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Using executive control training to suppress amygdala reactivity to aversive information

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ABSTRACT

The ability to regulate emotions is essential for adaptive behavior. This ability is suggested to be mediated by the connectivity between prefrontal brain regions and the amygdala. Yet, it is still unknown whether the ability to regulate emotions can be trained by using a non-emotional procedure, such as the recruitment of executive control (EC). Participants who were trained using a high-frequent executive control (EC) task (80% incongruent trials) showed reduced amygdala reactivity and behavioral interference of aversive pictures. These effects were observed only following multiple-session training and not following one training session. In addition, they were not observed for participants exposed to low-frequent EC training (20% incongruent trials). Resting-state functional connectivity analysis revealed a marginally significant interaction between training group and change in the connectivity between the amygdala and the right inferior frontal gyrus (IFG). Amygdala–IFG connectivity was significantly increased following the training only in the high-frequent EC training group. These findings are the first to show that *non-emotional* training can induce changes in amygdala reactivity to aversive information and alter amygdala–prefrontal connectivity.

Introduction

Excessive emotional arousal can impair individuals' ability to achieve their goals (Ochsner et al., 2002). This is especially true when heightened arousal emerges from an encounter with task-irrelevant emotional stimuli. Although emotional processing was considered automatic for many years (Öhman et al., 2001), the prevalent notion among emotion scientists today posits that emotions can be down-regulated using voluntary (Goldin et al., 2008; Ochsner and Gross, 2008) and implicit (Dolcos et al., 2006; Okon-Singer et al., 2007; van Dillen et al., 2009) emotion regulation strategies. These regulation mechanisms are associated with enhanced activation in prefrontal regions such as the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), and the right inferior frontal gyrus (IFG) and reduced activation in the amygdala, a key region in emotional processing (Dolcos et al., 2006; Iordan et al., 2013; Okon-Singer et al., 2014; Van Dillen et al., 2009; see reviews in Okon-Singer et al., 2013, 2015).

Importantly, the same prefrontal regions that are activated during emotion regulation tasks are also activated in tasks that recruit executive control (EC) (Aron et al., 2004; Fan et al., 2005; MacDonald et al., 2000). EC is a high-order cognitive operation that enables goal-directed behavior by suppressing irrelevant distraction (Banich, 2009; Fan et al., 2002; Miller and Cohen, 2001). Several studies reported that EC plays a role also in suppressing irrelevant emotional information (Blair et al., 2007; Cohen et al., 2011, 2012) and that there are functional and anatomical connections between EC-related regions and the amygdala (Quirk and Beer, 2006; Rohr et al., 2015; Roy et al., 2009). Thus, the inverse link between activation in prefrontal regions and the amygdala may be explained by EC activation.

Indeed, behavioral findings indicate that EC-based training can reduce emotional distraction and emotion dysregulation symptomatology (Cohen et al., 2015a; Daches and Mor, 2014; Schweizer et al., 2011, 2013; Siegle et al., 2007). Specifically, training participants to exercise inhibition over emotional information was found to reduce state (Cohen et al., 2015a) and trait (Daches and Mor, 2014) rumination, a maladaptive coping strategy that is highly associated with depression and other psychopathologies (Nolen-Hoeksema et al., 2007). In addition, training participants with an emotional working memory task led to increased activation in frontal and parietal regions during an emotion regulation task (Schweizer et al., 2013).

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The findings regarding the effects of *non-emotional* EC training on emotional behavior are equivocal. While some studies have found that non-emotional EC training reduces psychopathological symptoms related to emotion dysregulation (Calkins et al., 2014; Sari et al., 2015; Siegle et al., 2007), contradicting evidence shows that only training consisting of emotional information alters emotional behavior (Schweizer et al., 2011). Moreover, it is yet unknown whether non-emotional EC training can induce changes in emotion-related brain activity and in amygdala–prefrontal connectivity. The use of a non-emotional training is important for the understanding of cognition–emotion interactions and for clinical purposes. Specifically, in order to reveal the mechanisms involved in emotion regulation it is important to distinguish emotional from non-emotional effects. In previous studies in which emotional stimuli were embedded in the training it was hard to distinguish effects related to executive control from effects related to the emotional information. Therefore, using non-emotional training can uncover the specific cognitive mechanisms that subserve emotion regulation. Moreover, such training can be easily employed with different populations, such as children, elderly adults, and individuals with neurological or psychiatric disorders.

The current work examined the effects of single-session and multiple-session EC training on emotional reactivity (Fig. 1A). Participants were randomly assigned to one of two training groups; a high-frequent EC group (H-EC) and a low-frequent EC group (L-EC). Each participant performed an initial training session, as well as additional 18 training sessions (over 6 days). Each training session contained an arrow-flanker task, which is commonly used to test EC (MacLeod et al., 2010). The arrow-flanker task consisted of congruent and incongruent stimuli. Incongruent stimuli necessitate the recruitment of EC (Gratton et al., 1988; Norman and Shallice, 1980). The proportion of incongruent trials was 80% in the H-EC group and 20% in the L-EC group. Functional magnetic resonance imaging (fMRI) was used to assess amygdala activation during an emotional interference task and resting-state functional connectivity between the amygdala and prefrontal regions implicated in the EC task. The emotional interference task consisted of negative and neutral pictures from a validated set (International Affective Pictures System: IAPS; Lang and Bradley, 2007). Negative pictures from the IAPS are commonly used to assess emotional reactions and are known to elicit amygdala activation (e.g., Hariri et al., 2002). On each trial a picture was followed by a simple discrimination task (deciding whether a presented square is blue or green). Previous studies that used similar tasks demonstrated that emotional distractors delay performance when irrelevant to the task at hand (Buodo et al., 2002; Hartikainen et al., 2000). Using this task enabled us to assess both behavioral and functional effects related to emotional processing. Importantly, we chose a very simple emotional interference task because we were interested in the effects of a "pure" executive control training on a "pure" emotional processing task. Choosing basic executive control and emotional interference tasks fits best our question whether a non-emotional training can alter emotion-related behavioral and functional reactions.

Compared to the L-EC group, the H-EC group was predicted to show reduced amygdala activation in response to distracting aversive pictures following training, associated with a reduction in behavioral interference by aversive pictures. Furthermore, we expected the H-EC group to show enhanced resting-state functional connectivity between the amygdala and prefrontal regions implicated in the flanker task. These predictions were based on previous findings showing that non-emotional EC training can reduce emotion dysregulation symptoms (Calkins et al., 2014; Siegle et al., 2007; although as noted contradicting evidence was shown by Schweizer et al., 2011), as well as on data from our lab showing that the behavioral (Cohen et al., 2011, 2012, 2015b) and psychophysiological (Cohen et al., 2015c) reactions to aversive information are attenuated following the recruitment of EC.

Materials and methods

Subjects

Thirty-six healthy participants without any history of neurological or psychiatric diseases participated in the study in return for payment. The study was approved by the ethics committee of the University of Leipzig and all subjects gave informed consent prior to the experiment. All of the participants were right-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were randomly assigned to one of the two training groups. Three participants did not complete the training and thus did not participate in the second scanning session. The data of seven additional participants were excluded

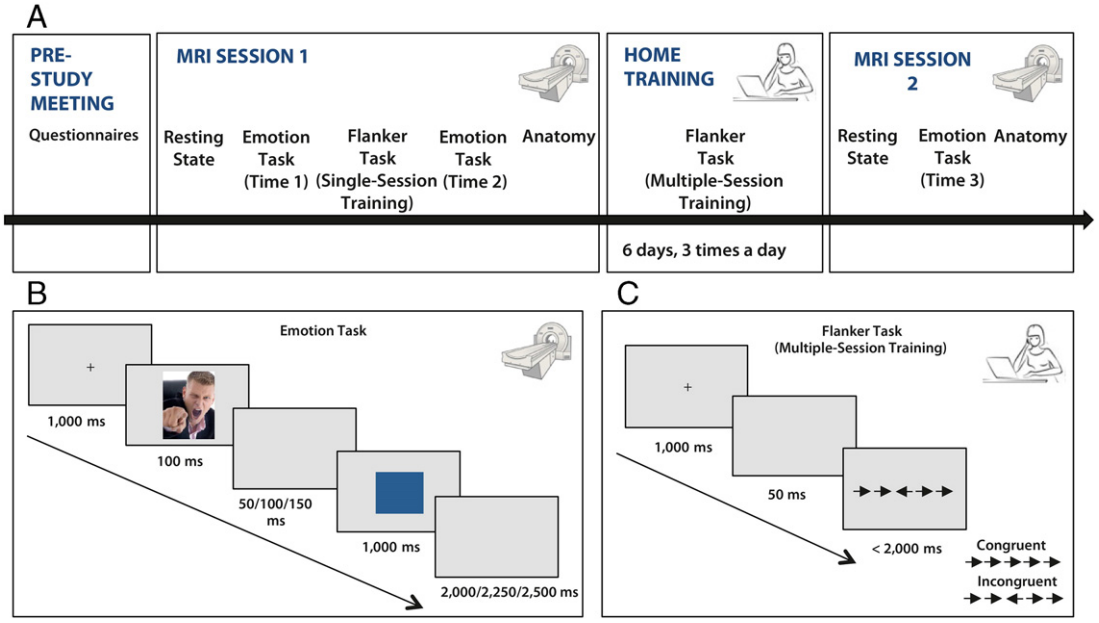

Fig. 1. A — general study timeline; B — emotional task procedure: negative and neutral pictures appeared before a choice reaction task; participants were asked to indicate whether a square was blue or green; C — home training procedure: arrow-flanker task; participants were asked to indicate the direction of the middle arrow and ignore the flanking arrows, which could be congruent or incongruent to the target arrow. Image courtesy of imagerymajestic at FreeDigitalPhotos.net.

due to technical problems during the home training or the scanning sessions. The resultant sample included 26 participants, 13 in the L-EC group and 13 in the H-EC group. The groups did not differ in age, sex, and trait measures of depression, anxiety, and emotion regulation (see Table 1 for demographic characteristics).

Procedure

Pre-study meeting

Participants came to the lab about a week before the first MRI session for a meeting with the experimenter, which lasted around 1 h. In this meeting participants gave informed consent, completed personality questionnaires, and the training program was installed on their laptops. Participants were given a short demonstration of the training program and completed a short practice session.

MRI session 1

The first MRI session began with a 7-minute resting-state measurement, followed by an emotion task (time 1), a brief training task (with either 80% or 20% incongruent targets, for the H-EC and L-EC group, respectively), and additional administration of the emotion task (time 2). All fMRI tasks were administered using Presentation Software (Presentation, version 14.9; Neurobehavioral Systems, Inc., Albany, CA, USA). At the end of the fMRI acquisition, participants underwent an anatomical scan.

Home training

The training task (which included mood assessment and an arrow-flanker task) was programmed using visual basic and was installed on the participants' personal laptops. The use of participants' personal laptops induced variations in screen size and refresh rate, which might have slightly affected the visual properties of the stimuli and timing parameters related to the task. Notably, stimulus size did not differ between different laptops. Following the installation of the task, participants performed several training trials and we verified that the stimuli were presented properly. The means and standard deviations (SDs) observed in the flanker task in the current work resemble previous studies (e.g., Davelaar and Stevens, 2009). Thus, it is unlikely that the variations in laptop type and in screen size affected performance. Participants were instructed to perform the training three times a day (morning, noon, evening) for 6 consecutive days. Each training session lasted about 15 min. Participants were asked to perform the training in a quiet room without distractions. During the pre-study meeting, participants wrote the times they planned to perform the training. An e-mail was sent to each participant on each day of the training with a request to inform the experimenter whether he/she completed the three training sessions and to mention if he/she experienced any technical or personal issues that prevented him/her from completing the sessions. During the training we collected reaction times and accuracy data. In addition, we asked the participants about their experience during the training at the end of the study. Participants were generally positive about the training and some of them even mentioned they enjoyed it. Integrating this information (e.g., RT, accuracy, reports during the training, debriefing comments) suggests that compliance was very good in both groups.

Table 1
Demographic characteristics of the two training groups.

Group	L-EC	H-EC
F/M	7/6	7/6
Age	25 (4)	26 (3)
ERQ: suppression	14 (4)	12 (3)
ERQ: reappraisal	30 (6)	28 (5)
Anxiety (STAI-T)	34 (8)	37 (10)
Depression (BDI-II)	3 (3)	5 (6)

Note. F = female; M = male; age is in years; standard deviation in parentheses. ERQ = emotion regulation questionnaire (Gross and John, 2003). STAI-T = trait anxiety inventory (Spielberger et al., 1970). BDI-II = Beck depression inventory (Beck et al., 1996). Higher scores in the ERQ subscales represent a more frequent use of the emotion regulation strategy. Higher scores in the STAI-T and the BDI-II represent a higher level of anxiety and depression symptoms, respectively. The groups did not significantly differ from each other in each of the measures.

MRI session 2

The second MRI session took place one day following the last training day. The session began with a 7-minute resting-state measurement, followed by an emotion task (time 3) and an additional task that will not be discussed here. At the end of the fMRI acquisition, participants underwent an anatomical scan. After exiting the scanner, participants were debriefed, paid, and thanked for their participation.

Tasks

Home training task

The home training consisted of the flanker task (Fig. 1C). In the H-EC group, 80% of the trials were incongruent (e.g., →→←→→) and 20% were congruent (e.g., →→→→→), and vice versa in the L-EC group. Each trial started with a fixation cross presented for 1,000 ms, followed by an interval of 50 ms. Then, the flanker stimulus was presented until response but no longer than 2,000 ms. Participants were asked to indicate the direction of the middle arrow (right or left) by pressing a key on the keyboard. They were requested to respond as fast and as accurately as possible. Each training session included 400 trials that were presented in random order. Namely, participants completed 1,200 trials on each training day.

Flanker task (administered in MRI session 1)

Twenty seconds of instructions preceded an arrow-flanker task. The flanker task consisted of congruent and incongruent stimuli. In the H-EC group, 80% of the stimuli were incongruent (e.g., →→←→→) and 20% were congruent (e.g., →→→→→), and vice versa in the L-EC group. Each trial started with a fixation cross presented for 1,000 ms, followed by an interval of 50, 100, or 150 ms. Then, the flanker stimulus was presented for 1,000 ms. Each trial ended with an ITI of 2,000, 2,250, or 2,500 ms. Participants were asked to indicate the direction of the middle arrow (right or left) by pressing a key on the keyboard. They were requested to respond as fast and as accurately as possible. The task included 108 trials (1/6 of the trials were "null trials", in which a fixation cross appeared for the entire trial duration). Similar to the emotion task, trials were presented in a pseudo-randomized order, with the criteria that no more than two consecutive "null trials" were presented, and participants performed a short practice before entering to the MRI.

Emotion task

Stimuli pictures were taken from the IAPS (International Affective Picture System; Lang et al., 2008). Fifty-four negative and 54 neutral pictures were chosen, based on their IAPS valence and arousal scores. The pictures were randomly divided into three sets of pictures (A, B, C; one set for each time point). Sets A and B appeared at time 1 and time 2 (counterbalanced across participants). Set C appeared at time 3. Thus, each picture was presented at only one of the time points measured.

Fig. 1B describes the order of events in an experimental trial. Twenty seconds of instructions preceded the task. Each trial started with a fixation cross presented at the center of the screen for 1000 ms, followed by a negative or a neutral picture for 100 ms. The picture was followed by an interval of 50, 100, or 150 ms. Then, a target square was presented for 1000 ms. Participants were asked to indicate whether the target square was blue or green by pressing a key on the response box. They were requested to respond as fast and as accurately as possible. Each trial ended with an inter-trial interval (ITI) of 2000, 2250, or 2500 ms. The task included 180 trials. Out of these trials, 20% (36) were "null trials", in which a fixation cross appeared for the entire trial duration. The remaining 80% (144) of the trials included 72 negative and 72 neutral trials (each of the

18 negative and 18 neutral pictures was presented 4 times). Trials were presented in a pseudo-randomized order, with the criteria that no more than two consecutive "null trials" were presented. Before entering the scanner, participants performed a short practice session in order to familiarize themselves with the task.

Neuroimaging

fMRI data acquisition

The experiment was carried out on a 3T scanner (Siemens VERIO). Functional images were acquired using a 12-channel head coil. We employed a gradient-echo EPI sequence that was based on parameters recommended for limbic regions (Robinson et al., 2004) (FOV — 19.2 cm, matrix size — 64 × 64, voxel size — 3 × 3 × 2.5 mm^3, TR/TE/FA = 2000 ms/22 ms/90 degrees, 36 axial slices with an inter-slice gap of 20%). Each scan (task and rest) started with 20 s of instructions. Participants were asked to keep their eyes open for the entire scan and to look at a fixation cross which was presented in the middle of the screen (for the entire scanning session in the resting-state phase, and in the beginning of each trial in the tasks). Rest scan lasted for 7 min (210 volumes after removing the first 10 instruction volumes); emotional task lasted about 14 min (410 volumes after removing the first 10 instruction volumes); and flanker task lasted about 8 min (236 volumes after removing the first 10 instruction volumes). Anatomical scans were acquired using a 32-channel head coil. A T1-weighted 3D MP-RAGE sequence was used (FOV — 256 × 240 mm^2, spatial resolution — 1 × 1 × 1 mm^3, TR/TE/FA = 2300 ms/2.98 ms/10 degrees, 176 sagittal slices). Geometric distortions were characterized by a B0 field-map scan. The field-map scan consisted of gradient-echo readout (24 echoes, inter-echo time 0.95 ms) with a standard 2D phase encoding. The B0 field was obtained by a linear fit to the unwrapped phases of all odd echoes.

Data pre-processing

fMRI: emotion and flanker tasks

Functional data were processed and analyzed using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) with MATLAB (Version 7.14.0, MathWorks, Sherbon, MA). Pre-processing included the following steps: removal of the first 20 s (first 10 volumes) in which instructions were presented on the screen; motion correction using realignment to the first volume; geometric distortions correction using a field map; and slice timing correction to the middle slice. Functional images were co-registered to the individual high-resolution anatomical image, and normalization to Montreal Neurological Institute (MNI) space (Mazziotta et al., 1995) was performed using the unified segmentation approach (Ashburner and Friston, 2005). After normalization, the resulting voxel size of the functional images was interpolated to 3 × 3 × 3 mm^3. Images were then spatially smoothed with a 4.5 mm full width at half maximum (FWHM) Gaussian kernel, and a high-pass filter of 1/128 Hz was applied.

Resting-state fMRI

Functional data obtained in the resting-state phase were processed and analyzed using both FSL (Jenkinson et al., 2012) and AFNI (Cox, 1996). Pre-processing included the following steps: removal of the first 20 s (first 10 volumes) in which instructions were presented on the screen, 3D motion correction, time series de-spiking, 6 mm FWHM spatial smoothing, 4D mean-based intensity normalization, band-pass temporal filtering (0.01–0.1 Hz), removing linear and quadratic trends, and regressing out eight nuisance signals (white matter, cerebrospinal fluid, and six motion parameters). The output of these pre-processing steps was one 4D residual functional volume for each participant. Functional images were normalized to MNI space using FSL registration algorithm (flirt) with the anatomical T1 scan as a prior.

Data analysis

Training task

Analysis of the behavioral data (RT) was performed using SPSS (version 18, http://www-01.ibm.com/software/analytics/spss/). The analysis included only correct responses. Mean RTs were subjected to a 2-way mixed analysis of variance (ANOVA) with condition (congruent/incongruent) as a within-subjects factor and group (H-EC/L-EC) as a between-subjects factor.

Manipulation check

In order to examine whether the improvement in the flanker task was larger in the H-EC compared to the L-EC group, we calculated conflict score for each participant for each of the 18 training sessions separately. The conflict score, calculated by subtracting congruent from incongruent reaction times, is commonly used to assess EC recruitment (Fan et al., 2005). A larger conflict score indicates reduced ability to ignore irrelevant information and thus lower EC abilities (Norman and Shallice, 1980). Next, a regression model was used to calculate the slope of the conflict scores for each participant when the session number served as predictor. Since 5 participants did not complete all 18 sessions, the slope was calculated over 15 sessions (excluding the 3 last sessions). Of the five participants who did not complete all training sessions, 3 were in the H-EC group (one completed 15 sessions and two completed 17 sessions) and 2 were in the L-EC group (one completed 15 sessions and one completed 16 sessions). A coefficient comparison test (Paternoster et al., 1998) was used to examine the difference between the slopes of the two groups and one-sample *t*-tests were conducted in order to examine whether the slope of each group differed from zero.

Flanker task (administered in session 1)

In order to define brain regions involved in EC for further analyses and to examine the immediate effects of the training on emotional reactions (i.e., time 1 vs. time 2; see Fig. 1A), the training task was performed once in the first scanning session. Each participant conducted either H-EC or L-EC flanker task that was identical to his/her home training task in the proportions of incongruent and congruent trials. Task timings (i.e., jittered intervals and the addition of null events) were adjusted for fMRI.

Behavioral data analysis

Analysis of the behavioral data (RT) was performed using SPSS (version 18, http://www-01.ibm.com/software/analytics/spss/). The analysis included only correct responses (97% of the trials). Mean RTs were subjected to a 2-way mixed analysis of variance (ANOVA) with condition (congruent/incongruent) as a within-subjects factor and group (H-EC/L-EC) as a between-subjects factor.

fMRI analysis

The regressors of interest were defined by convolving a vector of flanker onsets (event duration = 1 TR) with the canonical HRF. A first-level model included task conditions (i.e., congruent, incongruent) and six motion realignment nuisance regressors. A general linear model design was applied with condition (congruent/incongruent) as within-subjects factor and group (H-EC/L-EC) as a between-subjects factor. For the whole-brain analysis we used a voxel-level threshold of $p < 0.001$ and a cluster-level threshold of $p < 0.01$. AlphaSim, a Monte Carlo simulation tool implemented in AFNI (Cox, 1996), calculated a minimum cluster-size threshold of 35 voxel or higher (using the residuals FWHM values). Following results of the whole-brain analysis, 10 mm radius spherical mask was created using WFUpickatlas toolbox (http://fmri.wfubmc.edu/software/PickAtlas) in the right inferior frontal gyrus (IFG). We used this mask to extract the mean time course of each participant in the resting state data.

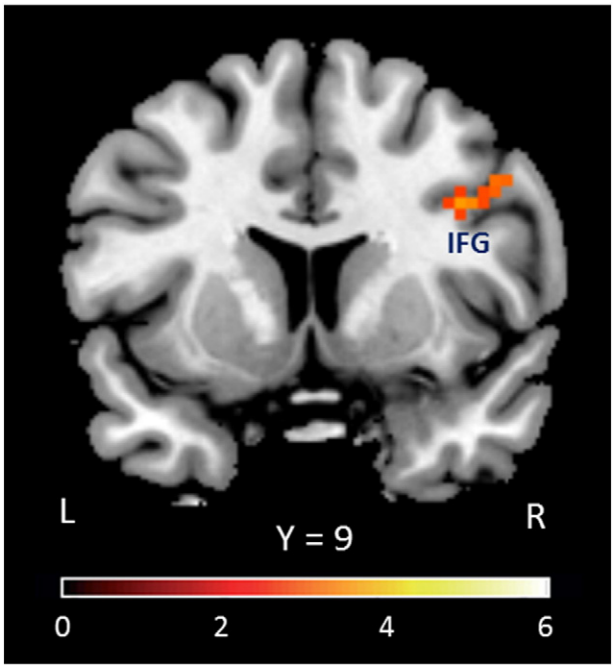

Fig. 2. Coronal slice depicting the incongruent > congruent contrast in the flanker task across both groups. The colored region represents the cluster found in the whole-brain analysis ($p < .001$, corrected; colored bar indicates the *t*-values). Inferior frontal gyrus (IFG).

Emotion task

Behavioral data analysis

Analysis of the behavioral data (RT) was performed using SPSS (version 18, http://www-01.ibm.com/software/analytics/spss/). The analysis included only correct responses (time 1 – 94% of the trials; time 2 – 96% of the trials; time 3 – 95% of the trials). Mean RTs were subjected to a 3-way mixed analysis of variance (ANOVA) with valence (negative/neutral) and time (time 1, time 2, time 3) as within-subjects factors and group (H-EC/L-EC) as a between-subjects factor.

fMRI analysis

The regressors of interest were defined by convolving a vector of picture onsets (event duration = 1 TR) with the canonical hemodynamic response function (HRF). A first-level model was done separately for each task administration (time 1, time 2, time 3) and included task conditions (i.e., negative, neutral) and six motion realignment nuisance regressors. A general linear model design was applied with valence (negative/neutral) and time (time 1, time 2, time 3) as within-subjects factors and group (H-EC/L-EC) as a between-subjects factor.

To examine whether the task resulted in activation in brain regions previously implicated in processing of emotional pictures a whole-brain analysis was performed on the contrast negative vs. neutral pictures across the three time points. This analysis was performed using a family-wise error rate (FWE) threshold of pFWE <.05. To examine the effect of the training on amygdala activation, two separate contrasts were conducted. The first contrast examined the effects of single-session training and the second contrast examined the effects of multiple-session training. In both contrasts group (L-EC, H-EC) served as a between-subject variable while time (time 1, time 2/time 3) and valence (negative, neutral) served as within-subject variables. A small volume correction (SVC) analysis using a threshold of pFWE <.05 (Friston et al., 1996) was performed on bilateral amygdala masks defined based on the Talairach Daemon Atlas (Lancaster et al., 2000) using WFUpickatlas toolbox (Maldjian et al., 2003; http://fmri.wfubmc.edu/software/PickAtlas).

In addition, based on the findings of these analyses, the right amygdala mask was used to test the links between amygdala activation and behavioral performance. For this purpose, we extracted the mean parameter estimates averaged across the whole mask using Marsbar toolbox (http://marsbar.sourceforge.net/). Regression models were used to examine the link between changes in amygdala activity and RT as a function of training group. Significant interactions were explored using a procedure outlined by Aiken and West (Aiken and West, 1991).

Right amygdala mask was also used to extract the mean time course of each participant from the resting state data. The connectivity between the right amygdala and EC region of interest (identified by the flanker task; right IFG) was entered into a mixed ANOVA as dependent variable with group (H-EC/L-EC) and time (pre-training, post (multiple-session) training) as factors.

fMRI analysis of the resting state

Mean time courses of the right amygdala (using anatomical mask) and the frontal region implicated in the flanker task (using a 10 mm radius spherical mask) were extracted. Then, Pearson correlation was calculated between the right amygdala and the executive mask, for each participant for each of the two sessions (pre and post training). Fisher's r-to-z transformation was used before entering the data into statistical tests. The transformed correlations were entered into a mixed ANOVA, with time (pre/post training) as within-subjects factor and group (H-EC/L-EC) as between-subjects factor. Post-hoc comparisons were used to probe interactions of interest.

Results

Home training task

A 2-way mixed ANOVA with condition (congruent/incongruent) and group (H-EC/L-EC) as factors revealed a significant main effect for condition, indicating slower RT for incongruent compared to congruent trials ($F(1, 24) = 485.23$, $p < .0001$, partial $\eta^2 = .95$). In addition, the interaction between condition and group was significant ($F(1, 24) = 49.54$, $p < .0001$, partial $\eta^2 = .67$). The difference in RT between incongruent and congruent trials (i.e., conflict score) was larger in the L-EC (69 ms) compared to the H-EC (36 ms) group. The relatively large conflict score in the L-EC group probably resulted from the low frequency of incongruent trials in this group, which created larger task-demands in these trials. In contrast, the small conflict score in the H-EC group suggests an efficient EC recruitment that became even more effective when the training progressed. These results are in line with previous findings showing that when the proportion of incongruent trials increases, EC becomes more efficient and the conflict score decreases (Braver et al., 2001; Carter et al., 2000; Gratton and Donchin, 1992; Tzelgov et al., 1992).

Manipulation check

The slopes (i.e., change in conflict score during the training) of the two groups differed from one another ($Z = 1.66$, $p < .05$). Slope of the L-EC group did not differ from zero ($t(12) = -1.38$, $p = .19$), while the slope of the H-EC group was significantly smaller than zero ($t(12) = -4.26$, $p < .001$). Thus, participants in the H-EC but not in the L-EC group showed a significant improvement in EC abilities during the training. Conflict scores in the L-EC group were unaffected by the training, suggesting that a task that rarely activates EC (20% incongruent trials) is ineffective in training EC abilities.

Flanker task (administered in MRI session 1)

Behavioral results

A 2-way mixed ANOVA with condition (congruent/incongruent) and group (H-EC/L-EC) as factors revealed a significant main effect for condition, indicating slower RT for incongruent compared to congruent trials ($F(1, 24) = 78.38$, $p < .0001$, partial $\eta^2 = .77$). In addition, the interaction between condition and group was significant ($F(1, 24) = 18.01$, $p < .0001$, partial $\eta^2 = .43$), indicating smaller conflict scores in the H-EC group compared to the L-EC group similarly to what was found in the analysis of the home training.

fMRI results

Whole-brain analysis was conducted for the purpose of ROI selection ($p < .001$, corrected). A planned comparison (incongruent > congruent in both groups) yielded significant results in the right inferior frontal gyrus (IFG) (peak MNI coordinates: x = 39, y = 5, z = 31, t = 4.12, cluster size = 36 voxels; see Fig. 2), a brain region usually associated with response inhibition (Hampshire et al., 2010; Verbruggen and Logan, 2008).

Emotion task (administered in MRI sessions 1 and 2)

fMRI results

A whole-brain analysis (pFWE < .05) testing negative vs. neutral pictures across the three time points showed activation in brain regions previously implicated in processing of emotional pictures (Sabatinelli et al., 2011). These regions included the amygdala, orbitofrontal cortex, and fusiform gyrus (see Fig. 3 and Table 2).

To examine the 3-way interaction between group (H-EC/L-EC), time (pre-training/post-training) and valence (negative/neutral) in the amygdala, two separate analyses were conducted. The first analysis examined immediate training effects (time 1 and time 2 served as time levels), and the second analysis examined the effects of the multiple-session training (time 1 and time 3 served as time levels). These analyses were performed using a small volume correction (SVC; pFWE < .05) on bilateral amygdala masks. Both analyses were not significant. However, lowering the threshold revealed a significant activation in the right amygdala in the SVC analysis testing the 3-way interaction of the multiple-session training (i.e., time 1 vs. time 3 served as time levels; t = 2.07, $p = .02$). To explore this interaction we conducted the analysis testing multiple-session training effects separately on negative and neutral trials. The right amygdala showed a significant activation in the analysis testing multiple-session training effects on negative trials (pFWE < .05; Fig. 4), but not in the analysis testing multiple-session training effects on neutral trials.

These results imply that only multiple-session, but not single-session training of EC influenced amygdala response. Thus, there was no indication for effects of EC on phasic changes in amygdala activation. In addition, reduced amygdala activity following the multiple-session training was mainly seen during the presentation of negatively valenced pictures.

Functional activation as a predictor of task performance

A 3-way mixed ANOVA with valence (negative/neutral pictures), time (time 1/time 2/time 3), and group (H-EC/L-EC) as factors revealed only a main effect for valence ($F(1, 24) = 3.14$, $p = .02$, partial $\eta^2 = .20$), indicating slower RT for targets that followed negative compared

Table 2
Whole-brain analysis of the emotion task for negative compared to neutral trials across the three time-points.

Side	Region	MNI coordinates (x, y, z)			*t*-value	Cluster size (voxels)
R	Inferior frontal gyrus (operculum)	42	14	28	7.49	27
R	Inferior frontal gyrus (triangular)	51	26	16	5.62	21
R	Orbitofrontal cortex	30	29	−17	6.82	20
L	Orbitofrontal cortex	−36	32	−17	5.17	3
L	Orbitofrontal cortex	−39	29	−14	4.95	1
L	Orbitofrontal cortex	−24	26	−14	5.18	2
L	Inferior frontal gyrus (triangular)	−36	29	1	5.02	1
R	Fusiform gyrus	45	−49	−17	10.52	274
L	Fusiform gyrus	−39	−46	−20	10.09	93
L	Middle temporal cortex	−36	−67	−14	5.19	3
L	Middle temporal cortex	−45	−58	10	7.17	130
R	Amygdala	21	−7	−14	5.31	4
L	Amygdala	−18	−7	−14	6.82	15
R	Superior temporal pole	30	5	−20	5.50	2
L	Insula	−24	11	−17	5.19	2
R	Olfactory	3	8	−11	5.22	2
L	Midbrain	−3	−31	−5	5.19	2
R	Optic tract	0	−16	4	6.15	5

Note. L = left, R = right. For each region, the table presents *t*-values for voxels of peak activation and their corresponding cluster sizes (pFWE < .05).

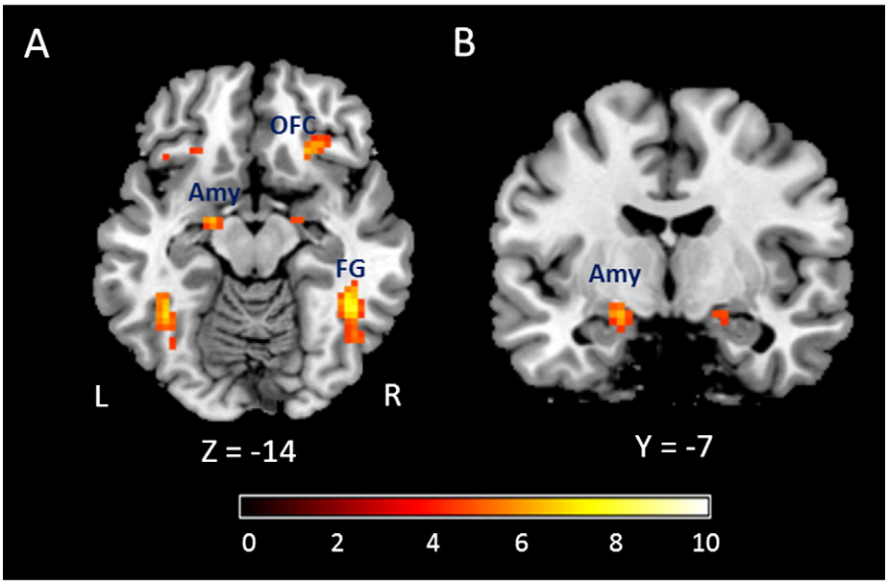

Fig. 3. Transverse (1A) and coronal (1B) slices for the negative > neutral contrast in the emotional task (across the two groups and all three time points). Colored regions represent the clusters that were significant in the whole-brain analysis (pFWE < .05; see also Table 2). The colored bar indicates the *t*-value of the plotted activation differences. Amygdala (Amy); fusiform gyrus (FG); orbitofrontal cortex (OFC).

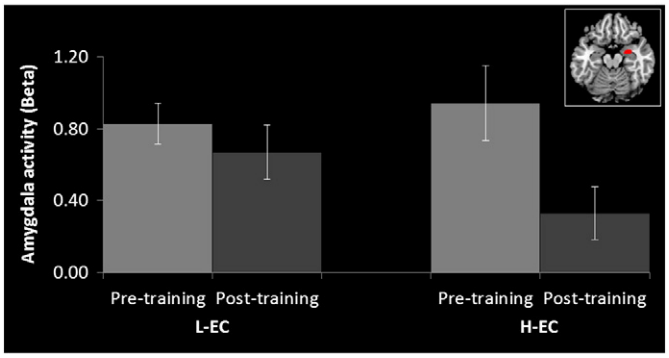

Fig. 4. Right amygdala beta weights for the interaction between time (pre-training/post (multiple-session) training) and group (H-EC/L-EC) for negative pictures. The figure shows a reduction in amygdala activity in the H-EC group (which was trained with an 80% incongruent flanker task), but not in the L-EC group (which was trained with a 20% incongruent flanker task). Error bars denote standard error of the mean. The anatomical mask of the amygdala is depicted in the right upper corner.

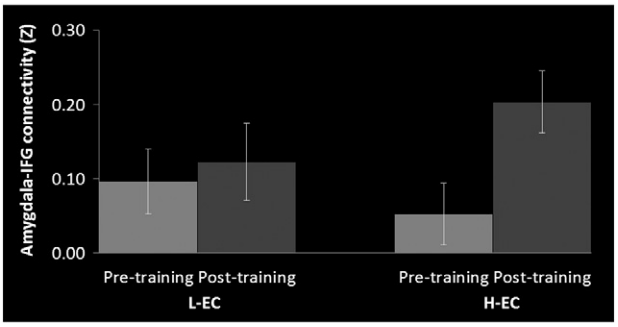

Fig. 5. Functional connectivity of the right amygdala and the right IFG, as assessed during the resting-state scan, for the interaction between time (pre-training/post-training) and group (H-EC/L-EC). The figure shows an increase in right amygdala – right IFG connectivity in the H-EC (which was trained with an 80% - incongruent flanker task), but not in the L-EC group (which was trained with a 20% - incongruent flanker task). Error bars denote standard error of the mean.

to neutral pictures. The absence of interaction between training group, valence and time may indicate that the training did not influence behavioral interference caused by aversive pictures. On the other hand, it is possible that training effects on emotional interference were modulated by individual differences in emotional reactivity (i.e., amygdala activation). Thus, following the findings showing training effects on right amygdala activation, we examined whether training-induced change in right amygdala activity predicts training-induced behavioral changes.

A regression model was used to predict change in RTs for negative pictures (time 3–time 1) using change in right amygdala activity (in standardized scores) for negative pictures (time 3–time 1) and group (H-EC/L-EC) as predictors. A second model included also the interaction between group and change in right amygdala activity. In the first model, neither group nor right amygdala change significantly predicted RT change ($\beta = .002$, $t = .009$, $p = .99$; $\beta = -.04$, $t = -.19$, $p = .86$, respectively). This model accounted for 0.2% of the variance in RT change ($F\,(2, 23) = .02$, *ns*). Importantly, the interaction between group and amygdala change, entered in the second model, predicted RT change ($\beta = .81$, $t = 3.18$, $p = .004$). The second model accounted for 32% of the variance ($F\,(3, 22) = 3.39$, $p = .04$) and added significantly to the first model, accounting for an additional 31% of the variance in RT change (Fchange $(1, 22) = 10.10$, $p = .004$). Similar analysis on trials depicting neutral pictures did not reveal significant results, corroborating the conclusion that training effects on amygdala activity and on its relation to RT are specific to aversive conditions, and are not evident during neutral distraction.

Examining the direction of the link between amygdala and RT change separately in the two training groups (Aiken and West, 1991) revealed that among participants in the H-EC group, the simple slope representing the association between amygdala and RT change was significant ($\beta = .76$, $t = 3.85$, $p = .003$), indicating that larger amygdala change was associated with larger RT change. Among participants in the L-EC group, the association between amygdala and RT change did not reach significance ($\beta = -.48$, $t = -1.83$, $p = .10$). Thus, change in amygdala activity was positively related to RT change only among individuals in the H-EC group but not among those in the L-EC group. Taken together, these findings indicate that the H-EC training was effective in reducing amygdala activation, and that those participants who showed larger reduction in amygdala activity also showed larger reduction in RT interference caused by aversive stimulation.

Resting-state functional connectivity

The interaction between group (H-EC/L-EC) and time (pre-training, post (multiple-session) training) revealed a marginally significant interaction when entering the connectivity between right amygdala and right IFG as a dependent variable ($F\,(1, 24) = 3.34$, $p = .08$, partial $\eta^2 = .12$; see Fig. 5). Although this interaction did not reach significance, we conducted follow-up analyses based on our a-priori prediction that the H-EC training would result in increased connectivity between the amygdala and EC-related prefrontal regions. We used the Wilcoxon signed rank test, which is more conservative than the common parametric tests. This test revealed that amygdala–IFG connectivity before the training was significantly lower than this connectivity following the training for the H-EC group ($p = .005$), but not for the L-EC group ($p = .55$). These findings suggest that high frequent EC recruitment (i.e., incongruent trials) can strengthen the connectivity between the right IFG and the right amygdala. However, this suggestion should be taken with caution since the interaction between group and time did not reach significance.

Discussion

Our study is the first to show that non-emotional EC training can induce changes in the amygdala, a key region in emotional processing. Results demonstrated reduced activation in the right amygdala following a high-frequent EC training (H-EC group). This reduction in amygdala activation was not found in the L-EC group and was found only following multiple-session training. Importantly, this reduction in amygdala activity was correlated with reduced behavioral interference of aversive pictures following the training. In addition, in contrast to participants in the L-EC group, participants in the H-EC group showed a training-induced increase in the connectivity between the right amygdala and the right IFG, a region associated with inhibition across various domains (Berkman et al., 2009). These findings imply that inhibitory control may be the mechanism subserving the training effects on both amygdala reactivity and functional connectivity with the right IFG. Notwithstanding, this suggestion should be treated cautiously since the interaction between time and group did not reach significance in the analysis assessing amygdala–IFG connectivity.

Emotion–attention interactions

The current work is related to a long-standing debate regarding the relation between emotion and attention. On one hand, it was claimed that emotion does not depend on attention (Öhman et al., 2001). On the other hand, recent work demonstrates that attentional manipulations modulate emotional reactions (Dolcos et al., 2006; van Dillen et al., 2009). These findings suggest that attention and emotion are related in terms of their underlying cognitive mechanisms and neural structures (Okon-Singer et al., 2015; Rohr et al., 2015). Our results are in line with this notion; we show that attention modulates emotional

reactions, but more importantly — we provide clear evidence that attention training that targets EC modulates emotion-related functional architecture.

Findings of the current study are in line with a recent proposal by Okon-Singer et al. (2013) on the mutual relations between emotion and attention. According to this proposal, individual traits and tendencies are reflected in neural connectivity in a network underlying emotional processing and control that includes limbic, brainstem, and fronto-parietal regions. These individual connectivity patterns, in turn, affect the behavioral, neural, and autonomic reactions to emotional stimuli. While many of the studies supporting this model are correlational, the current study provides causal evidence for the role of attention in regulating emotion. Our results are therefore, to the best of our knowledge, the first demonstration that neutrally-valenced attention training can alter emotion-related functional and behavioral markers.

Cognitive training and possible implications for psychopathology

The question whether cognitive training is effective and generalizes to other cognitive domains is still a matter of debate (Owens et al., 2010). Nevertheless, an accumulating body of evidence demonstrates the efficiency of cognitive training and its transfer to other cognitive functions in healthy (e.g., Erickson et al., 2007; Jaeggi and Buschkuehl, 2014), as well as depressed (Owens et al., 2013) individuals. In the context of emotional reactions, training that impacts executive functions has been shown to improve emotion control and alleviate emotional reactions in healthy individuals (Cohen et al., 2015a, 2015b; Schweizer et al., 2011, 2013), as well as in clinical populations (Iacoviello and Charney, 2014; Iacoviello et al., 2014; Siegle et al., 2007).

It is noteworthy that most of the existing training studies resulting in improvement in emotional behavior used a training task that consisted of emotional stimuli. Hence, the effects observed in these studies may be specific to situations in which EC is activated during an emotional stimulation (see Schweizer et al., 2011, for interesting results in this regard). Siegle et al. (2007), however, did show changes in emotional behavior and in emotion-related neural activity following non-emotional training. However, their training battery consisted of several cognitive tasks and as a result, it is unclear what the mechanism underlying the training effects was. The current work suggests that inhibitory control may be the mechanism responsible for shaping emotional behavior during EC training. Presumably, failure to find training effects using non-emotional tasks (Schweizer et al., 2011) may have resulted from the use of tasks that did not recruit inhibitory control (e.g., working memory task in Schweizer et al., 2011).

Our results have implications for the understanding and treatment of psychopathological processes, especially those related to emotion regulation deficits (although please note that our participants were healthy adults within the normal range as assessed using different questionnaires). Individuals suffering from depression and anxiety, disorders which are associated with excessive emotional reactions, show poor executive abilities (Bishop et al., 2004; Eysenck et al., 2007; Fossati et al., 2002; Liberzon and Martis, 2006; Siegle et al., 2007). Furthermore, training participants to recruit EC prior to the presentation of aversive pictures was found to reduce rumination (Cohen et al., 2015a), a maladaptive behavior that is associated with depression. The findings of the current study show that EC training by itself (i.e., not paired with emotional stimulation) can suppress emotional reactions, and thus might serve as a short-term and easy-to-implement treatment for individuals suffering from disorders characterized by emotion dysregulation. This idea is supported by additional post-hoc analyses that we conducted using the questionnaires scores (see Supplementary Information). Future studies with clinical samples may examine the effects of EC training on reduction of clinical symptoms.

Basolateral amygdala (BLA) and emotional processing

The training-induced reduction in amygdala activation observed in the current work seems to stem mainly from the basolateral region of the amygdala. Specifically, the peak activation observed in the interaction between time and group, in both the SVC analysis (using the anatomical ROI of the amygdala) and the whole-brain analysis (Supplementary Table 1), was located in the BLA. The BLA plays a major role in the encoding of aversive information into long-term memories (Fanselow and Ledoux, 1999). Studies on rodents and primates show that the BLA has extensive projections to the neocortex and the thalamus (Amaral and Insausti, 1992) and that emotion-related activation in the BLA, and not in other amygdala sub-regions, is positively related to trait anxiety (Etkin et al., 2004). These findings are consistent with our results of reduced activity in the basolateral region of the amygdala in the H-EC group following the training. Indeed, recent functional connectivity studies revealed that the BLA is connected both to regions implicated in aversive learning and to regions associated with emotion regulation (Robinson et al., 2010; Roy et al., 2009). This functional architecture suggests that the BLA regulates the intensity of emotional reactions and the encoding of aversive information into long-term memory. Our findings are thus highly encouraging because they imply that activity of the BLA can be altered following EC training, what leads to reduced behavioral interference and possibly to attenuated encoding of the aversive information. Further examination using high resolution functional imaging and assessments of memory/learning processes can indicate whether these effects are unique to the BLA or observed also in other amygdala subregions.

Integrating task- and rest-related functional patterns

Our design combined resting-state fMRI with cognitive (emotional and executive) tasks. Validated tasks were used to assess executive-related brain activations and the impact of the training on functional reactions to aversive pictures. In addition, regions which showed higher activation in the tasks were used as seeds in the resting-state fMRI analysis. In recent years, the use of resting-state fMRI was discussed in numerous papers (Biswal et al., 2010; Buckner et al., 2013; Dijk et al., 2010; Margulies et al., 2010; Rohr et al., 2013; Rosazza and Minati, 2011; van den Heuvel and Hulshoff Pol, 2010). Importantly, resting-state fMRI was found to be highly reliable (Friedman et al., 2008; Shehzad et al., 2009) and brain networks that are activated during rest resemble networks that are commonly found to be co-activated during tasks (Smith et al., 2009). Thus, the use of task-based ROIs in resting-state analysis and the use of resting-state activations in task-related BOLD analysis are becoming highly prevalent (Mennes et al., 2010). Using this method enabled us to discover changes in connectivity patterns between the two training groups. Specifically, by using task-based ROIs in the resting-state analysis, we revealed training-induced increase in right amygdala–rIFG connectivity in the H-EC group, but not in the L-EC group. Note, however, that the interaction between training group and time (pre/post training) was only marginally significant, possibly due to the relatively small sample size.

Limitations and future directions

One limitation of the current study concerns the relatively small sample size. Ten participants were not included in the final analyses due to technical problems related to the training or the scanning sessions. Having a larger sample of participants could have increased our ability to find a significant interaction between group (H-EC, L-EC), valence (negative, neutral) and time (time 1, time 3) in the threshold of pFWE $<.05$. This interaction showed a significant activation in the right amygdala using a lower threshold ($p = .02$). Importantly, the right amygdala showed a significant activation in a restrictive threshold (pFWE $<.05$) when entering only the trials containing negative pictures.

This effect was also evident in a whole-brain analysis (Supplementary Table 1). Larger sample size could have also helped in strengthening the marginally significant interaction between time and group in the resting-state data and the association between training improvement and functional changes during the emotional task (see Supplementary Information). It may also have allowed for increasing the cluster threshold for the whole-brain analysis of the executive task data, although we used a relatively stringent voxel threshold of $p < 0.001$ as suggested by Woo et al. (2014).

Another limitation concerns our ability to generalize our results to other EC processes. Our training was based on a specific EC task (the arrow-flanker task), and we did not test whether other EC tasks lead to similar training effects. The flanker task was chosen since it was previously shown to modulate emotional interference (Cohen et al., 2011, 2012, 2015a, 2015b; Cohen and Henik, 2012) and following our notion that inhibitory control is a core mechanism in emotional attenuation. This notion was supported by the connectivity analysis, which showed a training-induced increase in the connectivity between the right IFG, a region associated with inhibition, and the right amygdala. Future studies should explore whether other EC processes, such as working memory updating and set-shifting lead to similar effects on emotional reactions. Future studies can also examine the impact of EC training on additional behavioral measures of emotion, such as the subjective feeling associated with the presentation of aversive stimuli, and whether the effects of the training on emotional reactivity last days, and even weeks, following the training.

A third limitation concerns our limited information regarding the reliability of the emotional interference task. Our design was based on pre-/post-assessment, and therefore we made an effort to have high test–retest stability. Specifically, we used an emotional interference task which is similar to prevalent tasks in the literature, in which an emotional distractor precedes a simple discrimination or detection task (e.g., Buodo et al., 2002; Hartikainen et al., 2000). In addition, we used different IAPS pictures in the pre- and post-measurements to avoid habituation or sensitization. We also included a control group to enable the assessment of such processes, although a control group does not control for interaction effects of training and the specific task. Nevertheless, to the best of our knowledge, there is no clear prior data regarding the test–retest reliability of this type of emotional distraction tasks. This should be clarified in future studies.

Conclusions

The current work suggests that frequent EC recruitment strengthens emotion-regulation circuits and reduces the disruptive effect of irrelevant emotional information on behavioral and functional reactions. These findings provide the first evidence that non-emotional training based on EC can induce changes in emotional behavior through alteration of specific brain regions. It is our hope that the current work would lead to further testing and potentially the development of effective intervention for individuals suffering from maladaptive emotional behavior.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.10.069.

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