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TITLE

Resting-state fMRI detects the effects of learning in short term: a visual search training study

ABBREVIATED TITLE

Rs-FC detects learning in the short term

AUTHORS

Elisenda Bueichekú (1) (bueichek@uji.es), Anna Miró-Padilla (1) (amiro@uji.es), César Ávila (1) (avila@uji.es).

AFFILIATIONS

(1) Neuropsychology and Functional Neuroimaging Group, Department of Basic Psychology, Clinical Psychology and Psychobiology. Unviersitat Jaume I. 12071, Castellón. Spain.

AUTHOR RESPONSIBLE FOR CORRESPONDENCE

Elisenda Bueichekú (bueichek@uji.es) / +34964387665
Basic Psychology, Clinical Psychology and Psychobiology. Universitat Jaume I.
Avda. Sos Baynat, s/n. E-12071.
Castellón de la Plana, Spain.
ORCID: orcid.org/0000-0002-3059-9806

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ABSTRACT

Can resting-state functional connectivity (rs-FC) detect the impact of learning on the brain in the short-term? To test this possibility, we have combined task functional connectivity (task-FC) and rs-FC tested before and after a 30-minute visual search training. Forty-two healthy adults (20 men) divided into no-contact control and trained groups completed the study. We studied the connectivity between four different regions of the brain involved in visual search: the primary visual area, the right posterior parietal cortex (rPPC), the right dorsolateral prefrontal cortex (rDLPFC), and the dorsal anterior cingulate cortex (dACC). Task-FC showed increased connectivity between the rPPC and rDLPFC and between the dACC and rDLPFC from pre-training to post-training for both the control group and the trained group, suggesting that connectivity between these areas increased with task repetition. In rs-FC, we found enhanced connectivity between these regions in the trained group after training, especially in those with better learning. Whole brain independent component analyses (ICA) did not reveal any change in main networks after training. These results imply that rs-FC may not only predict individual differences in task performance, but rs-FC might also serve to monitor the impact of learning on the brain after short periods of cognitive training, localizing them in brain areas specifically involved in training.

MAIN DOCUMENT

1. INTRODUCTION

Resting-state functional connectivity (rs-FC) is a current topic in fMRI studies. This method makes it possible to study the neural activity patterns of regions that are functionally correlated but anatomically distant (Buckner and Vincent, 2007; Greicius et al., 2003; Gusnard and Raichle, 2001). Brain connectivity patterns at rest have largely been studied through fMRI from the observation of temporally correlated, low-frequency, spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals (Biswal et al., 1995; Raichle et al. 2001).

Some authors have argued that functional correlations between regions seem to reflect our lifetime learning experiences (Buckner and Vincent, 2007; Harmelech and Malach, 2013; Miall and Robertson, 2006). Resting-state networks have been associated with memory consolidation processes and the stabilization of neural activity for present or future actions (Buckner and Vincent, 2007; Harmelech and Malach, 2013; Miall and Robertson, 2006). Moreover, the Spontaneous Trait Reactivation (STR) hypothesis proposes that these network relations capture personal experiences and, thus, reflect individual cognitive differences (Harmelech and Malach, 2013). For example, the Human Connectome Project data (Van Essen et al. 2013) is allowing researchers to describe the relation between brain connectivity and several individual behavioral and demographic measures (e.g., Smith et al. 2015). Indeed, the study of brain-behavior relations broadens our understanding of cognitive training benefits such as improvements in cognitive abilities and their relationship with functional connectivity (FC). In this regard, the modulation of rs-FC networks has been observed after sensory, motor, or cognitive training programs that produced changes in the connectivity between brain regions (e.g., Albert et al., 2009; Powers et al., 2012; Takeuchi et al., 2013; Thompson et al., 2016; Taubert et al. 2011; Ventura-Campos et al., 2013).

Despite resting-state networks development is associated with learning through lifetime, connectivity is also susceptible to being modified by either recent or current experiences (Buckner et al., 2013; Guerra-Carrillo et al., 2014). Surprisingly, there is little evidence supporting this hypothesis. One example is found in Albert et al., (2009), which showed an enhanced pattern of connectivity in the left fronto-parietal network after 11 minutes of training to acquire a novel motor skill. The authors interpreted the changes in terms of short-term memory formation that was later going to be consolidated over time. In this study, there was a lack of correlation between brain and behavior changes, but it indicated that short-term cognitive training might lead to neuroplasticity in FC.

Therefore, the main goal of this study was to investigate the effects of short-term cognitive training in visual search on human brain FC patterns. Functional MRI data during resting-state and from the visual search task were collected to investigate brain network plasticity. Additionally, the ability of the resting-state to predict individual differences in learning was studied. The main expected result was that task automaticity after cognitive training would result in increased cognitive efficiency in trained participants at the functional network level. We understand that task automaticity is reached when significantly improved speed response is observed without compromising accuracy in trained participants compared to controls (Bueichekú et al., 2016; Posner and Snyder 1975; Posner, 1978; Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977). Our first hypothesis is that the trained group, compared to the control group, will have increased rs-FC after training between regions that also display increased task-FC. The increased task-FC indicates the regions that are involved in task learning. Secondly, we expected that the trained participants with better connectivity before training will perform the task better after training. Specifically, we expect that rs-FC will be able to make predictions about individual differences in task learning.

2. MATERIALS AND METHODS

2.1. Participants

Functional MRI data were collected from 42 healthy undergraduate students from the Universitat Jaume I. All the participants were right-handed (Oldfield, 1971), had normal or corrected-to-normal vision, and reported no neurological or psychiatric history or past or current use of any drugs. Participants were randomly assigned to a trained group (N = 21; 11 men; age: M = 20.95 SD = 1.43) or to a control group (N = 21; 9 men; age: M = 20.62, SD = 1.83). A between-groups *t*-test was used to determine that the experimental groups did not differ in age (*t*(40) = 0.65 *p* = 0.51). Intellectual level was evaluated with the Matrix Reasoning Test (WAIS-III-R) (Trained group: M = 21.29 SD = 2.26; Control group: M = 21.19 SD = 2.12). A between-groups *t*-test was used to determine that the experimental groups did not differ in intellectual level (*t*(40) = 0.14 *p* = 0.89). All the participants provided written informed consent prior to scanning. The study was approved by the Ethics Committee of the Universitat Jaume I. Participants were paid for testing and training.

2.2. Experimental design

A letter-based consistent mapping visual search paradigm was adapted to a block design. All the participants completed two identical MRI sessions, which always occurred 45 minutes apart. The experimental task details, as well as the task-fMRI data analysis results, have previously been reported in Bueichekú et al., (2016). In addition, please find Supplementary Figure 1, which explains the experiment and task details, in the Supplementary Materials.

2.2.1. Stimuli

In visual search conditions, there were two sets of target stimuli: *B C D F G H* and *L M N P Q R*. Distractors were always *J K Ñ S T V W X Y Z*. Each search frame consisted of the presentation of either six distractors or five distractors and one target. Stimulus locations were randomized in all the conditions, and no stimulus appeared twice in a row in the same location. In addition, a control condition was included in the experimental paradigm to measure a baseline response time and a baseline cerebral response. The control condition matched the visual array used in the visual search conditions. There were only two types of frames in the control condition: a six *A-letter* array and a six *X-letter* array.

2.2.2. Task

The task consisted of 42 active blocks and 42 passive blocks. The active blocks consisted of: 14 control task blocks, 14 search blocks that corresponded to targets *B C D F G H,* and 14 search blocks that corresponded to targets *L M N P Q R*. The blocks were counterbalanced throughout the experiment. In all the blocks, 50% of the trials constituted a target-present frame. Each block had 12 trials, which consisted of 300 ms of a fixation point, 1500 ms of a search frame, and 200 ms of a blank screen. Each block started by presenting the instruction display, which remained on the screen for 3000 ms. All the passive blocks consisted of periods of 8000 ms when the screen remained completely blank.

There were no restrictions to eye movement. Participants had to give manual responses with their right hand. Positive answers were given with their right thumb, and negative ones with their right forefinger. Participants had to give positive answers when they detected a target (either the *A's* on the control task or the letters defined as targets in the visual search conditions) and negative answers when there were no targets. Participants were asked to answer as quickly as possible, but without compromising accuracy.

Stimulus presentation was controlled by the E-Prime software (Schneider et al., 2002), professional version 2.0, which was installed in a Hewlett–Packard portable workstation (screen-resolution 800 × 600, refresh rate of 60 Hz). Participants watched the laptop screen through MRI-compatible goggles (VisuaStim, Resonance Technology, Inc., Northridge, CA, USA), and their responses were collected by MRI compatible response-grips (NordicNeuroLab, Bergen, Norway). The E-Prime's logfile saved several measures, including stimulus presentation timing (i.e., stimuli onset) and duration, along with participants' accuracy and reaction times (RTs) to each stimulus.

2.2.3. Experiment procedure and timing

Before the pre-training MRI session, participants performed a practice task with the visual search task that lasted 7 minutes. Participants had to obtain 80% correct responses on the practice task in order to participate in the fMRI experiment. All the participants included in this study reached this criterion (percentage of hits: Trained group: M = 85.57 SD = 3.99; Control group: M = 85.91 SD = 4.42). No between-groups differences were observed on the practice task, as assessed with a between-groups *t*-test analysis ($t(40) = -0.26$ $p = 0.80$). All the participants completed two identical MRI sessions, which always occurred 45 minutes apart. The in-scanner task lasted 25 minutes. Outside the scanner and in-between the MRI sessions, the trained participants completed the training task (840 trials distributed in 20 blocks) in around 30 minutes

(M: 28.51 minutes SD: 2.71; minimum: 24.38 minutes, maximum: 32.22 minutes). Training on the visual search task was intensive, and, as in the case of the MRI task, it was presented as a block design. Randomly, half the participants from the trained group were trained in searching for targets B C D F G H, whereas the other half were trained in searching for targets L M N P Q R. Therefore, after training, the trained group experienced two types of search conditions: 1) trained search; and 2) untrained search. Thus, searching for either of the two groups of targets would not represent any difference for the control group. It was noteworthy that the control group participants did not perform any training or cognitive tasks between scans, but they stayed outside the scanner for 45 minutes, just as the trained participants did. Apart from the training session, trained participants and control participants did not have different experiences between scans and all received the same instructions about what they were/were not allowed to do. Participants were not allowed to engage in any cognitive activity (e.g., video gaming, reading, etc.), they remained in the waiting area were experimenters could see them all the time, and they were not allowed to eat/drink any stimulant substance (e.g., coffee).

2.3. MRI acquisition procedure

The fMRI data were acquired in a 1.5 T Siemens Avanto scanner (Erlangen, Germany). The same protocol was used during the pre- and post-training sessions. All the participants were placed in the scanner in the supine position. Fixation cushions were used to reduce head motion. First, one high-resolution T1-weighted magnetization prepared rapid gradient echo imaging (MPRAGE) anatomical image was obtained per participant (TR = 2200 ms, TE = 3.8 ms, 256 x 256 x 160 matrix, 1 x 1 x 1 mm in-plane voxel size). Then, a gradient-echo T2*-weighted echo-planar MRI sequence was used to obtain 270 volumes for the rs-fMRI acquisition (24 interleaved ascending slices, 3.5 x 3.5 mm in-plane voxel size, slice thickness 4 mm, interslice gap 0.8 mm, repetition time (TR) = 2000 ms, echo time (TE) = 48 ms, flip angle 90º, 64 x 64 matrix). Finally, for the task-fMRI, a gradient-echo T2*-weighted echo-planar MRI sequence was also used to obtain 602 volumes (29 interleaved ascending slices, 3.5 x 3.5 mm in-plane voxel size, slice thickness 3.6 mm, interslice gap 0.4 mm, TR = 2500 ms, TE = 50 ms, flip angle 90 º, 64 x 64 matrix). All the scanner acquisitions were performed in parallel to the anterior commissure-posterior commissure plane (AC-PC), and they covered the entire brain.

2.4. Behavioral analysis

To assess the behavioral improvement in the performance on the visual search task, accuracy and RT data were separately processed with the IBM SPSS Statistics software (Version 23 Armonk, New York, USA). Only data from correct trials were used in all the behavioral analyses. For each experimental condition, a repeated-measures 2x2 ANOVA was conducted, with the Experimental Group (Trained group *vs*. Control group) as the between-subjects factor and Session (Pre-training session *vs*. Post-training session) as the within-subjects factor. In addition, the change in response speed during cognitive training was assessed by means of a repeated measures *t*-test (first *vs*. last block of the training task).

2.5. Image preprocessing for FC and ICA

The first step of image processing was done using Statistical Parametrical Mapping (SPM 12; Wellcome Department of Imaging Neuroscience, London, England). It involved each subject's task-fMRI and rs-fMRI data set alignment to the AC-PC plane by using its own anatomical image. Then, the Data Processing Assistant for Resting-State fMRI (DPARSF v4.1) (Chao-Gan and Yu-Feng, 2010) was used for standard image data preprocessing. Most of the following steps were common in the preprocessing for ICA and FC analysis, and the steps exclusively used in FC are specified.

i) Correction of the slice timing acquisition differences for interleaved ascending acquisitions. The 24th acquired slice was used as the reference in rs-fMRI, and the 29th acquired slice was used in task-fMRI.

ii) Correction of head motion during acquisition using the two-pass procedure in realignment: first registration to the first image, and then registration to the mean image. In task-fMRI analysis, three participants per group were removed from the analysis due to excessive movement. After that, no head motions that had more than 2.0 mm of maximum displacement in any direction or 2.0° of any angular motion while the scan lasted were found in any participant's data. In order to control the movement effect throughout the experiment, the Root Mean Squared movement values (RMS movement, of translation and rotation parameters) were used to conduct a repeated-measures 2×2 ANOVA with the Experimental Group (Trained group *vs*. Control group) as the between-subjects factor and Session (Pre-training session *vs*. Post-training session) as the within-subjects factor. This analysis was conducted separately for the rs-fMRI and the task-fMRI data. The ANOVA analysis results for the rs-fMRI data indicated that there were no statistically significant main effects of the Experimental Group ($F(1,40) = 1.48$ $p=0.230$), or the Session ($F(1,40) = 1.51$ $p = 0.699$),or the Group x Session interaction ($F(1,40) = 1.23$ $p=0.274$). In relation to the task-fMRI data, no statistically significant main effects were found for the Experimental Group ($F(1,34) = 0.025$ $p=0.875$), or the Session ($F(1,34) = 0.065$ $p=0.801$), or the Group x Session interaction ($F(1,34) = 0.588$ $p = 0.449$).

iii) Individual overlay of the anatomical image and the mean image of the rs-fMRI data or the task-fMRI data by using T1 co-register to functional images.

iv) For FC analysis: reduction in nuisance on the BOLD signal (e.g., respiratory and cardiac effects, motion effects, etc.) by using the nuisance covariates' regression step. First, the polynomial regression trend was set to regress the constant, linear, and quadratic trends out of the functional time series. Then, six-parameter, rigid-body transformation variables (i.e., three rotations and three translations) from the head motion correction step were set as regressors as well. The framewise displacement (FD) of time series was calculated according to Jenkinson et al., (2002). The FD threshold was set to 0.2 for motion censoring (i.e., scrubbing). Each time point above that threshold was identified as a "bad time point" and regressed out, along with one time point before it and two time points after each bad time point. Finally, the regression model included three parameters corresponding to the global mean signal, the white matter signal, and the cerebrospinal fluid signal.

v) Spatial normalization by using the echo-planar image (EPI) template provided by SPM and voxel size resampling to 3 mm^3 to the Montreal Neurological Institute (MNI) space.

vi) Spatial smoothing with a 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel.

vii) For FC analysis: band-pass temporal filtering (0.01 – 0.08 Hz) to remove low and high frequency drift effects.

2.6. Post-processing analysis for FC

2.6.1. Definition of the ROIs

The definition of the regions of interest (ROIs) was carried out using SPM Wake Forest University PickAtlas software (Maldjian et al., 2003). We centered the FC analyses in brain areas that have been signaled as involved in the dorsal stream pathway during visual attention processing (Deco and Rolls, 2005). Thus, we selected areas within the early visual cortex (V1/V2), the posterior parietal cortex, and the dorsolateral prefrontal cortex. We extracted the ROI coordinates from our previous visual search task-fMRI training study (see Figure 3 Bueichekú et al., (2016)), specifically from the whole-brain task contrast that tested which brain regions are generally involved in visual search task performance (all participants, *pre-training session: visual search conditions > control condition*). The results of the task contrast had a voxel-wise threshold of $p < 0.001$ uncorrected and a threshold of $p < 0.05$ Family Wise Error (FWE)-corrected for multiple comparisons at the cluster level; the cluster level was determined by Monte Carlo simulations using the AlphaSim method, with a cluster criterion of $k = 116$ voxels (see Bueichekú et al., 2016). All the coordinates corresponded to peak maximum cortical activations within the abovementioned dorsal stream pathway.

The same regions were used in task-fMRI data (8-mm radius spheres) and in rs-fMRI data (6-mm radius spheres). Slightly bigger spheres were used for the FC analysis of the task-data than for the resting-state data. The main reason for this decision is that task activation maps for visual search tasks are usually characterized by medium-to-large activations in terms of spatial extension (see Bueichekú et al., 2016). We matched the sphere size criterion to the spatial smoothing criterion, which was 6-mm^3. However, we were aware that the visual search task generates large brain activations; therefore, a small size criterion could be unrepresentative of task-data. In short, we wanted to use a representative sphere size for the task data that did not differ too much from the desirable size; thus, we ended up using 8-mm^3 for task data and 6-mm^3 for resting-state data.

Four spheres were defined (onwards seed regions) corresponding to: the right calcarine sulcus (rVisual, MNI: 15, -70, 13), right posterior parietal cortex (rPPC, MNI: 27, -64, 46), right dorsolateral prefrontal cortex (rDLPFC, MNI: 42, 38, 22; Brodmann area 46), and dorsal anterior cingulate cortex (dACC, MNI: 6, 23, 49) (see Figure 1A). To clarify, the region identified as right calcarine sulcus was mainly assigned to V1 (probability for V1 = 63% and for V2 = 27%) by means of the SPM Anatomy Toolbox ("Overlap between structure and function" toolkit) (Eickhoff et al., 2005; Eickhoff et al., 2006; Eickhoff et al., 2007).

2.6.2. Pairwise seed-based FC analysis

Separately for the task-fMRI and for the rs-fMRI data, pairwise seed-based FC analyses were conducted with DPARSF Advanced software. The DPARSF toolbox extracts the mean time course for all of the voxels from each seed region and for each session and subject. Then, the toolbox calculates pairwise linear Pearson's correlations, obtaining the *r*-values and *p*-values for each pair of seed regions. Afterwards, individuals' *r*-values were normalized to *z*-values using Fisher's z-transformation. The *z*-values were stored in a SPSS database and used to study the training effects on task-FC and rs-FC (see Figure 1B), and to study the rs-FC's ability to predict task learning after training.

2.6.3. Cross-sectional analysis in task-FC and in rs-FC

We used IBM SPSS Statistics software in cross-sectional analysis. We conducted between-groups, two-sample *t*-tests with pre-training session task-FC or rs-FC *z*-values to verify that the brain responses yielded by the groups were equal before the training session. If they were, we would attribute the brain changes to the visual search task training.

2.6.4. Training effects in task-FC

To study the training effects in task-FC, we performed an interaction analysis with the individuals' *z*-values. For each seed region pair, we conducted a 2x2 ANOVA with the Experimental Group (Trained group *vs*. Control group) as the between-subjects factor, and Session (Pre-training session *vs*. Post-training session) as the within-subjects factor, using the IBM SPSS Statistics software. This analysis allowed us to study the differences in FC between the pre-training and post-training sessions, while controlling for repetition effects using between-subjects controls (i.e., control group data).

2.6.5. Training effects in rs-FC

To study the visual search training effects in resting-state networks, we performed planned comparisons after a 2x2 ANOVA, defined in the same way as the task-FC analysis, with IBM SPSS Statistics software. Planned comparisons were made based on our hypothesis, which was that the effect of training would result in increased rs-FC in trained participants compared to controls, if increased task-FC was also observed. Therefore, first, the difference in rs-FC *z*-values between sessions was calculated for each participant (*post-training session* > *pre-training session*), and then this variable was used to conduct a between-groups, two-sample *t*-test for each seed region pair.

2.6.6. A priori learning prediction

To study the rs-FC's ability to predict behavioral improvements in task performance, we planned to conduct a correlation analysis with each seed region pair that showed statistically significant changes from the pre-training to post-training session and the behavioral data from the post-training session. We used IBM SPSS Statistics software to conduct linear bivariate Pearson’s correlation analysis between the pre-training session rs-FC *z*-values of each participant and the visual search RT values from the post-training session that corresponded to the trained condition (*trained condition* > *control condition*) for each group separately (N = 21 in each group). If the brain-behavior correlation result was found to be statistically significant, and additional correlation analysis was performed for the visual search RT values that corresponded to the untrained condition (*untrained condition* > *control condition*), then it was used as a control measure.

2.6.7. Complimentary analyses

In relation to the study of the training effects in rs-FC and the learning prediction, complimentary analyses with our original ROIs or with additional control ROIs have been done. The purpose of these analyses was to add reliability to the main rs-FC analyses.

Firstly, the possible differences in signal-to-noise ratio (SNR) were studied because low amplitudes of activity can be masked by noise and lead to apparent changes in FC. Therefore, the level of activity during task or resting-state was evaluated extracting the temporal variance of the signal in each ROI. Then, the following comparisons were made: 1) between group comparisons for each experimental session for which FC was calculated; and 2) within group comparisons for the pre-training session and the post-training session. Please see section *2.1.Analysis of the differences in signal-to-noise ratio (SNR) between groups and across sessions for resting-state FC data and task-FC data* in Supplementary Materials. Secondly, the variability of the resting-state FC patterns was analysed by means of F-tests with the standard deviation values of rs-FC data of each pair of seeds to ensure that resting-state patterns did not influence the subsequent brain activity during visual search task. Please see section *2.2.Additional* *analysis on the variability of the resting-state FC patterns* in Supplementary Materials. Thirdly, in relation to the learning prediction we performed three new Pearson's correlation analysis for: 1) baseline rs-FC and post-training session RT values for the seed pairs that did not show increased connectivity after learning; 2) baseline rs-FC and pre-training session RT values for all the pairs; and 3) baseline rs-FC and difference in RT across sessions for all the pairs. Please see section *2.3. Additional analysis supporting the resting-state FC prediction analysis* in Supplementary Materials. In relation to the main rs-FC analyses, we studied whether rs-FC between the originally selected ROIs and new control ROIs changed as a result of time or training. Please see section *2.4. Pairwise seed-based resting-state FC analyses between independent control seed regions (primary auditory cortex or primary motor cortex) and visual search task key regions* in Supplementary Materials.

2.7. Post-processing analysis for ICA

2.7.1. Group spatial ICA

In order to obtain the functional brain networks that underlie the rs-fMRI data, group spatial ICA was performed (Calhoun et al., 2001). The first step involved the estimation of the optimal number of components, which resulted in 19 independent components using minimum description length criterion (Li et al., 2007). Then, group ICA was performed using the Gift toolbox (http://icatb.sourceforge.net) and the Infomax algorithm (Bell and Sejnowski, 1995). In addition, and to ensure the stability of the results, 20 iterations of the ICA were conducted using ICASSO software (http://www.cis.hut.fi/projects/ica/icasso) (Himberg et al., 2004). The best estimated component for each independent component was used in subsequent analyses. This refers to the use of the centrotype of the cluster, or the average of the estimates belonging to a single cluster, by means of ICASSO software. According to Himberg et al., (2004), the use of the centrotype of the cluster is more reliable than the use of an estimate from a single run of ICA. Then, the group ICA-3 back-reconstruction approach was used to calculate the individual maps for each independent component and its time courses (Calhoun et al., 2001; Calhoun et al., 2002; Erhardt et al., 2001). The voxel values for the individual maps represent their contribution to the component time course. Usually the voxel values are scaled using *z*-scores in order to determine which voxels contribute significantly to a particular component map. These spatial maps are then used to study the brain between groups and/or across sessions. The aggregate independent component maps were matched to resting-state networks (Ventura-Campos, 2013, Damoiseaux et al., 2006) by visually inspecting the group maps, discarding the maps that corresponded to physiological noise or motion, and taking into account the average power spectra (Lowe et al., 1998).

2.7.2. Cross-sectional analysis in ICA networks

To test that there were no differences in baseline resting-state response, we conducted a between-groups two-sample *t*-test with the pre-training session maps for each identified network in SPM 12. The presence of equal brain responses by the groups before training was a necessary condition to later discuss training effects.

2.7.3. Training effects in ICA networks

To study the training effects in the ICA networks, we performed interaction analyses with the individuals' maps in SPM 12. Interaction analyses were conducted at the voxel-wise level, and the voxel values of the individual map represented the contribution of each voxel to the component time course. The aim of the analysis was to study the brain differences due to training at the whole-network level. In this analysis, we included the control group data and compared the resting-state networks across time (pre-training *vs*. post-training session). Therefore, for each network, we conducted a 2x2 ANOVA with the Experimental Group (Trained group *vs*. Control group) as the between-subjects factor, and Session (Pre-training session *vs*. Post-training session) as the within-subjects factor, using the SPM 12 software.

2.7.4. Brain and behavioral correlation in ICA networks

For each network, a multiple regression analysis with the RT values was performed in SPM 12. This analysis was conducted separately for each group (N=21 per group). On the one hand, we used the individual maps from the pre-training session (i.e., the voxels' contribution to the component's time course), and so the data would predict the individual differences in behavioral improvement. On the other hand, we introduced the RT values as a variable that measured behavioral improvement. The RTs were defined as *Trained condition > control condition in post-training session*, as in the abovementioned rs-FC brain-behavior correlation analysis.

3. RESULTS

3.1. Behavioral analyses results

In order to assess the effects of training on the performance of the visual search task, group comparison behavioral analyses were performed with RTs and accuracy scores collected during the task-fMRI sessions. For each experimental condition, a repeated-measures 2x2 ANOVA was conducted, with the Experimental Group (Trained group *vs*. Control group) as the between-subjects factor and Session (Pre-training session *vs*. Post-training session) as the within-subjects factor. Additionally, the change in response speed during cognitive training was assessed by means of a repeated-measures *t*-test.

With regard to the performance change during cognitive training, we found steadily decreasing RT values as trials were completed. When comparing the RTs from the first block (M=746.23 SD=211.88) to the last one (M=622.67 SD=182.94), a statistically significant difference was found in response speed ($t(20)= 3.57$ $p = 0.001$, paired *t*-test, one-tailed).

In relation to the RT values (see Figure 2), a main effect of Session was found in the trained condition data ($F(1,40) = 226.27$ $p < 0.001$) and in the untrained condition data ($F(1,40) = 70.84$ $p < 0.001$). These main effects were driven by statistically significant Group x Session interactions, found in both the trained condition data ($F(1,40) = 34.29$ $p < 0.001$) and the untrained condition data ($F(1,40) = 5.70$ $p = 0.022$). These interactions indicate that trained participants performed the search conditions faster than control participants in the post-training session compared to the pre-training session. Finally, in the control condition, a main effect of Session ($F(1,40) = 19.60$ $p < 0.001$) was found, indicating that all the participants were faster in the post-training session than in the pre-training session, but no significant Group x Session interaction was found ($F(1,40) = 0.106$ $p = 0.746$).

With regard to the accuracy values (see Table I), a main effect of Session was found in the trained condition data ($F(1,40) = 21.05$ $p < 0.001$) and in the untrained condition data ($F(1,40) = 6.80$ $p = 0.013$), but no Session effect was found in the control condition data. No significant interactions were found. The accuracy data indicate that both groups gave more accurate responses in the post-training session than in the pre-training session in the search conditions.

In summary, both groups of participants improved their performance as they gained experience on the task. However, it is noteworthy that only trained participants performed the task significantly faster in the post-training session, which must be the result of cognitive training. The effects of training were observable for both the trained and untrained targets. Further analyses revealed that training must be quite specific because response speeds were faster for the trained targets (M = 603 ms, SD = 122.68) than for the untrained targets (M = 692 ms, SD = 181.25), with a between-conditions difference that approached statistical significance ($t(20) = -2.05$ $p = 0.054$, paired *t*-test, two-tailed).

3.2. Task-FC analyses results

3.2.1. Cross-sectional analyses in task-FC

A between-groups, two-sample *t*-test with pre-training session task-FC *z*-values was conducted for each seed region pair to discard any possible baseline differences in connectivity. Cross-sectional analysis results yielded no significant group differences in the pre-training session; therefore, the connectivity differences from pre- to post-training were associated with training effects.

3.2.2. Training effect analysis results

Training effects on task-FC were studied by means of 2x2 ANOVAs using *z*-values between seeds as a dependent variable, with Experimental Group (Trained group *vs.* Control group) as the between-subjects factor, and Session (Pre-training session *vs.* Post-training session) as the within-subjects factor (see Figure 3). A significant main effect of Session ($F(1,34) = 5.25$ $p = 0.028$) was found when studying the training effects between rPPC and dACC (see Figure 3A), indicating that in general participants had more synchronous functional activity between these regions in the post-training session than in the pre-training session. This main effect was driven by a Group x Session interaction approaching significance ($F(1,34) = 3.685$ $p = 0.063$), indicating that the control participants (M = 0.26 SD = 0.22) had a more coupled pattern of connectivity between rPPC and dACC in the post-training session than the trained participants (M = 0.18 SD = 0.19). Here, we interpreted this pattern of results as showing that task-FC rapidly increased when repeating the task, but this effect disappeared with training.

A significant main effect of Session (*F*(1,34) = 4.75 *p* = 0.036) was found when studying the training effects between dACC and rDLPFC (see Figure 3B), and also between rPPC and rDLPFC, with a main effect of Session approaching significance (*F*(1,34) = 3.37 *p* = 0.075) (see Figure 3C). These results indicated that in general all the participants had more synchronous functional activity between these regions in the post-training session than in the pre-training session, suggesting that task-FC between areas increased from the beginning of the training (i.e., control group) to the end (i.e., trained group). No other significant main effects or significant interactions were found for the task-FC data.

3.3. Rs-FC analysis results

3.3.1. Cross-sectional analyses in rs-FC

A between-groups, two-sample *t*-test with pre-training session rs-FC *z*-values was conducted for each seed region pair to discard any possible baseline differences in connectivity. Cross-sectional analysis results yielded no significant group differences in the pre-training session; therefore, the connectivity differences from pre- to post-training were associated with training effects.

3.3.2. Training effects analysis results

Training effects in rs-FC were studied by means of planned comparisons according to our initial hypothesis, which was that the trained group would have increased rs-FC after training compared to controls in those pairs of seeds that showed increased task-FC. Thus, between-groups, two-sample *t*-tests with the difference in the rs-FC z-values from pre-training to post-training were conducted for each seed region pair. Compared to controls, the trained participants showed increased rs-FC after training in rPPC and rDLPFC ($t(40) = 2.67$ $p = 0.006$, one-tailed) (see Figure 4A and Figure 4B). In addition a between-groups difference approaching significance was found in dACC and rDLPFC ($t(40) = 1.49$ $p = 0.073$, one-tailed). The 2x2 repeated-measures ANOVAs conducted to investigate rs-FC in other pairs did not yield any significant effects or interactions.

3.3.3. Task learning prediction analysis results

Linear bivariate Pearson correlation analyses were used to study the rs-FC's ability to predict task performance improvement. Therefore, this analysis was performed with the regions that showed changes from the pre-training session to the post-training session, which were the rPCC and rDLPFC and the dACC and rDLPFC. We found a significant correlation ($p < 0.05$) between the pre-training session rs-FC of rPPC and rDLPFC and the trained condition RTs from the post-training session (*trained condition* > *control condition*) for trained participants ($r = -0.512$ $p = 0.018$ N = 21), but not for control participants ($r = -0.042$ $p = 0.856$ N = 21) (see Figure 4C). The difference between these two correlation coefficients was statistically significant (*Trained group* > *control group*, $z = -1.57$ $p = 0.05$, one-tailed). This means that the rs-FC between rPPC and rDLPFC is able to predict which participants will benefit more from training. In this case, having better connectivity between these two specific areas implies being able to find the trained targets faster. It is worth noting that the correlation result found for the trained targets was unique and contrasted with the result found for the untrained targets (*untrained condition* > *control condition*) (trained group: *r* = -0.120 *p* = 0.603 N = 21). The difference between the correlations was statistically significant (*Trained group: trained targets* > *untrained targets, z* = -2.06 *p* = 0.02, one-tailed), which highlights the specificity and accuracy of the study of neural connectivity in predicting human behavior. Finally, the rs-FC of dACC and rDLPFC failed to predict task performance improvement, as we did not find a significant correlation between pre-training session connectivity and trained condition RTs in the post-training session (trained group: *r* = 0.049 *p* = 0.833 N = 21; control group: *r* = 0.342 *p* = 0.129 N = 21). The difference between the correlations was not significant (*Trained group* > *control group, z* = -0.92 *p* = 0.18, one-tailed).

3.4. Resting-state ICA results

3.4.1. ICA maps and resting-state networks

Group spatial ICA was performed to obtain the functional brain networks that underlie rs- fMRI, and then study the connectivity differences due to training. Please find the Supplementary Figure 2, which includes a representative example of the maps, in the Supplementary Materials.

3.4.2. Cross-sectional analyses in ICA networks

A between-groups, two-sample *t*-test with pre-training session data was conducted for each network to discard any possible baseline differences in connectivity. Cross-sectional analysis results yielded no significant differences.

3.4.3. Training effect analysis results

We used interaction analysis (i.e., ANOVA) to test whether or not there were any connectivity differences in each network due to training. It should be noted that the individual maps associated with known resting-state networks are composed of voxels whose values represent their contribution to the component's time course. For each network, a 2x2 ANOVA was conducted, with the Experimental Group (Trained group *vs.* Control group) as the between-subjects factor, and Session (Pre-training session *vs.* Post-training session) as the within-subjects factor. The results yielded no significant differences in any possible direction at the pre-established threshold (p = 0.001).

3.4.4. Brain and behavioral correlations in ICA networks

We used multiple regression analysis to study whether individual differences in behavioral improvements were predicted by the resting-state at the whole-network level. No correlation results were found to be significant in the variable introduced in the models (*Trained condition > control condition in post-training session*).

4. DISCUSSION

The aim of this fMRI study was to investigate the changes in brain FC after a short-term visual search training. We expected that the trained group would have increased rs-FC after training, compared to controls, in those brain regions that had increased task-FC. During the task, the main results showed, in all the participants, an increased task-FC between dACC and rDLPFC also between dACC and rPPC, and a trend toward an increase between rPPC and rDLPFC in the post-training session, which reflect a time effect and must be related to task repetition. Some of these brain areas showed increased rs-FC in trained participants after training. Additionally, we found that the rs-FC between the rPPC and rDLPFC predicted learning. However, when studying the effects of training at the whole-network level by means of ICA, we did not observe any differences between groups across sessions. According to our results, rs-FC identifies the specific regions involved in improved functioning and predicts task learning after a short training, indicating that it could be used to monitor the changes in the brain produced by experience.

A general performance improvement across time was observed in all the participants, which could indicate task adaptation. We observed that trained participants improved in both search conditions, which may be related to slight specific transfer effects (Noak et al., 2014). With regard to the trained condition, the changes in search speed could be associated with a gradual change from controlled to automatic information processing (Neisser, 1963; Neisser et al., 1963; Prinz, 1979; Rabbit et al., 1979; Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977), especially after participants had completed a significant number of training trials (i.e., 840 training trials). Previous behavioral studies have demonstrated that 600 training trials in constant search conditions should be sufficient to observe changes in information processing (Shiffrin and Schneider, 1977). The slight improvement in response speed in control participants could be related to task adaptation and retest effects (Garavan et al., 2000; Schneiders et al., 2011).

Parallel to the behavioral changes, we observed brain FC changes due to training. Some authors have indicated that current or recent experiences are able to modify FC involving memory consolidation processes and information processing of present or future actions. Thus, short-term training could lead to enhanced connectivity (Albert et al., 2009; Buckner et al., 2013). Although long-term rs-FC studies are abundant, less attention has been paid to short-term or immediate changes. As far as we know, there are no previous rs-FC studies after short-term cognitive training (i.e., less than an hour and/or same day pre-post studies) on a visual search task, and few studies have focused on other systems, such as the motor system (Albert et al., 2009). In this study, trained participants completed around 30 minutes of visual search task training. We observed an increase in task-FC after training between dACC and rPCC or rDLPFC when the trained participants were compared to the controls. These results indicate that task-FC increases when participants start to gain experience, until asymptotic performance is achieved. In the pre-training session, both groups had low performance on task, but in the post-training session, the control participants performed the task as a group that was starting to gain experience, and the trained group had high performance because they had completed 840 trials of specific training. The enhancement of task-FC reveals that the cognitive systems involved in the task improved their functioning due to task repetition, which possibly included an improvement in the efficiency of the information processing system and memory consolidation processes (Buckner and Vincent, 2007; Miall et al., 2006).

The rs-FC detected the specific neuroplasticity changes that occurred due to training. It was more sensitive than the ICA, which showed no changes in whole-brain resting-state networks. This lack of differences in ICA is consistent with a recent investigation conducted by Gratton et al. (2018) focused on the variability of functional brain networks. The authors found that functional networks are ruled by common organization patterns, like genetics and structural connections, as well as, stable individual features, like long-term histories of co-activation. In addition, there was found a subtle modulation of functional networks by task-states and individual performance, including brain-behavior interactions; and this modulation was largely associated with individual-specific effects. Despite that, Gratton et al. (2018) found that task-state and day-to-day variability is modest. On the other hand, we observed enhanced rs-FC after training in trained participants between rPPC and rDLPFC. The enhanced rs-FC possibly reflects better communication between these areas, either because the system has learned that these areas are likely to be co-activated (Fair et al., 2009; Lewis et al., 2009), or, based on the environmental demands, the system is anticipating and predicting that these areas are going to work together on present or future tasks (Bar, 2007; Raichle, 2010). In summary, it is possible to say, that training strengthened the connectivity of two brain regions that typically work together. It is well known that the brain regions that usually co-work have synchronized patterns of activity and form a functional network during rest (van den Heuvel and Hulshoff Pol, 2010). In this sense, the idea that rs-FC is originated as a neural phenomenon is supported because of the overlap in neuroanatomy and function of brain regions that form networks, thus, functional networks at rest reflect the co-activation of brain areas that are anatomically separated. In our study, the pre-existing connectivity patterns of rPPC and rDLPFC were rapidly modified by a specific but individual experience, the training, and these modifications were observable especially at rest. It is thought that daily variability has a minor contribution to functional networks (Gratton et al. 2018), but the evidence found here and in previous works (e.g., Lewis et al. 2009) support that experience-based variability has an effect on functional brain connectivity, which might be due to the specificity and the intensity of the training session. In agreement with Gratton et al. (2018), these changes are specific and different for each individual; moreover, their effects are likely to affect higher-order processing and control areas (i.e., frontoparietal areas). As said, training was an individual experience that modified the brain networks; this gives support to the STR hypothesis, which proposes that rs-FC reflects individual cognitive differences derived from lifetime experiences (Harmelech and Malach, 2013). Here, we showed that a learning experience changed the connectivity between rPPC and rDLPFC, and that rs-FC was able to predict cognitive individuality.

Different perceptual learning investigations have been devoted to explore how functional networks change by using rs-FC (e.g., Lewis et al. 2009; Guidotti et al. 2015). In general lines, there is a good alignment between our results and previous research, in which it is consistently found a relationship between resting-state and behavioral improvement after training (Lewis, et al. 2009; Guidotti et al. 2015). Evidence supports that resting-state captures and reflects individual differences in sensorial and cognitive tasks, and these differences are associated with experience. For example, in Lewis et al. (2009), the authors concluded that the regions involved during a shape-discrimination task led to modifications of the same brain regions during rs-FC. In this line, we found that task-FC increases between areas implicated in task performance as participants gain experience in task execution. Another example is found when using multivariate pattern analysis; Guidotti et al. (2015) found that after learning, the resting-state networks reflected the processes and features that were learnt during training. As in our study, task data sets were useful to locate the areas that functionally support the task execution. Then, resting-state data was used to study the specific brain-behavior relations after training. On the other hand, one main difference between previous studies and the present investigation is the difference in training duration; so far, it was usually required that participants trained during several days (Lewis et al. 2009; Guidotti et al. 2015), our training lasted 30 minutes approximately. Additionally, their perceptual learning training was limited to one visual field (i.e., left lower visual quadrant) and used a shape-discrimination task, which is slightly different from using a visual search task. More importantly, and as a novelty, in our study it was found that cognitive training led to changes in task-FC that had a close relationship and were in the same direction that the specific rs-FC changes.

In general, our results agree with the hypothesis of *cognitive efficiency*, as the brain changes its network organization in order to become more efficient in information processing and, thus, adapt its functioning to the current demands (Buckner and Vincent, 2007; Miall et al., 2006; Bullmore and Sporns, 2012). The three regions that changed – the PPC, the DLPFC, and the dACC – have been related to visual search task and attentional control (Corbetta and Shulman, 2002; Dosenbach, et al., 2006; Dosenbach, et al., 2007; Power and Petersen, 2013; Seeley et al., 2007). Not so many investigations have been done with the same objective as this one. A general possible explanation is that increased FC represents greater attentional control dedicated to perform better a task that has been training, in this case, visual search. Right now, the observable changes in the brain connectivity of different brain regions can be described at the macroscopic level and associated with their different roles. One of the PPC's main functions is to link top-down, bottom-up, and motor information, and control the attention focus using priority maps during visual attention tasks, through which the evaluation of visual objects and the selection of relevant items are carried out (Bisley et al., 2010; Corbetta and Shulman, 2002; Hopfinger et al., 2000; Kastner and Ungerleider, 2000; Petersen and Posner, 2012; Ptak, 2012). The PPC seems to be crucial during visual information processing because it holds the visual templates for both the dorsal and ventral stream pathways (Peelen and Kastner, 2014). The DLPFC has been related to initiating and adjusting control on cognitive attention-demanding tasks, and to exerting top-down influence on the information stream pathways (Dosenbach, et al., 2006; Dosenbach, et al., 2007; Noudoost et al., 2010). In our opinion, the increased connectivity between rPPC and rDLPFC indicates a better interplay between these areas, as abovementioned, the increased connectivity possibly indicates a strengthened connection, which means a better synchronization of the activation of both areas. The synchronization of brain activity might be interpreted as a facilitation of the role that different brain areas perform jointly. Previous research has found that the neural response of the DLPFC is enhanced when attention shifts occur toward relevant stimuli and this area influences the information processing pathways, including the PPC's activity (Garavan et al., 2000; Dosenbach et al., 2008). Furthermore, we found that enhanced connectivity between the PPC and DLPFC predicted the development of automaticity. In other words, the participants with higher connectivity between these areas before training were able to search for the trained targets faster in the post-training session, and they produced more similar responses to these items and control targets in terms of response speed. This result agrees with neurocomputational models where both posterior and frontal brain association areas have important roles in the top-down control of attention (Deco and Rolls, 2005). Overall, the connectivity of the dorsal system improved through training, but having an enhanced fronto-parietal connection by default, or at least prior to cognitive training, is beneficial in performing visual attention tasks. Finally, the dACC activity has been associated with the role of supervisory attentional control, and it participates in inhibitory and control processes (Dosenbach, et al., 2006; Seeley et al., 2007; Power et al., 2011; Cieslik et al., 2015). The visual search task requires a great degree of control, like many cognitive tasks. Whereas the DLPFC has a specific top-down role in visual search tasks, the connectivity with dACC could be more general and related to inhibitory processes. This may explain why no brain-behavior predictive correlations were found with the rs-FC of these areas (dACC and rDLPFC).

Some limitations of our study are the use of a passive control group and the absence of follow-up sessions to test the stability of the behavior and brain modifications. It was challenging to find a control training task similar enough to our task that did not produce similar or identical brain effects. Previous studies focusing on the visual search domain did not include a control group or, at the most, used a passive control group (Jansma et al., 2001; Kübler et al., 2006).

5. CONCLUSIONS

This fMRI study combined task and resting-state measures to investigate the neuroplasticity changes that occur after completing a 30-minute visual search training. We found that task-FC between some of the regions involved in visual search task showed increased connectivity in all participants (e.g., rDLPFC, rPCC or dACC), which might be due to repetition effects. On the other hand, rs-FC showed increased connectivity after the training period (e.g., rPPC and rDLPFC) only in training participants, detecting the specific effects of training in the short-term. Positive brain-behavior correlations predicted the neuroplasticity changes, as the fastest trained participants in the post-training session had the highest connectivity between rPPC and rDLPFC before training. In conclusion, rs-FC detected the impact of learning on brain connectivity in the short-term and predicted which learners would benefit more from training.

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CONFLICT OF INTEREST

The authors declare no competing financial interests

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FIGURE LEGENDS

Figure 1. Seed regions for rs-FC analysis and correlation matrices. (A) ROIs selected for the task-FC and rs-FC analysis depicted in sagittal and axial slices (coordinates are in the MNI space) **(B)** Rs-FC (above) and task-FC (below) correlation matrices for each experimental group and session (matrices represent the mean pairwise FC *z*-values). Abbreviations: R = right; rVisual = right calcarine sulcus; rPPC = right posterior parietal cortex; rDPLFC = right dorsolateral prefrontal cortex (BA 46); dACC = dorsal anterior cingulate cortex; Pre = pre-training session; Post = post-training session.

Figure 2. Trained participants improved their response speed on a visual search task due to training. RT analysis results are presented for **(A)** control condition **(B)** trained condition and **(C)** untrained condition. Compared to controls, the trained participants were faster during the post-training session than during the pre-training session in both the trained and untrained conditions. Values express the averaged median RTs for each condition and session. * $p = 0.05$, ** $p < 0.001$.

Figure 3. Task functional connectivity changes. In relation to **(A)** rPPC and dACC, we found that, all participants had more connectivity in post-training session than in pre-training session, but the control group had more connectivity than the trained group in the post-training session, indicating that FC increased with task repetition and then returned to the pre-training state with training. In relation to **(B)** rDLPFC and dACC and **(C)** rPPC and rDLPFC, in general, all the participants, in the trained or control groups,

had more connectivity in the post-training session than in the pre-training session. To note that all the cross-sectional analysis results yielded no significant group differences in pre-training session. * $p < 0.05$. Abbreviations: rPPC= right posterior parietal cortex; rDPLFC= right dorsolateral prefrontal cortex (BA 46); dACC = dorsal anterior cingulate cortex; Pre = pre-training session; Post = post-training session.

Figure 4. Resting-state functional connectivity changes and learning prediction. **(A)** The rPPC and the rDLPFC were the regions associated with the visual search task training. **(B)** The trained participants had more rs-FC between rPPC and rDLPFC in the post-training session than the control participants and compared to the pre-training session connectivity values. **(C)** In addition, results showed that the trained participants with better performance after training, e.g. fast and accurate responses, initially had more synchronous FC between these areas. This correlation was found only for trained participants but not for controls (see *Task learning prediction results*). In **(C)**, connectivity values correspond to rs-FC mean z-values between rPPC and rDLPFC in the pre-training session. RT values represent the response speed during the post-training session (*trained search > control condition*). * $p = 0.05$. Abbreviations: rPPC= right posterior parietal cortex; rDPLFC= right dorsolateral prefrontal cortex (BA 46); Pre = pre-training session; Post = post-training session.

TABLES

Table I. Accuracy values. The table summarizes the accuracy values and their SD throughout the experiment. The values express the averaged correct responses per condition and session (maximum score = 12), and the SD appears in parentheses.

	PRE-TRAINING SESSION			**POST-TRAINING SESSION**		
	Control Condition	**Trained search**	**Untrained search**	**Control condition**	**Trained search**	**Untrained search**
Trained group	11.95 (0.21)	10.71 (0.64)	10.85 (0.47)	11.86 (0.36)	11.29 (064)	11.06 (0.74)
Control group	12.00 (0.00)	11.00 (0.71)	10.85 (0.63)	11.95 (0.23)	11.38 (0.67)	11.21 (0.52)

FIGURES

Figure 1

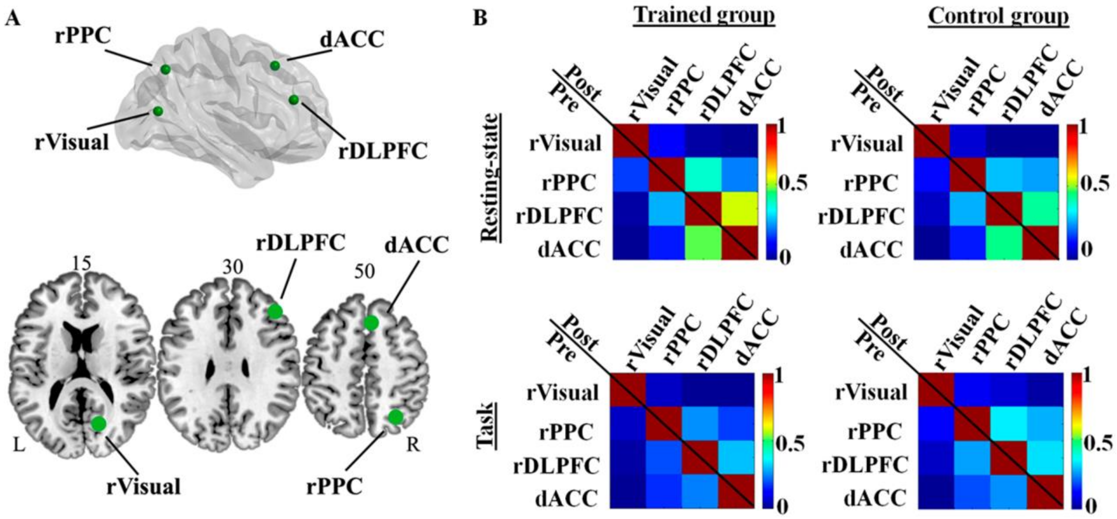


Figure 2

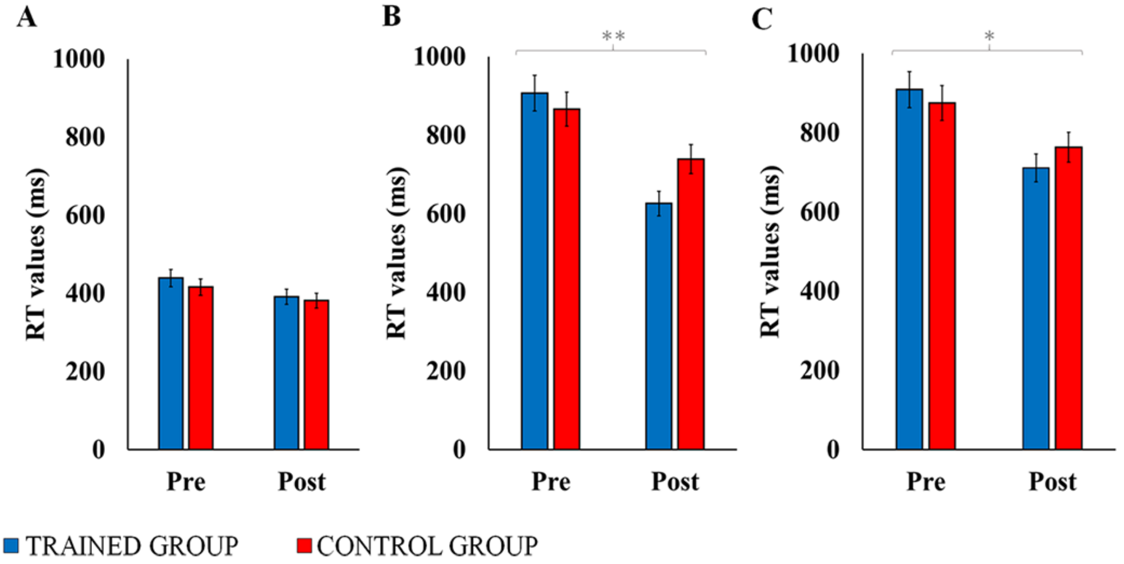


Figure 3

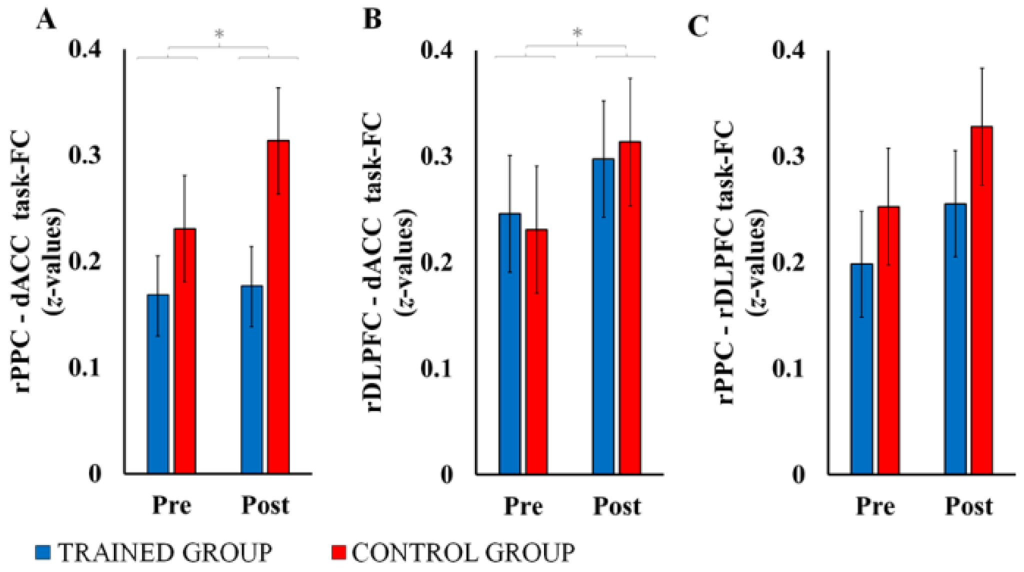
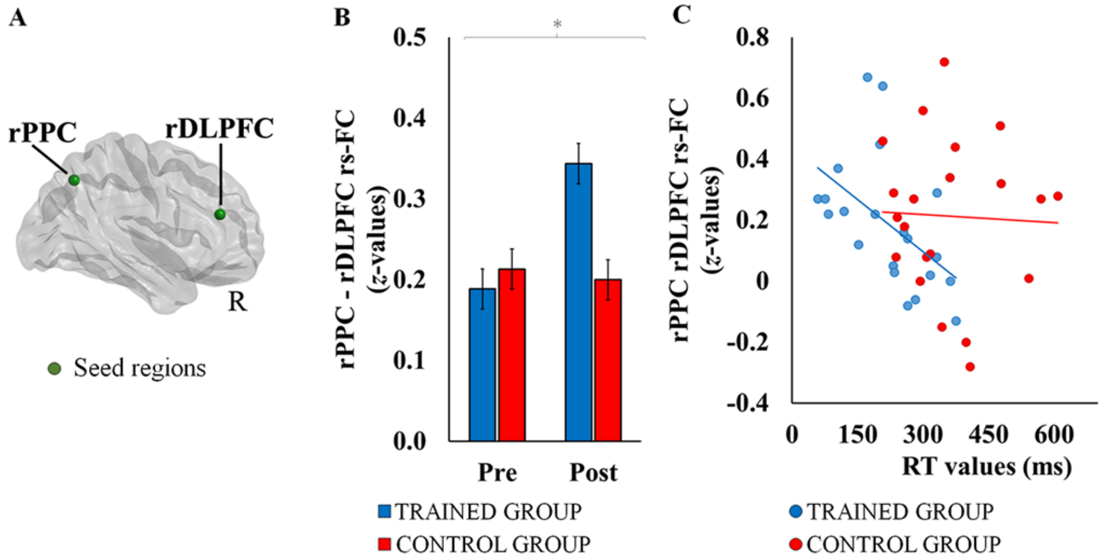


Figure 4



SUPPLEMENTARY MATERIALS

This document contains the following sections:

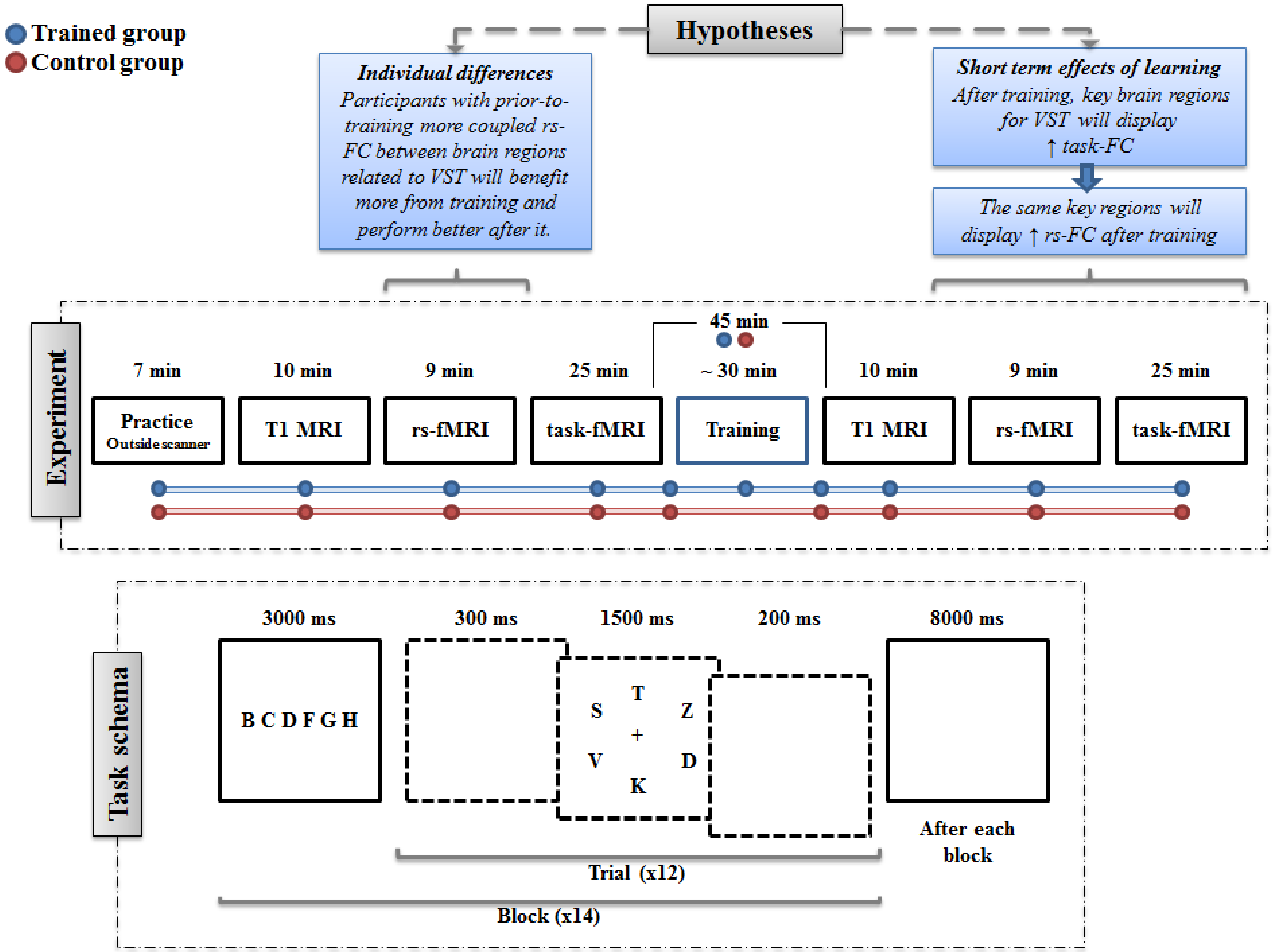
1. Supplementary figures
    1.1. Schematic representation of the experimental procedure
    1.2. Group ICA estimated resting-state networks

2. Complementary analysis
    2.1. Analysis of the differences in signal-to-noise ratio (SNR) between groups and across sessions for resting-state FC data and task-FC data.
    2.2. Additional analysis on the variability of the resting-state FC patterns.
    2.3. Additional analysis supporting the resting-state FC prediction analysis.
    2.4. Pairwise seed-based resting-state FC analyses between independent control seed regions (primary auditory cortex or primary motor cortex) and visual search task key regions.

1. SUPPLEMENTARY FIGURES

1.1. Supplementary Figure 1. Schematic representation of the experimental procedure.

At the top part of the figure, the experiment hypotheses have been summarized according to the experiment. The central part of the figure is dedicated to the organization of the experiment. The experiment was conducted in one day, and, as can be observed, each participant completed two fMRI sessions that took place 45 minutes apart. The trained participants are represented in blue (dots and lines), and the control participants in red (dots and lines). Note that only the trained group did the training session between the fMRI scans, but both experimental groups had 45 minutes between scanning sessions. The control group participants did nothing but rest (i.e., no cognitive or mental tasks). At the bottom part of the figure, the organization of the visual search task (VST) is displayed. The experimental design consisted of 42 active blocks and 42 passive blocks. The active blocks consisted of: 14 control task blocks, 14 search blocks that corresponded to targets *B C D F G H*, and 14 search blocks that corresponded to targets *L M N P Q R*. The image has been adapted with permission from Bueichekú et al., 2016, NeuroImage 135, 204–213.

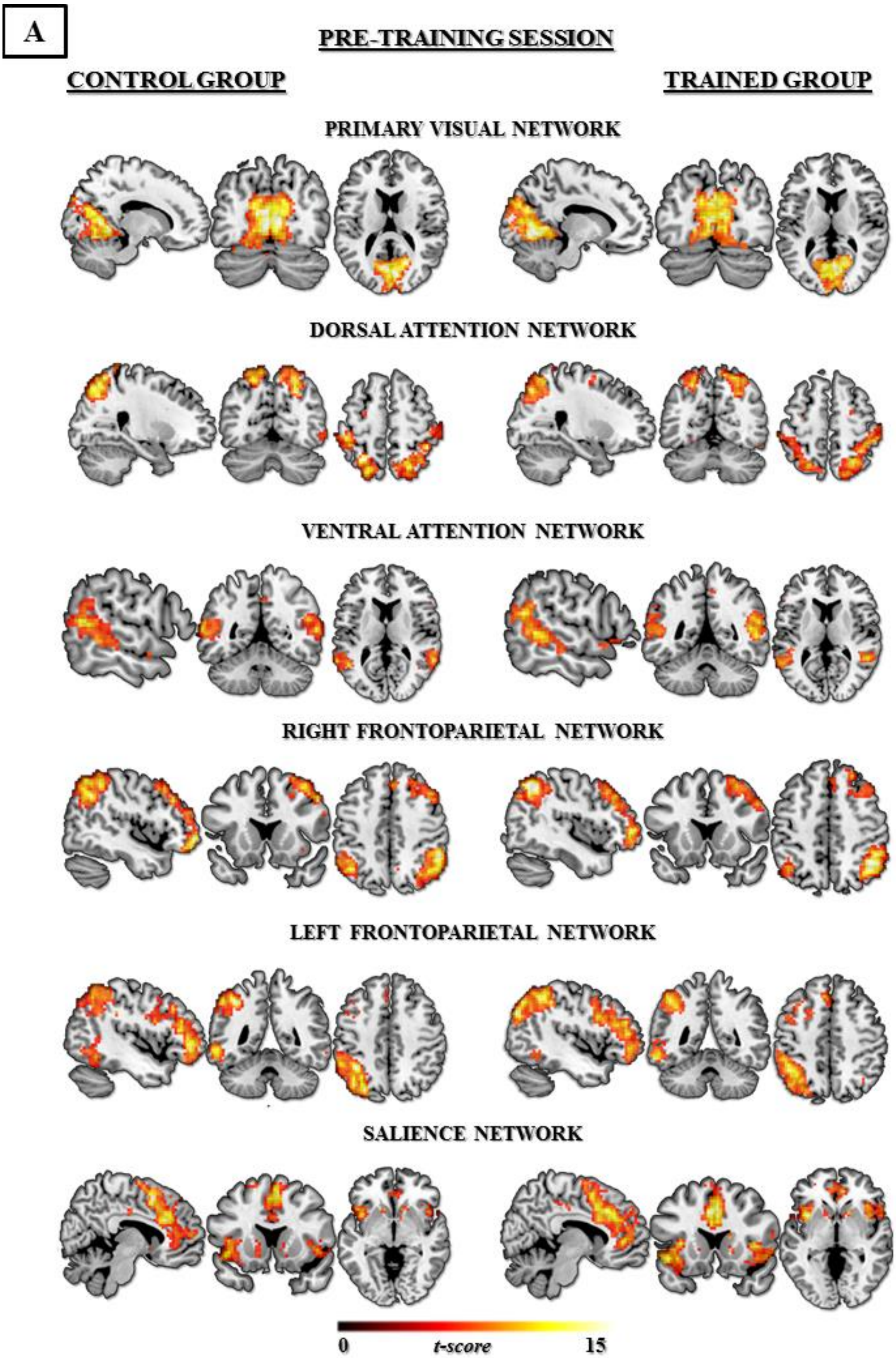


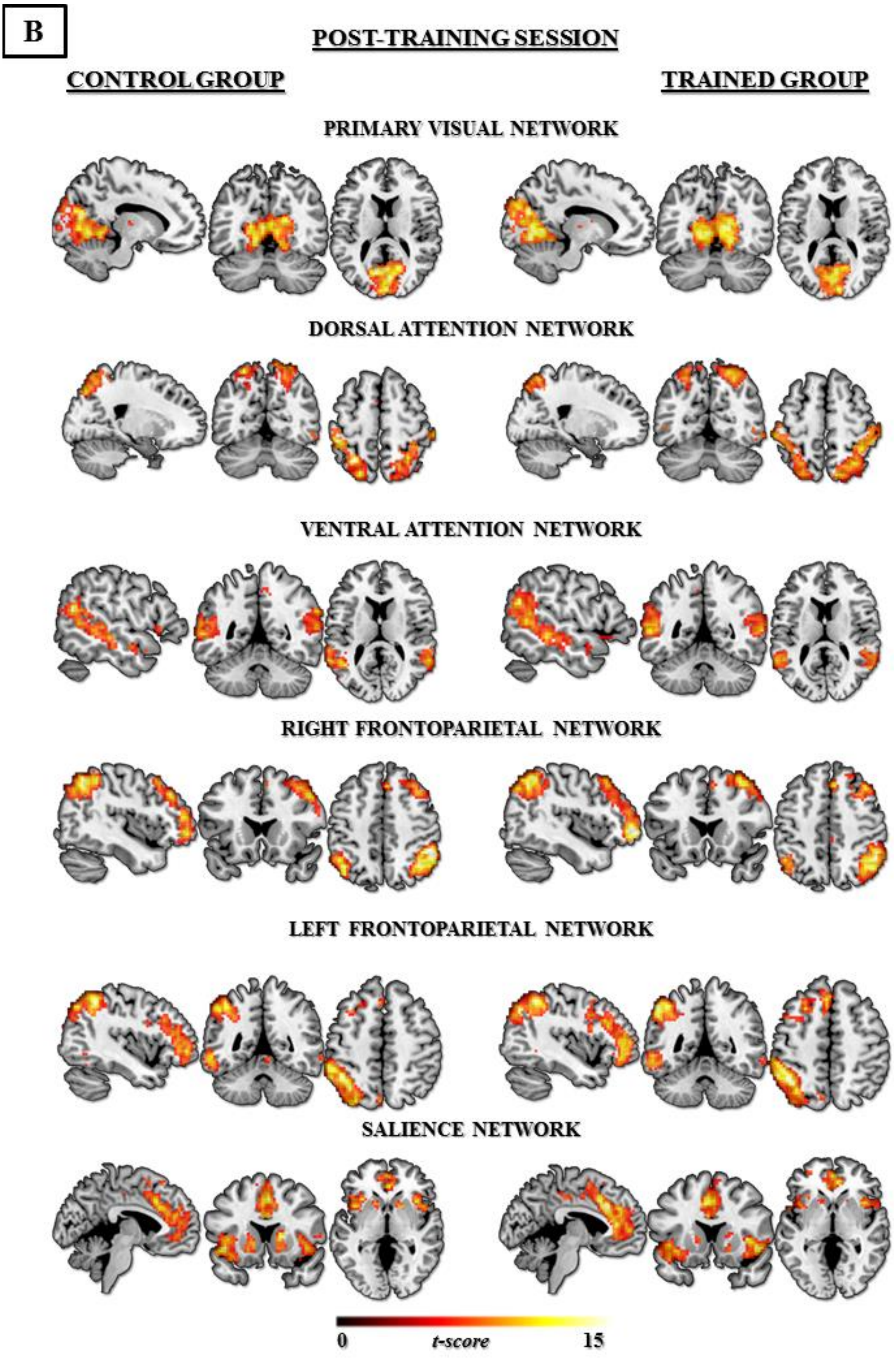
Individual differences
Participants with prior-to-training more coupled rs-FC between brain regions related to VST will benefit more from training and perform better after it.

Short term effects of learning
After training, key brain regions for VST will display ↑ task-FC

The same key regions will display ↑ rs-FC after training

1.2. Supplementary Figure 2. Group ICA estimated resting-state networks. Spatial maps of six independent components were identified as resting-state networks for both the control group and the training group in (A) the pre-training session and (B) the post-training session. No statically significant differences were found between groups or across time.


A
PRE-TRAINING SESSION
CONTROL GROUP
TRAINED GROUP
PRIMARY VISUAL NETWORK
DORSAL ATTENTION NETWORK
VENTRAL ATTENTION NETWORK
RIGHT FRONTOPARIETAL NETWORK
LEFT FRONTOPARIETAL NETWORK
SALIENCE NETWORK
0
t-score
15


B
POST-TRAINING SESSION
CONTROL GROUP
TRAINED GROUP
PRIMARY VISUAL NETWORK
DORSAL ATTENTION NETWORK
VENTRAL ATTENTION NETWORK
RIGHT FRONTOPARIETAL NETWORK
LEFT FRONTOPARIETAL NETWORK
SALIENCE NETWORK
0
t-score
15

2. COMPLEMENTARY ANALYSES

2.1. Analysis of the differences in signal-to-noise ratio (SNR) between groups and across sessions for resting-state FC data and task-FC data.

Differences in signal-to-noise ratio (SNR) may affect FC because low amplitudes of activity can be masked by noise, leading to an apparent reduced FC. In order to discard this possibility, the level of activity in each ROI was evaluated between the groups and across the sessions. The temporal variance in each ROI was extracted in either task data or resting-state data and the following comparisons were made: 1) between group comparisons for each experimental session for which FC was calculated (**Supplementary table 1** and **Supplementary table 2**); and 2) within group comparisons for the pre-training session and the post-training session (**Supplementary** t**able 3**). The analysis results are present below. The lack of differences in any of the comparisons support that training effects are not due to an influence of SNR over the FC.

Results

Supplementary table 1. *Task-FC data: between group comparisons analysis results (trained group vs. control group)*

		Pre-training		**Post-training**	
	Df	**F**	***p***	**F**	***p***
rVisual	1	0.173	0.680	2.000	0.186
rPPC	1	0.240	0.628	3.416	0.073
rDLPFC	1	0.051	0.822	1.196	0.282
dACC	1	0.419	0.522	1.727	0.198

Supplementary table 2. *Resting-state FC data: between group comparisons analysis results (trained group vs. control group)*

		Pre-training		**Post-training**	
	Df	**F**	***p***	**F**	***P***
rVisual	1	0.139	0.711	1.845	0.182
rPPC	1	0.445	0.509	0.303	0.585
rDLPFC	1	2.599	0.115	0.407	0.527
dACC	1	0.073	0.789	0.663	0.420

Supplementary table 3. *Resting-state FC data: Within group comparisons analysis results*

			Pre-training *vs.* Post-training	
		Df	**F**	***p***
rVisual	Trained	1	0.001	0.926
	Control	1	2.144	0.159
rPPC	Trained	1	1.491	0.236
	Control	1	0.045	0.833
rDLPFC	Trained	1	0.410	0.529
	Control	1	0.005	0.945
dACC	Trained	1	0.923	0.348
	Control	1	0.135	0.717

2.2. Additional analysis on the variability of the resting-state FC patterns.

The variability of FC during resting-sate was analyzed between groups and across sessions to ensure that resting-state FC patterns did not influence the subsequent brain activity during visual search task. In **Supplementary table 4**, the mean and standard deviation (SD) values of rs-FC data of each pair of seeds is presented by a function of group and session. In **Supplementary table 5**, the results of F-tests are presented. No statistically significant differences were found, therefore, the variability of rs-FC patterns was equal across groups and sessions.

Results

Supplementary table 4. *Resting-state mean SDs values for each pair of seeds across groups and sessions*

			Pre-training		**Post-training**	
		N	**Mean**	**SD**	**Mean**	**SD**
rVisual and rPPC	Trained group	21	0.629	0.19	-0.014	0.15
	Control group	21	0.479	0.18	-0.016	0.17
rVisual and rDLPFC	Trained group	21	-0.993	0.12	-0.091	0.15
	Control group	21	-0.029	0.14	-0.090	0.18
rVisual and dACC	Trained group	21	-0.117	0.14	-0.115	0.14
	Control group	21	-0.079	0.16	-0.089	0.19
rPPC and rDLPFC	Trained group	21	0.188	0.22	0.343	0.27
	Control group	21	0.213	0.26	0.201	0.23
rPPC and dACC	Trained group	21	0.025	0.26	0.142	0.31
	Control group	21	0.088	0.22	0.197	0.20
rDLPFC and dACC	Trained group	21	0.454	0.22	0.541	0.25
	Control group	21	0.407	0.16	0.405	0.24

Supplementary table 5. *Resting-state F-test for equality of variance analysis results*

		Pre-training		**Post-training**	
	df	**F**	***p***	**F**	***p***
rVisual and rPPC	1	0.067	0.797	0.001	0.979
rVisual and rDLPFC	1	2.805	0.102	0.000	0.989
rVisual and dACC	1	0.659	0.422	0.240	0.627
rPPC and rDLPFC	1	0.118	0.732	3.288	0.097
rPPC and dACC	1	0.722	0.401	0.467	0.498
rDLPFC and dACC	1	0.641	0.428	3.157	0.083

2.3. Additional analysis supporting the resting-state FC prediction analysis.

The second hypothesis of the present study was to test whether pre-training resting-state FC was able to predict improvement in behavioral performance after training. We planned to conduct a correlation analysis with each seed region pair that showed statistically significant changes from the pre-training session to the post-training session and the behavioral data from the post-training session. We found a significant correlation ($p < 0.05$) between the pre-training session rs-FC of rPPC and rDLPFC and the trained condition RTs from the post-training session (*trained condition* > *control condition*) for trained participants (r = -0.512 p = 0.018 N = 21), but not for control participants (r = -0.042 p = 0.856 N = 21).

The specificity of the training is robust and unique. As we predicted, it only affected one pair that showed FC changes after training (only affected to rPPC-rDLPFC), but **Supplementary table 7** shows that it did not affect other brain regions. Moreover, **Supplementary table 7** also shows that this correlation was not statistically significant for the post-training session RT values of untrained targets. **Supplementary table 8** corresponds to the results of the Pearson Correlation analysis between pre-training session RT values and all the pairs; no statistically significant correlations were found for the trained targets or for the untrained targets. Finally, **Supplementary table 9** corresponds to the results of the Pearson Correlation analysis between pre-training session rs-FC and the difference in RT values across sessions. The correlation analysis results for the rPPC – DLPFC pair approached statistical significance for the trained targets (trained group: r=0.422, p=0.056; control group: r=-0.04, p=0.85). This result indicates that participants with greater reductions in RT values from the pre-training to post-training sessions (faster performance after training) had more connectivity before training. This result is consistent with the result reported originally.

Results

Supplementary table 7. *Pearson's correlation analysis results between pre-training session rs-FC and post-training session RT values.*

	Post-training session RT values			
	Trained condition > control condition		Untrained condition > control condition	
Pre-training session rs-FC (pairwise seed-based rs-FC)	Trained group (N=21)	Control group (N=21)	Trained group (N=21)	Control group (N=21)
rVisual - rPPC	r = 0.125 p =0.588	r = 0.348 p = 0.123	r = 0.202 p = 0.380	r = -0.244 p = 0.287
rVisual - rDLPFC	r = -0.090 p =0.698	r = -0.079 p =0.733	r = -0.318 p =0.161	r = -0.106 p =0.647
rVisual - dACC	r = -0.138 p =0.551	r = -0.122 p =0.600	r = -0.044 p =0.849	r = -0.136 p =0.558
rPPC – rDLPFC	r = -0.512 p = 0.018	r = -0.042 p =0.856	r = -0.120 p =0.603	r = 0.002 p =0.992
rPPC – dACC	r = -0.232 p =0.313	r = -0.258 p =0.259	r = -0.472 p =0.031	r = -0.167 p =0.470
rDLPFC - dACC	r = 0.049 p =0.833	r = 0.342 p =0.129	r = -0.455 p =0.038	r = 0.222 p =0.333

Supplementary table 8. *Pearson's correlation analysis results between pre-training session rs-FC and pre-training session RT values.*

	Pre-training session RT values			
	Trained condition > control condition		Untrained condition > control condition	
Pre-training session rs-FC (pairwise seed-based rs-FC)	Trained group (N=21)	Control group (N=21)	Trained group (N=21)	Control group (N=21)
rVisual - rPPC	r = 0.005 p =0.984	r = 0.406 p =0.068	r = 0.193 p =0.401	r = -0.081 p =0.727
rVisual - rDLPFC	r = -0.530 p =0.013	r = -0.041 p =0.860	r = -0.358 p =0.111	r = -0.206 p =0.370
rVisual - dACC	r = -0.269 p =0.238	r = 0.084 p =0.717	r = -0.172 p =0.456	r = 0.145 p =0.531
rPPC – rDLPFC	r = -0.350 p = 0.120	r = -0.303 p = 0.182	r = -0.201 p = 0.383	r = -0.148 p = 0.522
rPPC – dACC	r = -0.430 p =0.052	r = -0.534 p =0.013	r = -0.549 p =0.010	r = -0.292 p =0.198
rDLPFC - dACC	r = -0.073 p =0.755	r = 0.249 p =0.277	r = -0.384 p =0.086	r = -0.073 p =0.754

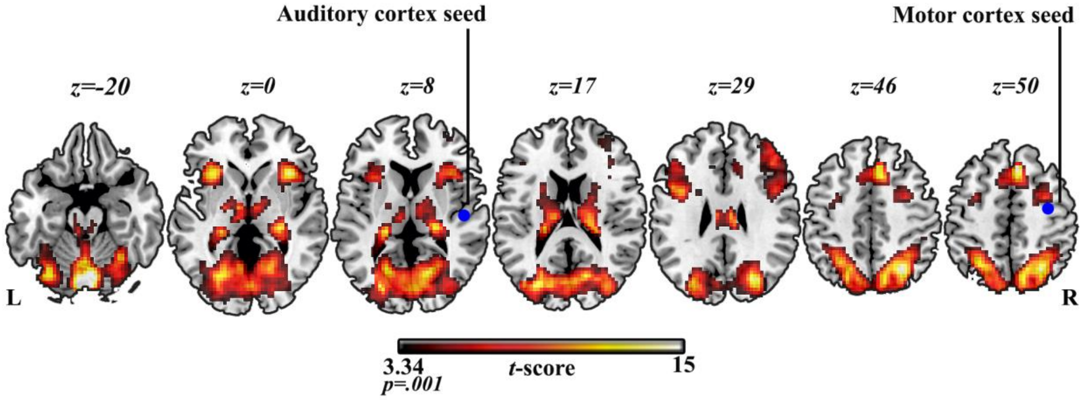
Supplementary table 9. *Pearson's correlation analysis results between pre-training session rs-FC and the difference in RT values across sessions (pre-training session > post-training session RT).*

	Pre-training session > Post-training session RT values			
	Trained condition > control condition		Untrained condition > control condition	
Pre-training session rs-FC (pairwise seed-based rs-FC)	Trained group (N=21)	Control group (N=21)	Trained group (N=21)	Control group (N=21)
rVisual - rPPC	r = -0.148 p =0.522	r = -0.034 p =0.884	r = -0.134 p =0.562	r = 0.215 p =0.350
rVisual - rDLPFC	r = -0.398 p =0.074	r = -0.130 p =0.576	r = 0.161 p =0.486	r = -0.254 p =0.266
rVisual - dACC	r = -0.158 p =0.495	r = -0.119 p =0.607	r = -0.061 p =0.794	r = -0.014 p =0.951
rPPC – rDLPFC	r = 0.422 p = 0.056	r = -0.043 p = 0.853	r = 0.240 p = 0.295	r = 0.152 p = 0.510
rPPC – dACC	r = 0.090 p =0.696	r = -0.280 p =0.220	r = 0.405 p =0.068	r = 0.049 p =0.833
rDLPFC - dACC	r = -0.13 p =0.954	r = -0.007 p =0.975	r = 0.332 p =0.141	r = -0.299 p =0.189

2.4. Resting state FC analysis with independent seed brain regions

Seed based rs-FC analyses with primary auditory or motor cortex have been conducted to add reliability to the main FC results. Seed based rs-FC analyses were conducted between our original four ROIs (right V1, right PPC, dACC and right DLPFC) and two different control ROIs (primary auditory cortex and primary motor cortex). We found no statistically significant differences from pre-training to post-training session in rs-FC as a result of time or training. Please find below more details of this analysis (**Supplementary table 10** and **Supplementary table 11)**.

The control seed regions were placed at the primary auditory cortex (MNI: 46, -18, 8) and at the primary motor cortex (MNI: 32, -10, 50). The seeds were defined as 6-mm radius spheres. In the picture below, both seed regions have been overlaid along with the visual search task general activation. The task activation results (*visual search* > *control task*) have been extracted from a previous visual search task study that used the exact same task (Bueichekú et al., 2016, NeuroImage 135, 204–213, please see Figure 3). None of the control seed regions overlap with the brain activation generated by the visual search task. For each control seed region and task region pair (i.e., primary motor cortex seed – PPC seed) we conducted a 2x2 ANOVA with the Experimental Group (Trained group *vs*. Control group) as the between-subjects factor, and Session (Pre-training session *vs*. Post-training session) as the within-subjects factor, using the IBM SPSS Statistics software. Results are presented below.



In this image the auditory cortex seed and the motor cortex seed have been represented in blue, and the brain activation associated with the visual search task is represented in warm gradient. The color bar represents *t*-values. Results are $p<0.05$ FWE cluster corrected (cluster size criterion $k = 116$ voxels). L = left. R = right. Coordinates are in the MNI space.

Results

Supplementary table 10. Primary auditory cortex seed (rAud)

Pair	Session	Session x Group
rAud – rVisual	*F* =2.362 *p* =0.132	*F* =0.242 *p* =0.625
rAud – rPPC	*F* = 2.211 *p* = 0.145	*F* = 0.415 *p* = 0.523
rAud – rDLPFC	*F* = 0.000 *p* = 0.996	*F* = 0.110 *p* = 0.742
rAud – dACC	*F* = 3.168 *p* = 0.083	*F* = 0.451 *p* = 0.506

Supplementary table 11. Primary motor cortex seed (rMot)

Pair	Session	Session x Group
rMot – rVisual	*F* =0.151 *p* = 0.700	*F* = 0.024 *p* = 0.878
rMot – rPPC	*F* = 1.045 *p* = 0.313	*F* = 0.143 *p* = 0.708
rMot – rDLPFC	*F* = 0.012 *p* = 0.913	*F* = 0.059 *p* = 0.809
rMot – dACC	*F* = 0.772 *p* = 0.385	*F* = 0.001 *p* = 0.971