.05 correction are surrounded by a white circle.
3.2.3. Neurofunctional change after the overall 9-month training

The contrast \([\text{positive} > \text{neutral}]\) revealed a significant Training-by-Timepoint interaction within a large cluster encompassing the left lingual gyrus and the posterior cingulate cortex \((p_{\text{unc(voxel)}} < 0.001; p_{\text{FWE(cluster)}} < 0.05)\). For exploratory purposes, we investigated changes in brain activation after the training with non-corrected threshold \((p_{\text{unc(voxel)}} < 0.001; k>10)\). We additionally found increased activation within the bilateral superior temporal cortices (angular gyrus), the posterior cingulate cortex, the thalamus and the brainstem in the TCs vs. RCC (Figure S4, Table S9). The contrast \([\text{negative} \text{ vs. neutral}]\) did not show suprathreshold 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 brain regions, the amygdala and the insular cortex in particular. Notably, we showed that the various 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 behavioral 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, was 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. Ventral visual cortex responses to emotional stimuli might be reinforced through feedback connections from the amygdala (Lang et al., 1998; Phan et al., 2002; Vuilleumier, 2002, 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 (Kong et al., 2016; LaBar, 1996; Lüdtke et al., 2012; Phan et al., 2002; Pruessel et al., 2019) or empathy (Ridler et al., 2012; Kanske et al., 2015; Lamm et al., 2011; Singer et al., 2006). The processing of positive vs. neutral stimuli further involved midline cortical structures (midline PFC, PCC), a set of brain areas that are known to be involved in motivational 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 behavioral 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; Yang 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; Keil et al., 2016; Lauter 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 behavioral 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; Keil et al., 2016). 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.
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 in the Affect vs. retest control (averaged from T0 to T3). This significant improvement in behavioral 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 data 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 module 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 state were congruent with 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 doro-lateral PFC in children predicted lower 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 & Klimesch, 2014), i.e., an arousal 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 and colleagues (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; Lounig 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 or compassion and concern. Of note, the Affect module also included daily 10-minute 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 seems to be driven by the change after the Perspective training module (Figure 2, Panels c and d and Figure S3, Panel b). The overall increase of positive ratings after the 9-month 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 to 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 one's own and others' thoughts and beliefs. The training of socio-cognitive skills could thus allow people to better understand and share positive emotions.

Although we found significant changes in subjective affect rating and in brain activity after the Affect and Perspective modules in comparison to re-test, we cannot conclude as to the specificity of the observed effects. Indeed, at both behavioral 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 ratings over the 9-month 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 rate 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 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 those 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 those 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, it is difficult to isolate the specific effect of each exercise on emotional reactivity. However, in comparison to previous studies focusing on 8-week programs such as MBSR, MBCT and compassion-based interventions (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 of 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 in 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.
2. Acknowledgments

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3. 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.

Author contributions

Pauline Favre: Methodology, Formal analysis, Writing – Original Draft, Visualization. Philipp Kanske: Conceptualization, Investigation, Writing – Review and Editing, Supervision.

Comment [AU1]: CE: Please check Author contribution coming twice.
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.

4. Competing interests
The authors declare no competing financial interest.

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