BEHAVIORAL NEUROSCIENCE

Structural plasticity of the social brain: Differential change after socio-affective and cognitive mental training

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Although neuroscientific research has revealed experience-dependent brain changes across the life span in sensory, motor, and cognitive domains, plasticity relating to social capacities remains largely unknown. To investigate whether the targeted mental training of different cognitive and social skills can induce specific changes in brain morphology, we collected longitudinal magnetic resonance imaging (MRI) data throughout a 9-month mental training intervention from a large sample of adults between 20 and 55 years of age. By means of various daily mental exercises and weekly instructed group sessions, training protocols specifically addressed three functional domains: (i) mindfulness-based attention and interoception, (ii) socio-affective skills (compassion, dealing with difficult emotions, and prosocial motivation), and (iii) socio-cognitive skills (cognitive perspective-taking on self and others and metacognition). MRI-based cortical thickness analyses, contrasting the different training modules against each other, indicated spatially diverging changes in cortical morphology. Training of present-moment focused attention mostly led to increases in cortical thickness in prefrontal regions, socio-affective training induced plasticity in frontoinsular regions, and socio-cognitive training included change in inferior frontal and lateral temporal cortices. Module-specific structural brain changes correlated with training-induced behavioral improvements in the same individuals in domain-specific measures of attention, compassion, and cognitive perspective-taking, respectively, and overlapped with task-relevant functional networks. Our longitudinal findings indicate structural plasticity in well-known socio-affective and socio-cognitive brain networks in healthy adults based on targeted short daily mental practices. These findings could promote the development of evidence-based mental training interventions in clinical, educational, and corporate settings aimed at cultivating social intelligence, prosocial motivation, and cooperation.

INTRODUCTION

With growing globalization, interconnectedness, and complexity of our societies, "soft skills" have become increasingly important. Social competences, such as empathy, compassion, and taking the perspective of another person, allow for a better understanding of others' feelings and different beliefs and are crucial for successful cooperation. Previous research has shown a reciprocal relationship between social abilities, mental health (1, 2), and altruistic behavior (3), suggesting that cultivating these capacities may have therapeutic and social benefits. Despite extensive research on the neural mechanisms underlying social skills such as empathy, compassion, and cognitive perspective-taking [Theory of Mind (ToM)] in healthy and clinical populations (4–24), it remains unknown whether training these capacities can induce structural brain changes. Plasticity research, despite its tradition and relevance to neuroscience, has, so far, mainly focused on learning-dependent brain reorganization of sensory, motor, and memory systems in animals and humans (25–33).

Recent mental training and mindfulness research in humans (34–38) has begun to address changes in gray matter volume after the training of higher-level skills, such as present-moment attention and mindfulness based on contemplative practices (38–41). However, most studies have been cross-sectional, focusing on meditation practitioners and not directly assessing training-related plasticity within training-naïve subjects (42). The few published longitudinal training studies on structural plasticity to date have mainly assessed the effects of cultivating a rather broad range of mindfulness-related capacities, including attention, acceptance, and interoceptive awareness (39–41). Notably, samples in these studies were relatively small, and studies often lacked active control groups; furthermore, testing intervals were short, providing neither generalizable and robust estimates of brain change nor information about the effects of different types of mental practices on plasticity (38–41).

An increasing body of social cognitive neuroscience research suggests that we can distinguish at least two major routes of interpersonal understanding: a socio-affective route encompassing social emotions and motivation, such as empathy [the sharing of affect with others (4)] and compassion [the concern for others and motivation to benefit the welfare of another (5)]. Conversely, there is also evidence for socio-cognitive mechanisms that enable an individual to understand others' beliefs and intentions [also referred to as ToM, mentalizing, or cognitive perspective-taking (6, 7)]. Functional neuroimaging supported this distinction by revealing dissociable brain substrates underlying these processes. For socio-affective processing, studies have consistently identified a network, including limbic/paralimbic cortical areas, such as the anterior insula (AI) and anterior cingulate cortex (ACC) for empathy (8, 9, 20, 21), together with lateral areas involved in emotion regulation, such as the dorsolateral prefrontal cortex (dlPFC) and supramarginal gyrus (SMG) (19, 24, 43). Compassion further involves orbitofrontal cortices and ACC, as well as subcortical structures such as the ventral striatum and ventral tegmental area (18, 22, 23). In contrast, cognitive perspective-taking or ToM is primarily supported by a network that includes the medial PFC, temporoparietal junction

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(TPJ), superior temporal gyrus/superior temporal sulcus (STS), and posterior midline regions such as the precuneus (7–17). Individual differences in empathizing and ToM competences have been found to show only a little correlation and to instead differentially relate to the function and structure of these networks (5, 11–13). Despite evidence of two dissociable functional networks supporting our capacity not only to empathize with and have compassion for others but also to infer their thoughts and beliefs, it is unknown whether these two functions can be differentially targeted by mental training and whether this intervention would result in changes in brain structure.

To study structural plasticity of attentional and social capacities in adulthood, we designed a secular mental training program that lasted over 9 months—the ReSource Project (44). The main goal was to investigate the effects of three different mental training modules (Presence, Affect, and Perspective; each lasting 3 months) on magnetic resonance imaging (MRI)–based markers of cortical morphology and to relate those to behavioral indices. The first module (Presence) focused on cultivating present-moment attention and interoception. This module resembled well-known mindfulness interventions (37, 45). On the basis of previous research, we expected increases in thickness in both attention-related networks in PFC, ACC, and parietal cortices (46, 47), as well as interoceptive regions, such as AI (48, 49). With respect to the two social intersubjective training modules (Affect and Perspective), we made predictions in line with the abovementioned literature showing dissociable networks underlying socio-emotional processes, such as empathy and compassion (8, 9, 18–23), and ToM (7–17). We expected that the socio-cognitive Perspective Module would result in changes in ToM networks, including the medial PFC, ventrolateral PFC, precuneus, temporal neocortices, and TPJ (7–17). We expected that the Affect Module would primarily target the structure of regions implicated in socio-emotional processing, such as AI, ACC, and orbital frontal regions, as well as the SMG and lateral PFC, the latter playing an important role in emotion regulation (8, 9, 18–24). Conversely, we expected that the socio-cognitive Perspective Module would result in changes in ToM networks, including the medial PFC, ventrolateral PFC, precuneus, temporal neocortices, and TPJ (7–17). Module-specific changes in morphology were expected to correlate with training-related behavioral changes in the same individuals, assessed via markers matched to the main functions trained in a module [that is, attention for Presence, compassion for Affect, and ToM for Perspective (8, 44, 47, 50)].

For details on cohort selection, training content, behavioral phenotyping, image processing, and analysis, see the Supplementary Materials. Briefly, two randomly assigned training cohorts (TC1 and TC2) underwent three distinct 3-month modules with weekly instructed group sessions at the testing sites and daily exercises completed via smartphone and internet platforms (Fig. 1, A and B, and table S1). Both cohorts underwent these three modules in alternating order (TC1: Presence→Affect→Perspective; TC2: Presence→Perspective→Affect), each serving as "active" control group for the other. In addition, we studied a matched retest control cohort (RCC) that did not undergo any training but followed the same measures as the training cohorts. Last, a third training cohort (TC3) completed only the Affect Module for 3 months, specifically to be compared to the first 3-month Presence training module.

Because the Presence Module fostered present-moment attention and interoception as abilities that may also support further practices (51), it was administered first in line with the sequencing of other contemplative traditions and secular mindfulness programs (37, 45). We

subsequently opted for a crossover design that trained Affect and Perspective Modules in different order in our two closely matched training cohorts (TC1 and TC2), allowing for direct comparison between both social capacity trainings while accounting for sequence effects. To test for the effects of the Presence Module, we added another control group (TC3) undergoing a 3-month Affect training (TC3) without a preceding Presence Module. This design enabled the assessment of specific effects of a module against the others, both within and between cohorts. Notably, it offered control over unspecific effects associated with engaging in group training, teacher effects, and test-retest.

Whereas the Presence Module aimed at calming and stabilizing the mind using classical meditative practices, Affect and Perspective Modules targeted intersubjective capacities by training socio-affective or socio-cognitive skills, using classical meditation–based and dyadic interpersonal exercises. The latter dyads were practiced with another partner for 10 min daily via a smartphone application or in person during the weekly group sessions [for details, see Singer et al. (44) and Kok and Singer (52)].

Participants were tested at baseline (T_0) and after each 3-month module (T_1, T_2, and T_3) using 3-T MRI and behavioral measures. Moreover, although all participants were scanned on the same MRI platform in Leipzig, participants were recruited and trained at two different sites (Berlin and Leipzig), with site-based subcohorts being matched for gender, age, education, and several socio-emotional trait markers (44). Assessing these subcohorts separately allowed for the testing of consistency across sites.

Extensive quality control by two independent raters (S.L.V. and B.C.B.) corrected for segmentation faults and excluded cases with MRI artifacts by consensus (table S1). Surface extractions underwent manual corrections (11, 53, 54). At the time of study initialization (2013), emerging techniques to prospectively control for so-called micromotion in structural MRI data were not yet fully established (55–58). However, by means of a parallel-acquired resting-state functional MRI (fMRI) acquisition in the same session, we assessed overall head motion as a proxy for the tendency of a subject to move in the scanner (59, 60) and evaluated whether the effects were consistent after regressing out this surrogate marker. For details on quality control, sample selection, and analysis, see Materials and Methods. Longitudinal changes in the brain structure were assessed using mixed-effects analysis of MRI-based cortical thickness (61), and data were smoothed at 20-mm full width at half maximum (FWHM). Results were corrected for multiple comparisons using random field theory (see Materials and Methods for details).

To assess structural change following each of the three training modules and to test for behavioral and functional specificities, we applied three canonical analyses: (i) We compared thickness change of each training module against the other modules and RCC; (ii) correlated individual differences in training-related thickness change with training-related behavioral change in markers of attention (Presence), compassion (Affect), and ToM (Perspective); (iii) and assessed the overlap between functional brain activation maps measured in these tasks at baseline and the observed structural change after training.

RESULTS

By investigating changes over the 9-month period of testing in the RCC, we observed only decreases in cortical thickness in lateral frontal regions [family-wise error (FWE) <0.025] (Fig. 1C and table S2), consistent with findings showing aging-related cortical atrophy (62, 63). Conversely,
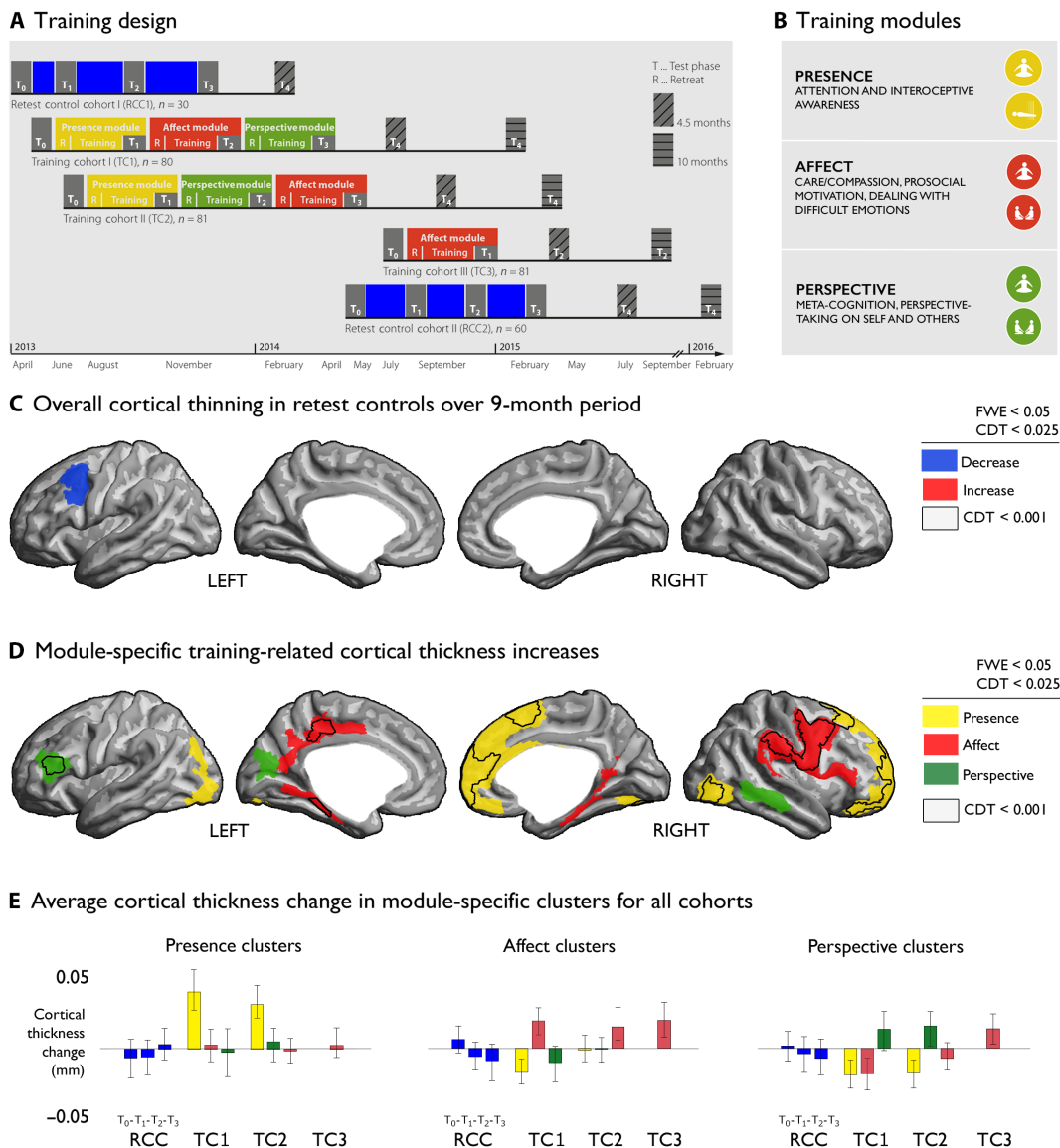
Fig. 1. Training design and overall change. (**A**) Training design of the 9-month ReSource intervention. After baseline testing (T_0), participants trained Presence followed by Affect and Perspective (TC1) or Presence followed by Perspective and Affect (TC2). An RCC not undergoing any training was also studied. A further Affect cohort (TC3) was included to specifically compare Affect to Presence training in comparable testing intervals. Note that the full design of the ReSource Project also included follow-up measurements (T_4), which were not assessed in the current study. (**B**) Training modules and core daily practices of each module. Details can be found in Singer et al. (44) and Materials and Methods. (**C**) Thinning in RCC ($T_0{\rightarrow}T_1$, $n = 72$; $T_1{\rightarrow}T_2$, $n = 65$; $T_2{\rightarrow}T_3$, $n = 68$) over the full duration of the ReSource study. No significant increases were observed in these participants. (**D**) Differential structural increases in the three training modules (Presence, $n = 132$; Perspective, $n = 120$; Affect, $n = 193$), contrasted against each other across time points ($T_0{\rightarrow}T_1$, $T_1{\rightarrow}T_2$, and $T_2{\rightarrow}T_3$) and in all training groups (TC1, TC2, and TC3). Structural change in Presence (yellow; TC1 and TC2, $T_0{\rightarrow}T_1$), Affect (red; TC3, $T_0{\rightarrow}T_1$; TC1, $T_1{\rightarrow}T_2$; TC2, $T_2{\rightarrow}T_3$), and Perspective (green; TC2, $T_1{\rightarrow}T_2$; TC1, $T_2{\rightarrow}T_3$). Each training module was contrasted against the average effect of the other two modules, serving as an active control condition. The findings were corrected for multiple comparisons using random field theory for nonisotropic images (105) controlling the probability of reporting an FWE of <0.05 [cluster-defining threshold (CDT), $P = 0.025$]. The findings significant at an FWE of <0.05 with a conservative CDT ($P = 0.001$) are highlighted with black outlines. (**E**) Bar charts of mean change ± 95% confidence interval of the combined clusters of relative increase in each module, plotted per cohort. The colors represent the content of the training or RCC (blue).

examining both training cohorts (TC1 and TC2) over the same 9 months revealed increases in thickness in right lateral and medial frontal regions (FWE <0.001), together with focal decreases in the right lingual gyrus (FWE <0.025) (fig. S1 and table S3).

To assess changes specific to the different mental practices, we compared longitudinal thickness changes between the training modules (Fig. 1). For Presence (targeting interoception and attention), we

observed thickness increases in the right PFC extending to ACC (FWE <0.001) and in bilateral occipital regions extending to inferior temporal cortices [FWE <0.05 (left) and <0.001 (right)] in both training cohorts relative to Affect and Perspective Modules (Fig. 1D and table S2). These findings were consistent across training cohorts (Fig. 1E), clusters (fig. S2), sites (that is, Berlin and Leipzig; fig. S3 and table S2), and when comparing TC1 and TC2 undergoing Presence to RCC

(fig. S4 and table S4). Affect (socio-affective training) induced increases in a cluster extending from the right SMG to the insular-opercular regions and dlPFC (FWE <0.001), left mid/posterior cingulate (FWE <0.001), and bilateral parahippocampal areas [FWE <0.005 (left) and <0.025 (right)] (Fig. 1D and table S2). Patterns were again consistent across cohorts (Fig. 1E), clusters (fig. S2), and sites (fig. S3). A similar pattern was observed when testing Affect versus Perspective within-subjects only (TC1 and TC2; fig. S5 and table S5). Last, Perspective (socio-cognitive training) resulted in increases in thickness of the left ventrolateral PFC (FWE <0.05), left occipital regions (FWE < 0.025), and right middle temporal gyrus (FWE <0.05) (Fig. 1D and table S2). These findings were again consistent in both cohorts (Fig. 1E), clusters (fig. S2), and when testing Perspective versus Affect within-subjects only (fig. S5 and table S5).

In addition to assessing differential plasticity induced by the three modules, we were also interested in how changes would relate to improvements in targeted behavioral capacities. We developed and adapted behavioral tasks assessing components of attention (47), as well as compassion and ToM (8), each being a target outcome of one of the three training modules (Fig. 1B). In a related publication (50), we showed that the Perspective Module increased performance in the interactive video task assessing ToM, whereas Affect led to increased compassion ratings after watching neutral and emotionally distressing videos. Moreover, the Presence Module was associated with improvements in attention (50). Here, we tested whether individual differences in training-related cortical thickness increases correlated with those in attention (after Presence), compassion (after Affect), and ToM (after Perspective) in the same individuals. Our analyses revealed that improvements in attentional scores during Presence related to increased thickness in left middle temporal regions ($T_0 \to T_1$; TC1, $r = 0.46$; TC2, $r = 0.19$; Fig. 2A and table S6). Conversely, compassion increases after Affect training were associated with thickness increases of the right insula extending to the temporal pole, with findings consistent across all cohorts undergoing Affect training [TC1, $T_1 \to T_2$ ($r = 0.37$); TC2, $T_2 \to T_3$ ($r = 0.28$); TC3, $T_0 \to T_1$ ($r = 0.31$); Fig. 2A and table S6]. Last, enhanced ToM performance after Perspective training was related to increased thickness in left parietal regions [TC1, $T_2 \to T_3$ ($r = 0.32$); TC2, $T_1 \to T_2$ ($r = 0.32$); Fig. 2A and table S6] and right TPJ [TC1, $T_1 \to T_2$ ($r = 0.44$); TC2, $T_2 \to T_3$ ($r = 0.24$); Fig. 2A and table S6], with findings again being consistent across cohorts.

To finally explore whether areas showing training-associated thickness increases that were related to behavioral performance overlapped with postulated functional networks, we overlaid a significant structural change with fMRI activations at baseline in the same participants during tasks probing attention, socio-affective, or socio-cognitive processing (8, 47). Functional networks overlapped with module-specific structure-behavior modulations: Compassion-related AI increases overlapped with activations during the socio-affective task, whereas ToM performance–related increases in TPJ thickness overlapped with functional activations observed during the socio-cognitive task (Fig. 2B). However, attention-related thickness increases did not overlap with functional activation during the attention task at baseline.

DISCUSSION

MRI and behavioral results derived from a 9-month longitudinal mental training study, the ReSource Project (44), provide evidence for structural plasticity of the social brain in healthy adults between 20 and 55 years of age. We demonstrated a training-specific change

in cortical morphology after three different mental training modules focusing on improving mindfulness-based attention (Presence), socio-affective skills (Affect), and socio-cognitive capacities (Perspective). Notably, module-specific thickness increases correlated with individual improvements in attention, compassion, and ToM in respective behavioral markers after training and, in part, overlapped with functional networks obtained from tasks targeting module-specific functions at baseline before training.

After 3 months of Presence training, our two independently matched cohorts (that is, TC1 and TC2) showed increases in thickness in the anterior PFC extending to ACC relative to RCC. This finding is in accordance with meta-analytical synthesis of cross-sectional studies reporting altered PFC/ACC morphology in expert mindfulness meditators relative to controls (42, 64). To capture attention-related increases after Presence training in the ReSource Project, a measure of executive attention/conflict resolution was selected (47, 50). Consistent with these findings, we observed improved attention after Presence training. However, significant correlations between training-related thickness changes and attentional improvements did not lie within the functional network classically linked to executive attention, including the lateral PFC and ACC (47, 65), but rather in inferior temporal regions. Arguably, the applied task may not have tapped into the full content of the Presence Module, which also encompassed interoception and metacognitive awareness (44). Monitoring and meta-awareness–related processing could be in line with thickening in the medial PFC, a region suggested by cross-sectional studies to participate in these functions (66–68).

Our results revealed evidence that two further mental training modules focusing on socio-affective and socio-cognitive capacities induced structural plasticity in nonoverlapping brain networks. A priori, the Affect Module was expected to result in changes primarily in affect-relevant cortices, such as AI, midcingulate, and orbital frontal regions, as well as the subgenual ACC, SMG, and dlPFC (8, 9, 18–24). For Perspective, we primarily expected changes in ToM networks including the medial PFC, ventrolateral PFC, precuneus, temporal neocortices, and TPJ (7–17). Contrary to mindfulness-based Presence training, Affect training resulted in structural increases in regions implicated in empathy and emotion regulation (8, 9, 18–24, 43). Notably, changes following Affect overlapped partially with functional activations associated with empathy and compassion at baseline (8). Affect training–related right anterior to mid-insula thickening was associated with enhanced compassion ratings after training. This supports a role of insular cortex in representing and integrating interoceptive and affective signals into feeling states (21, 48) and for social emotions such as empathy (21, 69) and compassion (18, 70). By comparing Affect-only training (in TC3) with the 3-month Presence module in TC1 and TC2, we observed increases in SMG and sensorimotor regions extending to the insular cortex in the former, whereas TC1 and TC2 showed medial PFC thickening after Presence. This raises the possibility to target socio-affective functions without prior training in stabilizing the mind, which is to be addressed in future work.

In contrast to Affect training, Perspective aimed at improving metacognitive skills and perspective-taking on one's own thoughts, aspects of the self, and the mental states of others (ToM). Relative to the other modules, it resulted in increased thickness of the middle temporal gyrus, a region reliably associated with ToM (7–10), and left ventrolateral PFC. The latter has been related to self-perspective inhibition, an executive control process supporting the reduction of interference arising in ToM tasks when one's own perspective differs
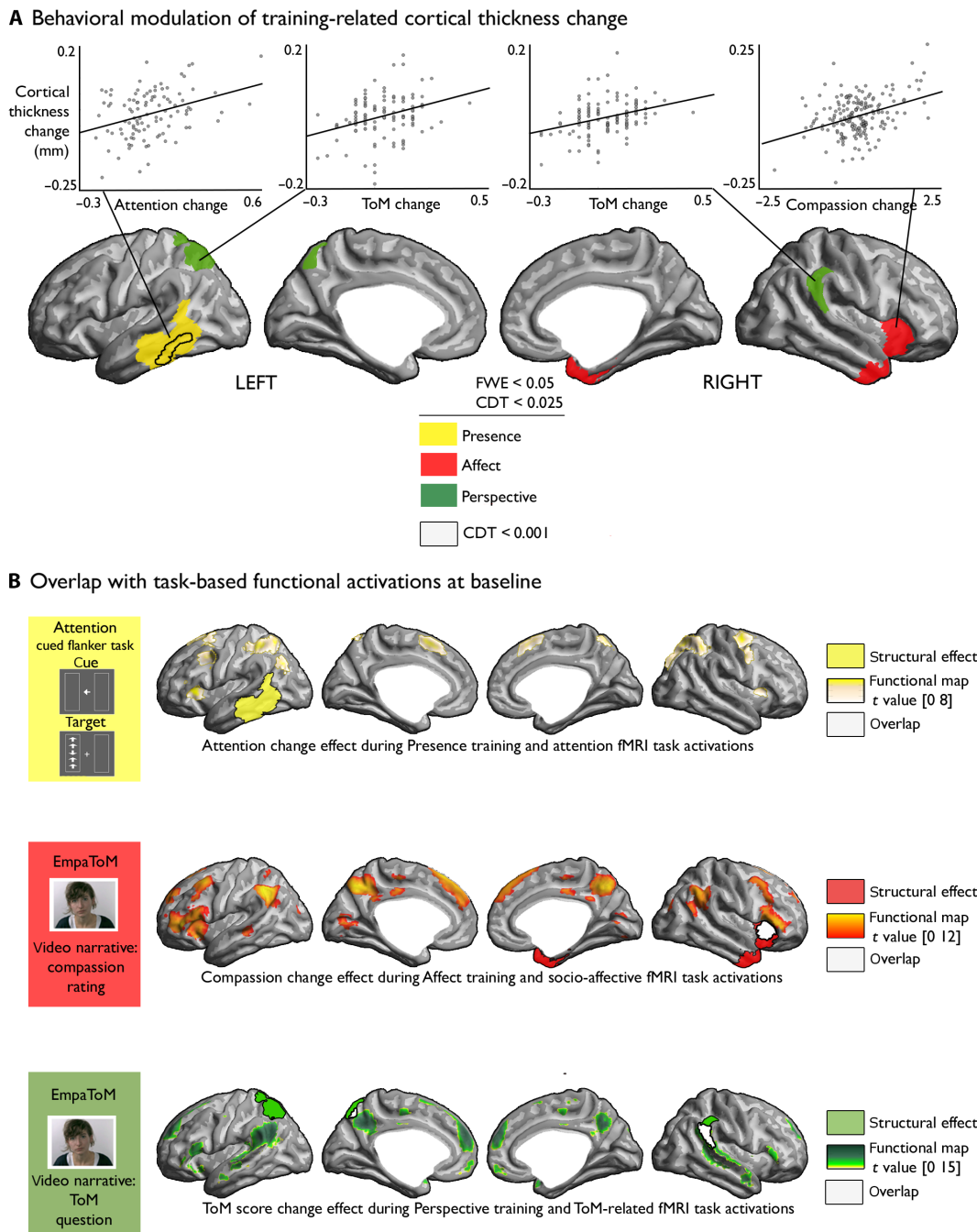
Fig. 2. Behavioral modulation of brain change. (**A**) Positive modulation of brain change by increases in (i) attentional performance assessed in the cued flanker task (47) after Presence (n = 102) (yellow; TC1, T$_0$→T$_1$; TC2, T$_0$→T$_1$), (ii) compassion ratings (8) after Affect (n = 184) (red; TC3, T$_0$→T$_1$; TC1, T$_1$→T$_2$; TC2, T$_2$→T$_3$), and (iii) ToM accuracy (8) after Perspective (n = 115) (green; TC2, T$_1$→T$_2$; TC1, T$_2$→T$_3$). Scatters visualize the relation between average change in significant clusters and individual change in the respective behavioral measure. (**B**) Findings in (A) superimposed on activation maps from fMRI studies using baseline data from the current sample (8, 47), illustrating overlap with networks involved in attention, socio-affective processing, and ToM. For details on statistical thresholds, see Fig. 1.

from that of another person and needs to be inhibited (71). Changes observed in Perspective partially overlapped with functional activation when the participants performed a ToM task at baseline (8). However, no thickness increases were found in the dorsomedial PFC and precuneus, regions a priori associated with ToM. Notably, thickness increases in the posterior parietal cortex and TPJ correlated with

individual differences in ToM performance improvements after training and may reflect the implication of both regions in cognitive perspective-taking processes (8–10, 17, 72). Although we observed cortical thickness increases following Perspective relative to the other modules, we acknowledge that unlike the direct comparison of the 3-month Affect and Presence Modules, we could not test directly for

specific effects of the 3-month Perspective training. For practical reasons, we could not include another active training cohort that focused only on perspective-taking in the first 3 months.

In addition to the reliability of effects across cohorts and analyses, the findings were largely consistent across both subcohorts from Berlin and Leipzig. Notably, however, training-related change (Fig. 1) did not show close spatial correspondence to thickness correlations with behavioral improvements (Fig. 2). Each module aimed at cultivating broader categories of mindful attention, socio-affective, and socio-cognitive processes but not a specific function per se. This might have possibly resulted in a different pattern of average change as compared to investigating the brain areas underlying specific core functions, such as ToM or compassion. Although STS or ventrolateral PFC may have a more general role in socio-cognitive processing, TPJ may be specifically sensitive to mentalizing abilities, as measured in the present ToM task (8). This view would be in line with the hypothesis of a specific role of TPJ for false-belief attribution (15, 16). Similarly, although Affect-related thickness increases in parietal and frontal networks might reflect general enhancement in emotion regulation, insular morphology may be particularly sensitive in capturing individual differences in social emotions, such as empathy and compassion (8, 21, 73).

Training-related changes may not always follow a linear trajectory (28, 74–76), and morphological changes have been reported to consolidate following an initial increase. This argument may be supported by our results, as we found overall training-induced increases in PFC regions, mainly driven by change in the first 3 months. In humans, PFC is central to high-level cognition (77) and social cognition, in particular (8–10, 17, 72, 78), and is likely targeted by all three modules. This might also explain why we did not find a priori predicted increases in medial PFC (for Perspective) and ACC and orbitofrontal regions (for Affect) relative to Presence (ending at T_1), as these regions support functions already targeted in Presence. Post hoc analyses referring to potential sequence effects of Presence on the following modules (see the Supplementary Materials) suggest that initial changes in PFC after Presence modulated changes in subsequent Perspective Modules. Possibly, participants learned functions associated with increases in frontal regions during Presence training that are also needed for perspective-taking. Consolidation processes secondary to the continued practice and increased task skill (74) could also be the cause of observed decreases in cortical thickness in the training groups compared to RCC. Although we had no a priori hypothesis for learning-dependent decreases of gray matter, cortical thinning may also play a role in learning (64, 79, 80), possibly through usage-dependent selective elimination of synapses (81, 82).

Because plasticity research based on this high-level mental training can only be conducted in living humans with noninvasive neuroimaging, we can merely speculate about the neurobiological mechanisms driving the observed structural changes. Learning-induced plasticity might involve synaptic remodeling and changes in neuronal morphology (27, 83), as well as non-neuronal processes such as angiogenesis and divisions of astrocytes and oligodendrocyte progenitor cells (84). Because the focus of the current study was on the thickness of the cortical mantle, further research should assess subcortical regions using methods developed to probe whole-brain gray matter (85) and white matter (86) changes.

In conclusion, our findings of structural plasticity in healthy adults in faculties relevant to social intelligence and social interactions suggest that the type of mental training matters. Depending on whether participants' daily practice focused on cultivating socio-emotional capacities (compassion and prosocial motivation) or socio-cognitive skills (putting oneself into the shoes of another person) gray matter increased selectively in areas supporting these functions. Our findings suggest a potential biological basis for how mindfulness and different aspects of social intelligence could be nurtured. Research will be needed to evaluate the utility of training in individuals suffering from deficits in social cognition, such as autism or psychopathy. In addition, it should be investigated whether social cognitive training can contribute to an increase in cooperation and well-being in corporate settings. In the context of education, it may be interesting to evaluate the potential of these techniques to promote children's soft skills and social intelligence.

MATERIALS AND METHODS
Experimental design
Participants
A total of 332 healthy adults (197 women, mean ± SD = 40.7 ± 9.2 years, 20 to 55 years), recruited in 2012/2013 and 2013/2014, participated in the study. More than 95% of our sample was Caucasian. Participant eligibility was determined through a multistage procedure that involved several screening and mental health questionnaires, together with a phone interview [for details, see the study of Singer et al. (44)]. Subsequently, a face-to-face mental health diagnostic interview with a trained clinical psychologist was scheduled. The interview included a computer-assisted German version of the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I DIA-X) (87) and a personal interview for Axis II disorders (SCID-II) (88, 89). Participants were excluded if they fulfilled the criteria for (i) an Axis I disorder within the past 2 years and (ii) schizophrenia, psychotic disorders, bipolar disorder, substance dependency, or an Axis II disorder at any time in their lives. No participant had a history of neurological disorders or head trauma, based on an in-house self-report questionnaire used to screen all volunteers before taking part in imaging investigations. Participants furthermore underwent a diagnostic radiological evaluation to rule out the presence of mass lesions (for example, tumors and vascular malformations). All participants gave written and informed consent, and the study was approved by the Research Ethics Committees of the University of Leipzig (376/12-ff) and Humboldt University of Berlin (2013-02, 2013-29, and 2014-10). The study was registered at ClinicalTrials.gov under the title, "Plasticity of the Compassionate Brain" (NCT01833104). For details on recruitment and sample selection, see Singer et al. (44).
Study design
Our study focused on two training groups, TC1 (n = 80 at enrollment) and TC2 (n = 81), as well as an RCC that was measured partly before (n = 30) and partly after (n = 60) measurement of TC1 and TC2. TC3 (n = 81) underwent a 3-month Affect Module only and was included as an active control for the Presence module. Participants were selected from a larger pool of potential volunteers by bootstrapping without replacement, creating cohorts not differing significantly with respect to several demographic and self-report traits. The total training duration of TC1 and TC2 was 39 weeks (~9 months), which was divided into three modules [Presence, Affect, and Perspective (see below for details)], each lasting for 13 weeks (Fig. 1). TC3 only participated in one 13-week Affect training. Our main cohorts of interest, TC1 and TC2, underwent Affect and Perspective Modules in different order to act as active control cohorts for each other. Specifically, TC1 underwent "Presence→Affect→Perspective," whereas TC2 underwent

"Presence→Perspective→Affect." TC1, TC2, and RCC underwent four testing phases. The baseline testing phase is called T_0; testing phases at the end of the xth module are called T_x (that is, T_1, T_2, and T_3). In RCC, testing was carried out at similarly spaced intervals. The study had a slightly time-shifted design, where different groups started at different time points to simultaneously accommodate scanner and teacher availability. Because we focused on training-related effects, we did not include analysis of a follow-up measurement T_4 that was carried out 4 or 10 months after the official training had ended. For details on training and practice setup, timeline, and measures, see Singer *et al.* (*44*).

Training modules

Each module started off with a 3-day intensive retreat, followed by weekly group sessions with the teachers and daily home practice facilitated by a custom-made internet platform and smartphone applications providing (i) audio streams for guided meditations and (ii) an interface for dyadic exercises (Fig. 1) (*44*). During the retreat, participants were introduced to topics and corresponding core exercises of the upcoming module. Training during the subsequent 8 weeks included weekly 2-hour-long sessions with teachers that included discussion of training challenges and effects, practice of the core exercises, and introduction to new contemplative practices. The last 5 weeks of each module were used to consolidate previous topics, with no new topics being introduced.

Presence Module. Core exercises, practiced repeatedly during the retreat, in the weekly sessions, and at home (instruction was to practice at least five times per week), were Breathing Meditation and Body Scan (*37*). The basic instruction for Breathing Meditation was to focus attention on sensations of breathing and to refocus attention whenever it wandered. The Body Scan involved focusing on various parts of the body in a systematic fashion (for example, from toes to head) while paying close attention to sensations occurring in these body parts. Additional exercises of Presence, also practiced during the retreat and weekly sessions, were walking meditation, meditations on vision, sound, and taste, as well as an open-presence meditation. These practices require a deliberate focus of attention on certain aspects of present moment-to-moment experience, monitoring of distractions, and reorienting toward the object of attention in the meditation, be it the breath, a sound, or a visual object.

Affect Module. Core exercises were Loving-Kindness Meditation (*90*) and the so-called Affect Dyad (*44, 52*). For Loving-Kindness Meditation, participants were first introduced to ways of connecting with the feeling and motivation of love and care, such as imagining a baby, a cute animal, a close benevolent other, and a place of safety and comfort or focusing on feelings of warmth in the body. These feelings can then be directed toward oneself and others. The typical instruction for the Loving-Kindness Meditation was to start with imagining oneself and then a benefactor, where these feelings might arise naturally, and then to extend feelings of loving-kindness and good wishes to self and then the benefactor. Over the course of several meditation sessions, participants were asked to successively extent these feelings to others to whom one feels neutral, people with whom one has difficulties with, and ultimately all humans and beings. To stabilize and foster experiences of loving-kindness, we instructed participants to mentally repeat phrases such as "May you be happy," "May you be healthy," "May you be safe," and "May you live with ease."

The Affect Dyad is a partner exercise performed face-to-face during the retreat, during the weekly sessions, and via the Web- or smartphone-based application during daily practice at home. During this exercise, participants contemplated situations that they experienced as difficult and they experienced as difficult or for which they were grateful during the past day. Partner A was instructed to listen attentively to what the speaker (partner B) had to say without giving a verbal or nonverbal feedback, cultivating empathic listening. The speaker remembered the situation and how it felt like and focused on the immediate subjective affective and bodily experience without engaging in abstract reasoning or interpretation. After a first run, roles were switched. This contemplative dialog allows cultivating empathic listening in the listener, observing difficult emotions and their effect on the body, and developing gratitude and positive affect in the speaker.

Additional elements of Affect were exploration of emotions in an attitude of acceptance and care, a guided meditation that contrasts empathy and compassion and teaches participants how to transform an empathic response into a loving and compassionate response when confronted with the suffering of others (*23*), forgiveness meditation, and development of self-compassion (*91*). Thus, all exercises focused on developing an accepting, kind, and compassionate stance toward oneself and others.

Perspective Module. Core exercises were Observing-Thoughts Meditation and a Perspective Dyad. In the former, the objective was to observe thoughts as mental events or natural phenomena and not as direct representations of reality. In the initial phase of the practice, this was supported by labeling thoughts using opposite poles such as me/other, past/future, positive/negative, or more generic labels such as "judging" and "thinking." Later in the Module participants were instructed to just observe the coming and going of thoughts without getting involved in them.

The Perspective Dyad is a partner exercise with a structure similar to the Affect Dyad. This exercise was, in part, based on the Internal Family Systems approach by Schwartz and colleagues (*92, 93*) and on theoretical accounts distinguishing between affective (for example, compassion and empathy) and cognitive (for example, ToM) routes of social cognition (*5, 94*). For this perspective-taking exercise on self and others, participants were first introduced to the concept of inner parts, personality-trait–like patterns of cognition, emotion, and behavioral tendencies that dominate in certain situations and shape experience, as well as behavior (*92*). During the retreat and throughout the course, participants were supported in identifying the inner parts. In the Perspective Dyad, the speaker described a situation of the last day from the perspective of one of his/her inner parts, that is, how the experience might have been if a certain inner part had been dominant. The other participant listened attentively without giving a verbal or nonverbal feedback and tried to find out from which inner part the speaker was recounting the situation. The listener thus had to engage in cognitive perspective-taking on the other to find out "who is speaking" and to infer the needs, desires, and beliefs of the other. The speaker, in turn, needed to take a metaperspective onto its own self-related aspects and to decouple from a lived and experienced reality. Additional elements of Perspective were exercises, in which participants needed to take the perspective of people with whom they have difficulties with in their daily lives, reflections on the central role that thoughts play in our lives, how these might differ from thoughts of others, and why understanding them differs from approving their behavior. This description of the training protocol was adapted from Singer *et al.* (*44*).

MRI markers

Image acquisition. Using a 3T Siemens Verio scanner (Siemens) with a 32-channel head coil, we acquired a T1-weighted three-dimensional (3D) magnetization-prepared rapid gradient-echo (MP-RAGE) sequence [176 sagittal slices; repetition time (TR), 2300 ms; echo time (TE), 2.98 ms; inversion time (TI), 900 ms; flip angle, 7°; field of view

(FOV), 240×256 mm^2; matrix, 240×256; $1 \times 1 \times 1$–mm^3 voxels]. Throughout the duration of our longitudinal study, imaging hardware and console software (Syngo B17) were held constant.

Cortical thickness measurements. Each T1-weighted MRI was processed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) to generate cortical surface models and measure cortical thickness. All processing procedures were carried out on the same 32-core computer with the same software version (5.1.0). Because the overall ReSource Project contains both longitudinal and cross-sectional study goals [for example, see the study by Valk *et al.* (*11, 66*)], with data acquisition over the course of more than 2 years, we opted for the most general cross-sectional image processing procedure, enabling baseline data analysis before the completion of latter time points. Furthermore, given the variability in time points (TC3 had only two time points, and T$_4$ was not compulsory), we did not want to influence the analysis because of variations in number of data points for longitudinal analyses. FreeSurfer was validated against histological analysis (*95*) and manual measurements (*96*). Processing steps are detailed elsewhere (*61, 97, 98*). Briefly, MPRAGE images underwent intensity normalization, followed by skull-stripping and tessellation of the gray/white matter cortical boundary. After topology correction, surface deformations following intensity gradients approximated the inner (gray/white matter) and outer [gray matter/cerebrospinal fluid (CSF)] cortical interfaces, placed at the location where the greatest shift in intensity defines the transition to the other tissue class. Cortical thickness was calculated as the shortest distance from the gray/white matter boundary to the gray matter/CSF boundary at each vertex on the tessellated surface. After surface extraction, the sulcal and gyral features of an individual were warped to an average spherical representation, fsaverage5, which allows for the accurate matching of thickness measurement across participants. Surfaces were visually inspected, and inaccuracies were manually corrected (S.L.V. and B. C.B.). Thickness data were smoothed on tessellated surfaces using a 20-mm FWHM Gaussian kernel, which reduces measurement noise while preserving the capacity for anatomical localization, as it respects cortical topological features (*99*).

Behavioral markers

We assessed a battery of behavioral markers developed and adapted to target the main goals of the Presence, Affect, and Perspective Modules: selective attention, compassion, and ToM. Behavioral changes of these markers elicited by the different modules are reported elsewhere (*50*).

Attention was quantified as executive control of attention and stimulus-driven reorienting of attention (*47, 50, 65*), which was assessed under both isolated and concurrent demand conditions in a cued flanker task. Specifically, reorienting was measured through invalid versus valid cueing of the target location (*46, 100*), and executive control was assessed through flanker-target conflict (*101*). To assess improvements on attention comprehensively, our analysis focused on the concurrent demand condition. For details on the task, see the study of Trautwein *et al.* (*50*).

The measure for compassion was based on the EmpaToM task, a recently developed and validated naturalistic video paradigm (*8*). Videos showed people recounting autobiographical episodes that were either emotionally negative (for example, loss of a loved one) or neutral (for example, commuting to work), followed by Likert scale ratings of experienced valence and compassion. Because the conceptual understanding of compassion might change through the training, we ensured a consistent understanding by defining it before each measurement as experiencing feelings of care, warmth, and benevolence. Compassion was quantified as mean of compassion ratings across all experimental conditions.

The EmpaToM task (*8*) also allowed for measurement of ToM performance. After the ratings, multiple-choice questions requiring inference of mental states (thoughts, intentions, and beliefs) of the person in the video or factual reasoning on the video's content (control condition) were asked. Questions had only one correct answer, which had been validated during prestudy piloting (*8*). Here, we calculated participants' error rates during the ToM questions after the video, collapsed across neutral and negative conditions. As for our previous assessment of behavioral change effects (*50*), we ran additional analyses that also took account of changes in response time by (i) adding response time as a covariate to the model or (ii) using an unweighted composite score of response time and error rate.

Functional masks

We overlaid our main brain-behavior correlative results (Fig. 2) with functional activation maps from previously published studies (*8, 47*) of the baseline data in subgroup of study participants (T$_0$) that were also used to assess behavioral markers (see above): For compassion, we overlaid the EmpaToM task contrast during negative versus neutral socio-emotional videos (*8*); for ToM, we overlaid the EmpaToM task contrast between ToM versus no ToM questions (*8*); for Presence, we overlaid the conjunction map of the reorienting (invalid versus validly cued congruent targets) and executive control (validly cued incongruent versus congruent targets) contrasts in the cued flanker task (*47*).

Final sample

Because of dropouts, missing MRI, or missing behavioral data, there were small variations in the number of subjects for each analysis. Of a possible 251 participants who started the study as TC1, TC2, and RCC, 23 (10.9%) dropped out before T$_3$ was completed; in TC3 (only 3 months of training) of a possible 81 participants, 3 dropped out (3.7%), resulting in a total dropout rate of 7.8%, with high compliance across all modules (*44, 52*).

To measure brain change within subjects and the relation between brain and behavioral changes in Presence, Affect, and Perspective, we computed difference scores for all subjects during sequential time points, for example, [T$_0$→T$_1$], [T$_1$→T$_2$], and [T$_2$→T$_3$]. This resulted in a total of 660 change scores. This left us with Presence ($n = 133$), Affect ($n = 195$), Perspective ($n = 121$), and Controls ($n = 211$). We excluded participants with more than 3 SD change, resulting in Presence ($n = 132$; TC1, $n = 68$; TC2, $n = 64$; Berlin, $n = 69$; Leipzig, $n = 63$) Affect ($n = 193$; TC1, $n = 62$; TC2, $n = 64$; TC3, $n = 67$; Berlin, $n = 97$; Leipzig, $n = 96$), Perspective ($n = 120$; TC1, $n = 57$; TC2, $n = 63$; Berlin, $n = 61$; Leipzig, $n = 59$), and Controls ($n = 205$; Berlin, $n = 97$; Leipzig, $n = 108$). Of these participants, 102 had complete attention change scores, 184 had complete compassion change scores, and 115 had complete ToM change scores. For further details on dropouts and missing data in our behavioral markers, see the study of Trautwein *et al.* (*50*). For details regarding subject inclusion procedures, see table S1.

Statistical analyses

Analysis was performed using SurfStat for MATLAB (*102*). We used linear mixed-effects models, a flexible statistical technique that allows for inclusion of multiple measurements per subject and irregular measurement intervals (*103*). In all models, we controlled for baseline age and sex, given their established effects on brain structure (*104*), as well as time of measurement, and a random effect term of subject. Inference was performed on subject-specific cortical thickness change maps, ΔCT, which were generated by subtracting vertex-wise thickness maps of subsequent time points for a given participant. Before change calculation, we normalized thickness data at each vertex by regressing out

effects of global thickness to emphasize relative, region-specific change patterns. We then assessed whole-brain modulation of ΔCT. Comparisons between modules were made directly without removing the effects due to testing without training. Our design enabled us to use the different modules as active controls for each other, as they underwent different types of mental training.

Assessing module-specific change. To compare the three modules against each other, we contrasted the change of one given module against the average of both other modules, considering the differences in timing of measurement by controlling for time point. To evaluate differences between two modules, we compared module A to module B. To compare a given module against RCC, we estimated contrasts for training cohort change relative to RCC and intersected the results of TC1 versus RCC and TC2 versus RCC for each training module (Presence, Perspective, and Affect).

Relation to behavioral improvements and functional networks. To assess the relation between behavioral and brain changes, we correlated difference scores in behavior and brain changes in the specific module. To visualize convergence between training-related morphological changes and functionally relevant networks, we intersected cortical thickness effects with previously published task-based fMRI activation maps in the domain of social affect and ToM (8), as well as attention (47), derived from a subset of the current sample at baseline.

Correction for multiple comparisons and assessment of robustness. The findings were corrected for multiple comparisons using random field theory for nonisotropic images (105). Given previous discussions in the fMRI community on the impact of cluster-forming thresholds on overall FWE levels and interpretability (106, 107), statistical results were corrected for multiple comparisons by means of random field theory using both typically used (108–111) cluster-defining thresholds for 20-mm FWHM smoothed surface-based 2D thickness data [where higher smoothing kernels relate to more readily fulfilled assumptions of Gaussian random field theory (106, 112)] and a more conservative cluster-forming threshold recently recommended for the analysis of 3D voxel-based functional data smoothed with smaller, isotropic kernels. We therefore superimposed significant findings on the basis of a cluster-forming threshold of $P = 0.025$ with a more stringent cluster-forming threshold of $P = 0.001$. To evaluate consistency across the cohorts, we extracted the percentage of participants per cohort showing change in significant clusters. Moreover, we verified consistency across our recruitment sites (that is, Berlin and Leipzig), as well as across the separate training cohorts.

The two trained raters (S.L.V. and B.C.B.) excluded all scans with excessive motion and corrected surface extractions in all remaining scans. Theoretically, the crossover design of the study and the inclusion of number of scans since baseline as covariance controlled for test-retest effects on motion (as participants may become calmer in scanner after repeated sessions). Furthermore, to address potential effects of head motion, we performed a recently proposed analysis by additionally controlling for frame-wise displacement [estimated from fMRI scans acquired in the same session as the structural scans to estimate subjects' extent of motion during scanning sessions (60, 113, 114)] post hoc on the significant clusters reported in our main analyses (Figs. 1 and 2).

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/10/e1700489/DC1

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Citation: S. L. Valk, B. C. Bernhardt, F.-M. Trautwein, A. Böckler, P. Kanske, N. Guizard, D. L. Collins, T. Singer, Structural plasticity of the social brain: Differential change after socio-affective and cognitive mental training. *Sci. Adv.* **3**, e1700489 (2017).

Science Advances

Structural plasticity of the social brain: Differential change after socio-affective and cognitive mental training

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