TITLE PAGE

TITLE

Visual search task immediate training effects on task-related functional connectivity

AUTHORS

Elisenda Bueichekú (bueichek@uji.es) [a], César Ávila (avila@uji.es) [a], Anna Miró-Padilla (amiro@uji.es) [a], Jorge Sepulcre (sepulcre@nmr.mgh.harvard.edu) [b c]

AFFILIATIONS

[a] Neuropsychology and Functional Neuroimaging Group, Department of Basic Psychology, Clinical Psychology and Psychobiology. University Jaume I. 12071, Castellón. Spain.

[b] Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts.

[c] Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

AUTHOR RESPONSIBLE FOR CORRESPONDENCE

Elisenda Bueichekú

Basic Psychology, Clinical Psychology and Psychobiology. University Jaume I.

Avda. Sos Baynat, s/n. E-12071.

Castellón de la Plana, Spain.

(bueichek@uji.es) / +34964387665 / ORCID: 0000-0002-3059-9806

ABSTRACT

Brain plasticity occurs over the course of the human lifetime. Learning and training modify our neuronal synapses and adapt our brain activity, from priming effects in modal areas to higher-order changes in the association cortex. The current state of the art suggests that learning and training effects might induce large-scale brain connectivity changes. Here, we used task-fMRI data and graph-based approaches to study the immediate brain changes in functional connections associated with training on a visual search task, and the individual differences in learning were studied by means of brain-behavior correlations. In a previous work, we found that trained participants improved their response speed on a visual search task by 31%, whereas the control group hardly changed. In the present study, we showed that trained individuals changed regional connections (local links) in cortical areas devoted to the specific visual search processes and to areas that support information integration, and largely modified distributed connections (distant links) linking primary visual areas to specific attentional and cognitive control areas. In addition, we found that the individuals with the most enhanced connectivity in the dorsolateral prefrontal cortex performed the task faster after training. The observed behavioral and brain connectivity findings expand our understanding of large-scale dynamic readjustment of the human brain after learning experiences.

KEYWORDS: Attention; Cognitive training; Functional Connectivity; Functional Magnetic Resonance Imaging; Graph-theory; Visual search task.

1. INTRODUCTION

For years, behavioral psychological experiments have found practice related gains in the performance of cognitive tasks after training completion (Shiffrin and Schneider 1977; Logan 1988; Kramer and Willis 2002), opening the possibility of generating hypothesis about how task practice affects brain functioning. Indeed, Buonomano and Merzenich (1998) signaled that plasticity changes due to life experiences, including learning and training, can occur at different brain levels: synaptic level, cortical maps or large-scale neural networks. Great progress has been made in relation to structural and task-evoked brain plasticity (e.g.s, reviews: Kelly and Garavan 2005; Pascual-Leone et al. 2005; Lövdén et al. 2013), yet it remains less studied how brain functional connectivity is modified due to practice, and mixed results emerge after sensory, motor and cognitive training (Kelly and Castellanos, 2014). The purpose of the present work was to study the immediate modifications in brain connectivity after intensive practice in visual search task (VST), as these changes could provide the bases for short- and long-term modifications.

In terms of task-evoked brain activity, training on cognitive tasks usually leads to extensive reductions in activity in the association areas, whose function is linked to exercising attentional control (Chein and Schneider 2005; Kübler et al. 2006). These reductions have been associated with improved brain functioning (Kelly and Garavan 2005), and some authors have drawn relations between post-training diminished activity and efficiency of the neuronal synapses (Petersen et al. 1988; Poldrack 2000). In this sense, the objective of our previous work was to study behavioral and task-evoked brain activity changes associated with intensive cognitive task training (Bueichekú et al. 2016). In agreement with previous studies (Chein and Schneider 2005; Kübler et al. 2006), we found that intensive VST training, which involves visual processing, attention and working memory components (Eimer 2014), leads to significantly improvement in task performance, and to general brain activity reductions in regions involved in task performance. As a novelty, we introduced some control measures in our study that made it possible to specifically locate the training related changes in the posterior parietal cortex (PPC) and inferior occipital cortex (Bueichekú et al. 2016) (i.e.,

the behavior and brain changes related to training were studied by controlling for repetition effects using between-subjects controls, that is, comparing the trained participants and the control participants). Now, as we know that brief but intensive VST training leads to cognitive gains, our focus moves from studying training effects in behavioral performance and task-evoked activity to functional connectivity.

In relation to functional connectivity, increased brain connectivity has been found after training on different tasks (e.g., Sami and Miall 2013; Mohr et al. 2016; Thompson et al. 2016; for a review: Guerra-Carrillo et al. 2014). Although other outcomes are possible, like decreased connectivity or complex network reorganization (Kelly and Castellanos, 2014), there is a growing corpus of evidence that associates better performance with increased network coherence (e.g.s., Tian et al. 2012; Mackey et al. 2013; Alavash et al. 2015; Bueichekú et al. 2015; Miró-Padilla et al. 2017). Connectivity changes usually affect the task-dependent regions, association areas, and higher-order cognitive areas (i.e., lateral and medial aspects of the parietal, premotor, and prefrontal cortices). When reaching a high level of performance, or even asymptotic performance, increased connectivity is only found between task-dependent regions (Kelly and Castellanos 2014). However, despite the progress made in this field, not much is known about how brain connectivity changes in a very short time to integrate new learning experiences, whether training induces large-scale brain connectivity changes, and particularly, whether the new specific functional networks that emerge are associated with behavioral training processes.

The main goal of this study was to investigate the training effects of a VST on brain connectivity. To accomplish our objective, we studied the changes in regional and distributed connections using a graph-based approach (i.e., segregation of local and distant links), comparing a group of trained participants to a control group. Graph-based approaches allow us to analyze individual properties of networks or global connectivity, making them flexible analytic approaches (Achard et al. 2006; Rubinov and Sporns, 2010). Degree centrality (or degree) is a brain network measure that quantifies the number of connections (i.e., links) departing from a voxel (i.e., node) (Rubinov and Sporns 2010). Some nodes (i.e., hubs) display a large number of links and are thought to converge the information from diverse pathways (Buckner et al. 2009; Sepulcre et al. 2012). In addition, it is possible to differentiate whether the links departing from each node are targeting local neighbors or distant regions during both active and passive task

states (Sepulcre et al. 2010). We hypothesized that: 1) the cerebral areas related to the attention-control system would exhibit a restructuring of local and distant functional connections after training, specifically increased connectivity, as the VST is supported by this system, and a reassembling of its functional connections would be expected after training; 2) the brain changes would be positively correlated with the behavioral improvement.

2. MATERIALS AND METHODS

The data sample used in the present work is the same data sample used in Bueichekú et al. (2016). The former study was focused on studying behavioral and task-evoked brain changes. Here we have a different objective, which is solely to study the task-related functional connectivity modifications associated with intensive training. For this reason, data analysis is centered on brain networks analysis, and behavioral analysis results have been omitted and can be found in our previous work.

2.1. Participants

Thirty-eight healthy undergraduate students from the Universitat Jaume I participated in this study and were paid for their participation. 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 = 19, 10 men; age: M = 20.84 SD = 1.45) or to a control group (N = 19, 10 men; age: M = 20.84, SD = 2.01). A between-groups t-test was used to determine that the experimental groups did not differ in age ($t(36) = 0$ $p = 1$). Intellectual level was evaluated with the Matrix Reasoning Test (WAIS-III-R) (Trained group: M = 21.58 SD = 2.11; Control group: M = 21.74 SD = 1.49). A between-groups t-test was used to determine that the experimental groups did not differ in intellectual level ($t(36) = -0.27$ $p = 0.79$). All the participants provided written informed consent prior to scanning. The study was approved by the Ethics Committee of the Universitat Jaume I.

2.2. Experiment

The experimental task and the experimental procedure were originally described and studied with a different focus in Bueichekú et al. (2016), thus, here we include a brief

summary of the experiment details (see also **Supplementary Figure 1**). We used a letter-based consistent mapping VST, which was adapted to a block design and presented with E-Prime Software (Schneider et al. 2002), and in scanner it was visually presented through MRI-compatible goggles (VisuaStim, Resonance Technology, Inc., Northridge, CA, USA).

The task consisted in a control condition (a detection task) and two visual search conditions (two sets of targets: B,C,D,F,G,H and L,M,N,P,Q,R), which were counterbalanced. For the search tasks, distractors were: J,K,Ñ,S,T,V,W,X,Y,Z. Each condition have 14 blocks with 12 trials (300 ms of a fixation point, 1500 ms of a search frame, and 200 ms of a blank screen), followed by a passive block, in which the screen remained completely blank (8000 ms). Stimuli were arranged circularly around a fixation cross. In control condition, the search frame were either a six A-letters array (target) or a six X-letters (no-target). In search conditions, the search frame consisted of the presentation of either six distractors or five distractors and one target. The frames were counterbalanced, and in all the blocks, fifty per cent of the trials constituted a target-present frame.

In all conditions, the participants gave manual responses only with their right hand: target detection was indicated with their right thumb, and target absence with their right forefinger (using MRI-compatible response-grips; NordicNeuroLab, Bergen, Norway). During task performance, there were no restrictions to eye movement. Even if eye movements could be problematic in some fMRI studies, we believe that in the present study eye movements did not affect our design because the distance between the fixation point and the stimuli (visual angle =1.21°) was small enough to make it possible to perform the task without eye movements. Participants were asked to answer as quickly as possible, but without compromising accuracy. Stimulus presentation timing and duration, and participants' accuracy and reaction times (RTs) to each stimulus were saved in the E-Prime's logfile.

The experiment was conducted on one day. The task was identical before and after training, and it lasted 25 minutes. Between pre-training session and post-training session there was a 45-minute period. In this period, the trained group did the training task outside the scanner, which was similar to the VST used in the scanner (840 trials divided in 20 blocks, and lasted on average M = 29.97 minutes SD = 2.13), and the

control group did nothing. Randomly, half the participants from the trained group were trained to search for one set of targets or the other.

2.3. Image acquisition

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. A gradient-echo T2*-weighted echo-planar MR sequence was used to obtain 602 volumes for the fMRI task (29 interleaved ascending slices, 3.5 x 3.5 mm in-plane voxel size, slice thickness of 3.6 mm, interslice gap of 0.4 mm, TR = 2500 ms, TE = 50 ms, flip angle 90 °, 64 x 64 matrix). Prior to task-fMRI data acquisition, one high-resolution T1-weighted 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). 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. Analysis

2.4.1. Functional MRI connectivity pre-processing analysis

Prior to pre-processing, each subject's fMRI data set was aligned to the AC-PC plane by using its own anatomical image. A total of 154 fMRI volumes per session corresponding to the trained condition were pre-processed and used in subsequent analyses. The volumes were concatenated as a function of session by using the stimulus onset time, that is, the 154 fMRI volumes that corresponded to the trained condition data were isolated from the total number of task-fMRI volumes and processed as a time series. To isolate the 154 fMRI volumes, we used the stimulus presentation timing and duration, which were saved in the E-Prime logfile.

DPARSF Advanced software (Chao-Gan and Yu-Feng 2010) was used for pre-processing. Standard pre-processing was conducted, which included the correction of the slice timing differences for interleaved ascending acquisitions (using the middle slice, which was the 29th, as the reference slice) and a two-pass procedure in realignment (first registration to the first image, then registration to the mean image) to correct head motion during acquisition. None of the participants had more than 2.0 mm

of maximum displacement in any direction or 2.0° of any angular motion while the scan lasted. In order to control the movement effect throughout the experiment, the Root Mean Squared movement values (RMS, of translation and rotation parameters) were used to conduct a repeated-measures 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. No significant differences were found (RMS: $F(1,36) = 0.061$ $p = 0.806$). Then, within the nuisance regression step, and in order to reduce respiratory and cardiac effects on the blood-oxygenation level-dependent (BOLD) signal, several sources of spurious variance were removed: the linear trend in the time series, six parameters from rigid body head motion (obtained from motion correction), and three parameters corresponding to the global mean signal, the white matter signal, and the cerebrospinal fluid signal (Biswal et al. 1995). Spatial normalization to the Montreal Neurological Institute (MNI) space (3 mm^3) was conducted using echo-planar image (EPI) templates. The temporal band-pass filtering step removed low and high frequency drift effects (retaining the fMRI signal between 0.01–0.08 Hz). Finally, for computational efficiency, the data were down-sampled from a 3 mm to a 6 mm voxel size by means of the SPM Image Calculator (ImCalc Toolbox, http://robjellis.net/tools.html).

2.4.2. Post-processing analysis: individual local and distant degree maps

Post-processing analyses were conducted with Matlab coding (v7.9, The Mathworks, Inc, Natick, MA). At the individual level, a whole-brain matrix Pearson Correlation Coefficient between each voxel pair's time course was estimated for each participant and session. A mask of 6332 voxels was used that covered the entire brain. Each participant had a total of four matrices, two of them containing the *r*-values, and the other two containing the *p*-values. According to previous graph-based functional connectivity approaches (Sepulcre et al. 2010), the functional connectivity matrices of positive correlations represent the strength of the connectivity between each pair of voxels across the brain (i.e., the degree), and the pattern of these connections represents the functional connectivity network supporting task-performance at each time point. Therefore, we used the positive correlations in the following steps of the analysis, and we removed the negative *r*-values due to their controversial interpretation in functional connectivity MRI (Murphy et al. 2009; Van Dijk et al. 2010).

Degree analyses were used to study the effects of training on task-related functional connectivity and its spatial distribution. Degree analyses make it possible to extract the spatial distance information from the connectivity patterns, differentiating between regional connections (local links) and interregional connections (distant links). This method was previously used to study the connectivity patterns underlying human information processing. To achieve this aim, a recently developed whole-brain voxel-wise method to differentiate between spatial local and distant connectivity in resting and task-evoked BOLD fMRI data was used (Sepulcre et al. 2010). This method was applied in the present study, as our goal was to study both local and large-scale functional connectivity changes due to cognitive training. As it is described in the original method, we used a restriction on degree centrality analysis based on physical distance, thus, the whole-brain voxel pairwise functional connectivity analyses results were spatially organized according to a neighborhood threshold. In Sepulcre et al. (2010), the authors investigated different distance thresholds until they determined that the optimal neighborhood threshold for analogous dimensional data is 3 voxels (>14mm) around the target neighborhood. The segregation of local and distant connections in physical distance allows the optimal separation between different types of cerebral cortex (such as primary modal vs. heteromodal cortex). Therefore, in the present manuscript, because we are applying the same technique and the voxel size of the functional MR images was down-sampled from 3 mm to 6 mm (to reduce the computational processing cost), the optimal neighborhood threshold was set to 21 mm to segregate local (<21mm radius) and distant (>21mm radius) connectivity on each individual matrix [radius of a sphere = 3mm from the center of the target voxel + 18 mm of three neighboring voxels (6mm each)]. Then group comparison analyses were conducted.

2.4.3. Post-processing analysis: pre-training session group comparison

We used the SPM8 software (Wellcome Department of Imaging Neuroscience, London, England) for pre-training group comparison, and later to study the training effects. In this analysis, a between-groups two-sample *t*-test was conducted with pre-training session data (comparison: pre-training session *trained group vs. control group*). This comparison was performed separately for the local degree maps and for the distant degree maps.

2.4.4. Post-processing analysis: training effects

To study the training effects, we used SPM8 software and 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. This analysis allowed us to study the differences in degree connectivity between the pre-training and post-training sessions, while controlling for repetition effects using between-subjects controls (i.e., the data for the control group). The results of the ANOVA analysis represent the change in the number of local or distant links of a given voxel from one session to the other. The results of all the analyses had a threshold of $p<0.025$ Family Wise Error (FWE)-voxel corrected for multiple comparisons using SPM 8. SPM 8 implements Random Field Theory (Worsley et al. 1992; Worsley et al. 2004) to control the FWE rate (i.e., the rate of false positives in all the results reported due to multiple testing).

2.4.5. Degree map visualization and network layout

Firstly, the degree maps' images were spatially smoothed with an isotropic Gaussian kernel of 6 mm, full-width at half-maximum (FWHM), by means of SPM8. Then, the Computerized Anatomical Reconstruction Toolkit (CARET, Van Essen and Dierker, 2007) was used to project the degree maps on the cerebral hemispheres of the PALS-B12 surface (Van Essen, 2005). More details about the projection can be found in **Fig. 1** legend.

2.4.6. Overlap analysis using network parcellation maps

The 7-network estimate parcellation liberal mask of the human cerebral cortex (Yeo et al. 2011) was applied to our degree maps in order to classify and describe the results. In Yeo et al. (2011), the 7-network map was obtained from fMRI data from 1000 subjects, and the clustering analysis yielded the convergence of brain voxels in resting-state known networks. The map includes an early sensory visual network (Vis), a sensorimotor network (Mot), the dorsal and the ventral attention network (dATN and vATN), a limbic system network (LMB), the frontoparietal control network (FPN), and the default mode network (DMN). Here, we used in-house developed MATLAB code to conduct overlap analysis, which allowed us to classify the results for the degree of training effects in different networks and estimate the percentage of change in each

network. The analysis was performed separately for the local degree map and for the distant degree map in a voxel-wise manner.

The method consisted of finding the voxels that changed within each network. Thus, bearing in mind that each network extends over a spatial portion of the brain (i.e., visual network), and that the entire brain surface is spatially subdivided into the 7-network estimate parcellation mask, each voxel that changed had to fall into one network (e.g., a voxel located in the medial occipital cortex falls into the visual network). Therefore, we calculated the number of voxels that changed within each network (i.e., voxels that showed a change in the number of distant links). Afterwards, a correction based on the total number of voxels in each network was applied, thus obtaining the proportion of change in each network. That is, the number of voxels that changes within each network was multiplied by 100 and divided by the total number of voxels in that network, obtaining the percentage of change. This final step is important because the association cortex extends over the majority of the brain's surface, but the networks have different extensions; for example, the DMN is the largest network, and the dATN the smallest. This percentage of network change must not be confused with the degree analysis, where the change in the number of links at each voxel was analyzed, making it possible to evaluate and characterize the VST training effects on the whole-brain.

2.4.7. Brain behavior correlation analysis

The aim of the correlation analysis was to examine individual differences in learning. We studied the relationship between relevant VST brain areas that showed increased connectivity in distant links and improved performance after training.

Behavioral variable. We used the behavioral data from the scanner that corresponded to the trained condition in the trained participants (and the equivalent condition in the control participants). The control condition data was used as a control measure. For each participant, the mean RT value for the trained condition and for the control condition data was calculated for each experimental session. Only the correct answers were used to calculate the mean RT values. Then, a subtraction between experimental conditions and experimental sessions was calculated to reflect the change in RT values from pre-training to post-training session: [*Pre-training session (trained*

condition - control condition) - Post-training session (trained condition - control condition].

ROI selection. To delimit the brain areas that presented greatest connectivity change, and were directly related to VST performance, we used the result of the task contrast (*visual search task - control task*) from Bueichekú et al. (2016), which serves as a localizer. By means of SPM 8, the image was converted to a binary mask and introduced as an inclusive mask in the brain connectivity analysis that compared the effects of training between groups and across sessions (i.e., 2x2 ANOVA described in *2.4.4 Post-processing analysis: training effects; specifically, in the contrast trained group - control group and pre-training - post-training session*). From this analysis, we selected the three areas within the VST map that showed greatest enhancement in connectivity for the trained group compared to the control group: the right dorsolateral prefrontal cortex (rDLPFC, MNI: x=42 y=38 z=38 BA 46), the right posterior parietal cortex (rPPC, MNI: x=18 y=-70 z=56, BA 7), and the precuneus (MNI: x=12 y=-64, z=38). Around their coordinates, a binary 6-mm radius sphere mask, or region of interest (ROI), was defined using SPM Wake Forest University PickAtlas software (Maldjian et al. 2003) to extract the connectivity values for each participant.

Correlation analysis. After ROI selection and definition, a linear bivariate Pearson's correlation analysis was conducted using IBM SPSS Statistics software. The correlation analysis was done for each group separately between each ROI connectivity values (rDLPFC, rPPC or precuneus), and the change in response speed values [*Pre-training session (trained condition - control condition) - Post-training session (trained condition - control condition*] > 0. The connectivity values for each ROI were the distant links values in pre-training session, the distant links values in post-training session or the change in distant links values (a subtraction was calculated: *Post-training session distant link values - Pre-training session distant link values*).

ANCOVA analysis. To further investigate the relation between the brain functional connectivity changes and the behavioral performance (i.e., response speed) a Potthoff analysis was conducted according to Wuensch, 2016, http://core.ecu.edu/psyc/wuenschk/MV/multReg/Potthoff.pdf). In this analysis, an ANCOVA model was defined to study the connectivity by experimental group effect by means of IBM SPSS Statistics software. For the model: $Y=a+b_1X+b_2G+b_3X*G$, the variables were defined as following: Y = criterion variable, the behavioral variable

(change in response speed); X = predictor variable, the connectivity variable (values of DLPFC distant links in post-training session); and G = grouping variable, the two experimental groups (trained group data and control group data). In addition, within the Potthoff analysis, two reduced models were studied for testing: a) whether predicting the response speed from the connectivity values is the same at the different levels of the grouping variable ($Y=a+b1X$) and; b) whether predicting the response time from the connectivity values is the same for the trained group and for the control group ($Y=a+b_1X+b_2G$).

3. RESULTS

3.1. Brain results

3.1.1. Pre-training session group comparison analysis results

The pre-training session group comparison analysis was conducted to verify that the groups had no brain response differences while performing the VST during the pre-training session. The between-groups *t*-tests were performed separately for the local and the distant degree maps and yielded no significant differences ($p < 0.05$ FWE voxel-corrected).

3.1.2. Training effects: degree map results

The results of the degree analyses appear in **Fig. 1**. An interaction analysis was conducted to study the brain connectivity changes due to training effects. Therefore, 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. Repetition effects were controlled by introducing the control group data in the analysis.

When studying the local changes [contrast: *Trained group (post-training - pre-training session) - Control group (post-training - pre-training session)*] > 0 (left part of the **Fig. 1a**), increases in the number of links were found in the occipito-temporal cortex (BA 19, 21 and 37), including some portions of inferior occipital gyrus and fusiform gyrus; the bilateral PPC, including the superior parietal cortex (BA 7), supramarginal gyrus (BA 40), angular gyrus (BA 39) and medial portions like the precuneus, left posterior cingulate gyrus; the bilateral anterior temporal lobe and right posterior insular

cortex; and the bilateral dorsomedial (mPFC, BA 8/9), bilateral DLPFC (BA 9 / 46) and left ventrolateral prefrontal cortex (VLPFC, BA 45 / 47) prefrontal cortex. That is, the number of short links in these regions increased due to the training effects (i.e., nodes within the local neighborhood). This result was $p<0.025$ FWE voxel-corrected (with a minimum $t\text{-}score = 4.98$). The reverse contrast yielded no significant differences.

Some changes associated with distant links were found in similar regions [contrast: *Trained group (post-training - pre-training session) - Control group (post-training - pre-training session)*] > 0 (right part of the **Fig. 1a**), but increases in the number of links were extended to a greater proportion of the cortical surface than on the local degree maps. The distant degree maps represent the nodes whose connectivity beyond the specified neighbor changed due to training. These increases were found in the occipital cortex (more in medial than in lateral regions), inferior temporal gyrus, PPC (including the lateral surface of the superior parietal lobule, the intraparietal sulcus, the supramarginal gyrus, and the precuneus), posterior to anterior mPFC, including the supplementary and pre-supplementary motor area (SMA), DLPFC (BA 9/46), and the VLPFC, along with the anterior insular cortex (aI, BA 47/ 48). This result was $p<0.025$ FWE voxel-corrected (with a minimum $t\text{-}score = 4.98$). The reverse contrast yielded no significant differences.

A force-directed graph was used to represent the connectivity using Pajek software (De Nooy et al. 2004). The Kamada-Kawai (K-K) algorithm was used. The K-K algorithm is a force-directed graph drawing approach that assigns spring-like forces among all edges based on geodesic distances. The K-K algorithm pulls nodes that are not connected further apart and arranges nodes that share connections together. The mathematical properties of the K-K algorithm are explained in detail elsewhere (Kamada and Kawai, 1989). Our force-directed graph was created with the aim of visualizing the links in the areas that showed an increased number of distant links after training (see **Fig. 1b**). This graphic representation shows that, after training, there are some brain areas with a high degree number, or cortical hubs (i.e., the nodes in red color). Note that big nodes in **Fig. 1b** correspond to red areas on the Distant Map in **Fig. 1a**. The links departing from the hubs were mostly directed to the other hubs, (see **Fig. 1c**). Therefore, while participants improved their performance, the training also enhanced the connectivity of the specific brain network that underlies the VST performance.

The overlap analysis results using the 7-network estimate parcellation map, which focused on describing the percentage of each network's change, are presented in bar charts in **Fig. 2**. Regarding local links, it can be observed that the proportions of change in the visual network, the dATN, the FPN, and the DMN are similar (see **Fig. 2d**). As for distant links, the visual network and the dATN had the greatest number of changed voxels, followed by the sensorimotor network, the vATN, the FPN, and the DMN, with all of them having a similar proportion of change (see **Fig. 2e**). Therefore, it could be said that as a consequence of VST training and the development of automaticity, local changes were found in the visual sensory cortex, but also in the association cortices, and new large-scale connections were developed that mostly came from visual networks or from the dATN.

3.1.3. Brain behavior correlation analysis results

Please see **Table 1** which shows all these correlation analyses results. The relationship between performance improvement and brain connectivity values of each ROI was studied by means of bivariate Pearson's correlation analysis. In relation to the connectivity of the right DLPFC after training, a positive correlation was found for the trained group's data ($r = 0.497$ $p = 0.031$ N = 19), and no correlation was found for the control group's data ($r = -0.223$ $p = 0.169$ N = 19). Thus, the participants with more connections after training also had more improvement in VST performance after training (see **Fig. 3**).

After performing the correlation analyses, and finding a significant correlation between performance improvement and right DLPFC's connectivity values after training, we studied whether the difference in correlation coefficients between groups was significant. In order to calculate the difference between correlations, we used the procedure developed by Fisher (1921) implemented in the Cocor package (Diedenhofen and Musch, 2015). Specifically, the null hypothesis was set as ($r_{trained group} - r_{control group}$) = 0, and an alpha value of 0.05 was used. We found that the difference between correlation coefficients is $r_{trained group} - r_{control group} = 0.729$, $z = 2.2107$ and $p = 0.014$ one-sided; the confidence interval (95%) for the difference is $CI = 0.0764 - 1.2076$ (Zou, 2007). Based on this result, we rejected the null hypothesis and concluded that the correlation coefficients are different. Finally, the coefficient of determination and the slope of the regression were also calculated and the results are summarized in **Table 2**. The slopes of the curves were compared using the Free Statistics Calculators (version 4,

software and formulas available at http://www.danielsoper.com/statcalc). Specifically, the null hypothesis was set as ($B_{\text{trained group}}$ - $B_{\text{control group}}$) > 0, and an alpha value of 0.05 was used. We found that the slopes of the regression were different: $t = 1.92$ and $p = 0.031$ one-sided, degrees of freedom = 34, concluding that the slopes of the regression are different.

In addition, and to further support the bivariate Pearson's correlation analysis, a Potthoff analysis testing the connectivity by experimental group effect was conducted. The model $Y=a+b_1X+b_2G+b_3X*G$ was defined and the analysis results at the $p<0.05$ level found that $R^2=0.419$, R^2 corrected=0.368 and the corrected model $F(3,34)=8.17$, $p<0.001$ indicating that individual differences in response speed were predicted by the functional connectivity values of DLPFC which were modulated by the training. Next, we tested whether predicting the response speed from the connectivity values is the same at the different levels of the grouping variable. We defined a reduced model ($Y=a+b_1X$) removing the grouping variable and the interaction term. At $p<0.05$ level, it was found $R^2=0.328$, R^2 corrected=0.309 and the corrected model $F(1,36)=17.55$, $p<0.001$. The null hypothesis was rejected, therefore, predicting the response speed from the connectivity values is not the same at all levels of the grouping variable. The comparison of the full model against this reduced model yielded $t=2.31$ $p<0.01$. Therefore, the full model is the best model to explain the prediction of the response speed. Finally, we tested whether predicting the response speed from the connectivity values is the same for the trained group and for the control group. We defined the reduced model ($Y=a+b_1X+b_2G$), including again the grouping variable but not the interaction term. At $p<0.05$ level it was found $R^2=0.353$, R^2 corrected=0.316 and the corrected model: $F(2,35)=9.55$, $p<0.001$. The null hypothesis was rejected, therefore, predicting the response speed from the connectivity values is different for each group. The comparison of the full model against this reduced model yielded $t=1.96$ $p<0.02$. Therefore, the full model is the best model to explain the prediction.

Based on these results, we believe that the differences between the correlation coefficients are due to the experimental treatment, and that the effect of training leads to a relationship between right DLPFC's connectivity and the improvement in task performance in the trained group. No other significant correlations were found between response speed and the connectivity values of the PPC or the precuneus.

4. DISCUSSION

At present, systems neuroscience research is advancing our comprehension of brain mechanisms associated with learning by incorporating large-scale connectivity approaches to existing behavioral and task-fMRI training studies. In this study, we investigated the effects of learning new experiences and cognitive training on brain functional connectivity systems. VST training led to changes in task-related functional connectivity, specifically it was found an increased number of local and large-scale connections in visual networks and the association cortices.

4.1. Training effects on brain connectivity

Our brain imaging results showed that, after a short but intensive training, the number of local and distant connections increased on a distributed cortical surface. These results were controlled with the data from a passive control group, and were accompanied by performance improvements (reported in Bueichekú et al. 2016), which were later correlated with the task-related functional connectivity enhancement.

In general, similar patterns of changes were found in local and large-scale connections, but the changes shown on the distant links degree map were more widely distributed (**Fig. 1**). The effects of training were associated with changes in the connectivity of networks that have been previously linked to the visual attention system (Corbetta and Shulman 2002; Shulman et al. 2003; Cole and Schneider 2007): the visual network (lateral and medial networks), the dATN, and the FPN (**Fig. 2**). We noticed that when classifying the results into networks and studying the proportion of change in these networks, the change in local connections was similar for all of them, but for large-scale connections, the change was more prominent in the visual network and in the dATN. On the one hand, the results for local connections could be associated with an improvement in general cognitive functioning with better intra-area communication. In addition, these results could provide support for the idea that measures of local connectivity during task performance constitute indicators of the engagement of brain areas in task performance (Sepulcre et al. 2010). In other words, enhancement in local connectivity could indicate better engagement in task performance or better intra-area communication in visual networks, in addition to the dATN, FPN, and DMN. On the other hand, the increased number of distant connections might be more related to improved mechanisms of information processing and integration across cognitive

systems, which would explain the major changes in the higher-order association cortices and areas like the PPC and DLPFC.

Among others, the PPC and DLPFC are of special interest in VSTs. The PPC has been widely associated with the control of attention on priority maps, where bottom-up and top-down information converge, and the focus of attention is biased toward completing the task goals (Deco and Rolls 2005; Ipata et al. 2009; Bisley and Goldberg 2010). Moreover, the PPC has also been related to the maintenance of task rules and the specific features of visual objects (Rasposo et al. 2014; Ester et al. 2015). Meanwhile, the DLPFC transforms the representations of the visual stimuli into memory traces, which can be sustained over time according to the task demands and then transformed into action representations for task performance (Cole and Schneider 2007). The DLPFC has also been related to target detection, and it is a source of top-down attentional control because it has cognitive information about the target that is sent to the PPC and other association areas (Bisley and Goldberg 2010; Noudoost et al. 2010; Katsuki and Constantinidis 2012). Indeed, among the trained participants, those who had the greatest number of connections in the right DLPFC had the greatest improvement in response speed performance from pre-training to the post-training session (**Fig. 3**). In general, the brain-behavior correlation we found could imply that the right DLPFC is a neural marker of individual differences in performance on goal-directed tasks mediated by visual attention processes, which would agree with the top-down modulation role of the DLPFC in other attention areas like the PPC (Katsuki and Constantinidis 2012). Some authors have argued that functional connectivity at rest could reflect neural functions involved in learning, brain reorganization and preparation to action (Buckner and Vincent, 2007) and in off-line processing and processes that support consolidation of memories (Miall and Robertson, 2006). More recently, it has been found out that the individuality observed in resting-state functional connectivity measures remains present during the performance of tasks (Shah et al. 2016; Gonzalez-Castillo and Bandenttini, 2017). In relation to this, the Spontaneous Trait Reactivation hypothesis proposes that brain functional connectivity captures the personal experiences and, thus, reflects individual cognitive differences (Harmelech and Malach, 2013). This theory could be supported by neuroimaging learning studies where individuals show functional connectivity and behavior associations after the completion of sensory, motor, or cognitive training programs (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). In our particular case, post-training connectivity was related to changes in behavior. Within all participants that were trained, those who improved more had greatest number of connections in DLPFC. This association between enhanced connectivity after training (i.e., increased number of connections) and better task performance might be seen as a hallmark of individuality, as all the trained participants improved their response speed due to training but behavioral and functional connectivity differences were observed amongst them. The improved connectivity of the DLPFC probably has a determining effect on the visual search processes, and so the brain-behavior correlation was found for the trained participants, but not for the controls.

In addition, we observed increased connectivity in areas that belong to the DMN network. In our opinion, areas like the precuneus/posterior cingulate cortex, the mPFC, and the lateral temporal cortex could have a role in scaffolding the VST performance improvement. Some authors have found increased connectivity in DMN areas when task automaticity is developing (Shamloo and Helie 2016). It seems that the pattern of connectivity of the DMN is task dependent, and it is linked to the FPN in order to support the cognitive processes involved in goal-directed tasks (Spreng et al. 2010). Regarding our results, an increased number of local and distant connections in DMN regions, along with a similar proportion of change compared to the FPN (**Fig. 2**), show that the DMN may play a central role in globally integrating the information (van den Heuvel and Sporns 2011; Braga et al. 2013). Therefore, considering that brain changes observed in this study affected a wide variety of brain systems, our findings agree with the notion that the development of expertise in VST performance involves complex interactions among attention, control, memory, and task-specific systems (Eimer 2014).

4.2. Training effects on brain functioning and the neural efficiency hypothesis

Another topic of discussion is related to how to interpret the training effects at the brain activity and brain connectivity levels. In the case of our VST training effects on brain activity, there were decreases in general and specific task-related areas (i.e., PPC and occipital cortex), especially when the control group's data were used as a control measure for possible repetition effects (Bueichekú et al. 2016). According to the *neural efficiency hypothesis,* gaining experience in performing a task leads to improved information processing, along with less use of brain resources in task-related brain areas

(Haier et al. 1992). Reductions in brain activity have been associated with efficient functioning or enhanced neural efficiency due to improved utilization of regional resources or reallocation of the resources (Chein and Schneider 2005; Patel et al. 2013). For instance, from the cognitive control areas and the attentional areas to other brain areas, such as the DMN areas, it has been suggested that these cerebral changes indicate greater task automaticity (Patel et al. 2013).

In the present study, we found increased connectivity in terms of the number of connections (**Fig. 1**), which in our opinion does not contradict our previous findings, but rather supports the general idea of enhanced cognitive functioning after training. Having more connections within and between areas should be interpreted as an improved flow of communication (e.g., more channels of communication), and could be interpreted as a strategy to become more efficient in the transmission of information, perhaps by improving the information processing speed and/or increasing the direct paths between nodes. Indeed, one possibility is that the availability of more connections facilitates global brain functioning, enhancing information processing, integration, and large-scale communication, and reducing the response of brain areas, in order to properly perform the task. In this regard, functional connectivity changes could be the basis for activation changes. Therefore, enhanced connectivity but reduced activation could be interpreted as an improved system that makes less effort and is more efficient when performing the same task. This notion agrees with Bullmore and Sporns (2012), as the brain is thought to be a system that adapts in response to environmental demands by making changes in its network organization to become more efficient in information processing.

4.3. Limitations and future directions

Finally, we would like to mention that a possible limitation of the present study is the use of a passive control group. When designing the study, we took into consideration that the selection of the proper control group is a main issue in training studies. In their experimental designs, some authors include an active control group that completes a training program with a low-level task, a sub-domain task, or an adaptive task (Green et al. 2014). However, and as far as we know, there is no evidence about the most appropriate control group for carrying out cognitive training fMRI studies in the attention domain. Previous cognitive training fMRI studies with a focus on the attention domain used no control group or a passive control group (e.g., Jansma et al. 2001; Kübler et al. 2006). When considering the most suitable task for the control group, our

main concern was to find a task that: 1) was cognitively similar enough to our VST (e.g., stimulus-response relation, difficulty, domain); 2) was able to control all the no-interest possible reasons for an improvement; 3) did not produce similar or identical FC effects in the post-training session to the ones produced by our attention task when the control participants completed the training program. To our knowledge, there are very few, if any, cognitive tasks that truly meet all of these requirements. Therefore, we decided to include a passive control group that at least allowed us to control the behavioral and brain response changes due to test-retest effects. It is our hope that future fMRI studies will address the use of active control groups when studying brain changes produced by cognitive training on attention tasks.

4.4. Conclusions

In the present study, we describe how intensive training in VST modifies the organization of functional connections, providing insight into the information processing theories, the cognitive efficiency hypothesis, and the study of individual differences. Training led to increased local connectivity in areas typically involved in VSTs, such as visual areas, the PPC, and the DLPFC, along with areas belonging to the DMN. In general, the improved within-region connectivity could be indicating better task engagement and the attainment of task automaticity. In addition, cognitive training induced large-scale connectivity changes mostly in the visual network and the dATN, which would be related to improved integration and information processing. Finally, the DLPFC might be a neural marker of individual differences because better task performance after training was associated with enhanced DLPFC connectivity.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional Review Board of the Universitat Jaume I and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Funding

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

REFERENCES

Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. (2006). A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J. Neurosci.*, *26*(1):63-72. doi: 10.1523/JNEUROSCI.3874-05.2006

Alavash M, Doebler P, Holling H, Thiel CM, Gießing C. (2015). Is functional integration of resting state brain networks an unspecific biomarker for working memory performance? *Neuroimage., 108*:182–193. doi:10.1016/j.neuroimage.2014.12.046

Bisley JW, Goldberg ME. (2010). Attention, Intention, and Priority in the Parietal Lobe. *Annu. Rev. Neurosci.*, *33*(1), 1–21. doi:10.1146/annurev-neuro-060909-152823

Biswal B, Yetkin FZ, Haughton VM, Hyde JS. (1995). Functional Connectivity in the Motor Cortex of Resting. *Magn. Reson. Med., 34*(4):537–541. doi:10.1002/mrm.1910340409

Braga RM, Sharp DJ, Leeson C, Wise RJS, Leech R. (2013). Echoes of the Brain within Default Mode, Association, and Heteromodal Cortices. *J. Neurosci., 33*(35), 14031–14039. doi:10.1523/jneurosci.0570-13.2013

Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, et al. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J. Neurosci.*, *29*(6), 1860-73. doi: 10.1523/JNEUROSCI.5062-08.2009

Bueichekú E, Miró-Padilla A, Palomar-García MÁ, Ventura-Campos N, Parcet MA, Barrós-Loscertales A, et al. (2016). Reduced posterior parietal cortex activation after training on a visual search task. *Neuroimage*, *135*, 204-2013. doi: 10.1016/j.neuroimage.2016.04.059

Bueichekú E, Ventura-Campos N, Palomar-García MÁ, Miró-Padilla A, Parcet MA, Ávila C. (2015). Functional Connectivity Between Superior Parietal Lobule and Primary Visual Cortex "at Rest" Predicts Visual Search Efficiency. *Brain Connect. 5*(8):517-26. doi: 10.1089/brain.2015.0352

Bullmore E, Sporns O. (2012). The economy of brain network organization. Nat. Rev. Neurosci., *13*(5):336-49. doi:10.1038/nrn3214

Buonomano DV, Merzenich MM. (1998). CORTICAL PLASTICITY: From Synapses to Maps. *Annu. Rev. Neurosci., 21*(1), 149–186. doi:10.1146/annurev.neuro.21.1.149

Chao-Gan Y, Yu-Feng Z. (2010). DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. *Front. Syst. Neurosci. 4*:1. doi:10.3389/fnsys.2010.00013

Chein JM, Schneider W. (2005). Neuroimaging studies of practice-related change: fMRI and meta-analytic evidence of a domain-general control network for learning. *Brain. Res. Cogn. Brain. Res.*, *25*(3), 607–623. doi:10.1016/j.cogbrainres.2005.08.013

Cole MW, Schneider W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *Neuroimage*, *37*(1), 343–360. doi:10.1016/j.neuroimage.2007.03.071

Corbetta M, Shulman GL. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.*, *3*(3), 215–229. doi:10.1038/nrn755

De Nooy W, Mrvar A, Batagelj V. (2004). Exploratory network analysis with Pajek. *Ann. Phys*. doi: 978-0-521-60262-4. doi:10.1017/cbo9780511996368.021

Deco G, Rolls ET. (2005). Attention, short-term memory, and action selection: A unifying theory. *Prog. Neurobiol., 76*(4), 236–256. doi:10.1016/j.pneurobio.2005.08.004

Diedenhofen B, Musch J (2015). cocor: A Comprehensive Solution for the Statistical Comparison of Correlations. *PLOS One*, *10*(4): e0121945 https://doi.org/10.1371/journal.pone.0121945

Eimer, M. (2014). The neural basis of attentional control in visual search. *Trends. Cogn. Sci., 18*(10), 526–535. doi:10.1016/j.tics.2014.05.005

Ester EF, Sprague TC, Serences, JT. (2015). Parietal and Frontal Cortex Encode Stimulus-Specific Mnemonic Representations during Visual Working Memory. *Neuron. 87*(4), 893–905. doi:10.1016/j.neuron.2015.07.013

Fisher, RA. (1921). On the "Probable Error" of a Coefficient of Correlation Deduced from a Small Sample.*Metron., 1*: 3-32.

Green CS, Strobach T, Schubert T. (2014). On methodological standards in training and transfer experiments. *Psychol. Res.*, *78*(6), 756–772. doi:10.1007/s00426-013-0535-3

Guerra-Carrillo B, Mackey AP, Bunge SA. (2014). Resting-State fMRI: A Window into Human Brain Plasticity. *Neuroscientist.*, *20*(5), 522–533. doi:10.1177/1073858414524442

Haier RJ, Siegel BV, MacLachlan A, Soderling E, Lottenberg S, Buchsbaum MS. (1992). Regional glucose metabolic changes after learning a complex visuospatial/motor task: a positron emission tomographic study. *Brain. Res., 570*(1-2), 134–143. doi:10.1016/0006-8993(92)90573-r.

Ipata AE, Gee AL, Bisley JW, Goldberg ME. (2008). Neurons in the lateral intraparietal area create a priority map by the combination of disparate signals. *Exp. Brain. Res.*, *192*(3), 479–488. doi:10.1007/s00221-008-1557-8

Jansma, JM, Ramsey NF, Slagter HA, Kahn RS. (2001). Functional Anatomical Correlates of Controlled and Automatic Processing. *J. Cogn. Neurosci*, *13*(6), 730–743. doi:10.1162/08989290152541403

Kamada T, Kawai S. (1989). An algorithm for drawing general undirected graphs, *Inf. Process. Lett.*, 31 (1): 7–15. https://doi.org/10.1016/0020-0190(89)90102-6

Katsuki F, Constantinidis C. (2012). Early involvement of prefrontal cortex in visual bottom-up attention. *Nat. Neurosci., 15*(8), 1160–1166. doi:10.1038/nn.3164

Kelly AMC, Castellanos FX. (2014). Strengthening Connections: Functional Connectivity and Brain Plasticity. *Neuropsychol. Rev.*, *24*(1), 63–76. doi:10.1007/s11065-014-9252-y

Kelly AMC, Garavan H. (2005). Human functional neuroimaging of brain changes associated with practice. *Cereb. Cortex, 5*(8):1089-102. doi: 10.1093/cercor/bhi005

Kramer AF, Willis SL. (2002). Enhancing the Cognitive Vitality of Older Adults. *Curr. Dir. Psychol. Sci., 11*(5), 173–177. doi:10.1111/1467-8721.00194

Kübler A, Dixon V, Garavan H. (2006). Automaticity and Reestablishment of Executive Control—An fMRI Study. *J. Cogn. Neurosci.*, *18*(8), 1331–1342. doi:10.1162/jocn.2006.18.8.1331

Logan GD. (1988). Toward an Instance Theory of Automatization. *Psychol. Rev., 95*(4), 492-527. doi: 10.1037/0033-295X.95.4.492

Lövdén M, Wenger E, Mårtensson J, Lindenberger U, Bäckman L. (2013). Structural brain plasticity in adult learning and development. *Neurosci. Biobehav. Rev., 37*(9), 2296–2310. doi:10.1016/j.neubiorev.2013.02.014

Mackey AP, Miller Singley AT, Bunge SA. (2013). Intensive Reasoning Training Alters Patterns of Brain Connectivity at Rest. *J. Neurosci., 33*(11), 4796–4803. doi:10.1523/jneurosci.4141-12.2013

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage., 19*, 1233– 1239. doi:10.1016/s1053-8119(03)00169-1

Miró-Padilla A, Bueichekú E, Ventura-Campos N, Palomar-García, MÁ, Ávila C. (2017). Functional connectivity in resting state as a phonemic fluency ability measure. *Neuropsychologia., 97*, 98–103. doi:10.1016/j.neuropsychologia.2017.02.009

Mohr H, Wolfensteller U, Betzel RF, Mišić B, Sporns O, Richiardi J, et al. (2016). Integration and segregation of large-scale brain networks during short-term task automatization. *Nat. Commun., 7*:13217. doi:10.1038/ncomms13217

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *Neuroimage., 44*(3), 893–905. doi:10.1016/j.neuroimage.2008.09.036

Noudoost B, Chang MH, Steinmetz NA, Moore T. (2010). Top-down control of visual attention. *Curr. Opin. Neurobiol., 20*(2):183–90. doi: 10.1016/j.conb.2010.02.003

Oldfield RC. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia., 9(*1):97–113. doi: 10.1016/0028-3932(71)90067-4

Pascual-Leone A, Amedi A, Fregni F, Merabet LB. (2005). The plastic human brain cortex. *Annu. Rev. Neurosci., 28(*1), 377–401. doi:10.1146/annurev.neuro.27.070203.144216

Patel R, Spreng RN, Turner GR. (2013). Functional Brain Changes Following Cognitive and Motor Skills Training. *Neurorehabil. Neural. Repair., 27*(3), 187–199. doi:10.1177/1545968312461718

Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature., 331*(6157), 585–589. http://dx.doi.org/10.1038/331585a0.

Poldrack RA (2000). Imaging brain plasticity: conceptual and methodological issues – a theoretical review. *Neuroimage., 12* (1), 1–13. http://dx.doi.org/10.1006/nimg.2000.0596.

Raposo D, Kaufman MT, Churchland AK. (2014). A category-free neural population supports evolving demands during decision-making. *Nat. Neurosci.. 17*, 1784–1792. doi:10.1038/nn.3865

Rubinov M, Sporns O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage., 52*(3), 1059–1069. doi:10.1016/j.neuroimage.2009.10.003

Sami S, Miall RC. (2013). Graph network analysis of immediate motor-learning induced changes in resting state BOLD. *Front. Hum. Neurosci., 7*:166. doi:10.3389/fnhum.2013.00166

Schneider W, Eschmann A, Zuccolotto A. 2002. *E-Prime reference guide*. Pittsburgh, PA: Psychology Software Tools, Inc.

Sepulcre J, Liu H, Talukdar T, Martincorena I, Yeo BTT, Buckner RL. (2010). The Organization of Local and Distant Functional Connectivity in the Human Brain. *PLoS Comput. Biol.*, *6*(6), e1000808. doi:10.1371/journal.pcbi.1000808

Sepulcre J, Sabuncu MR, Yeo TB, Liu H, Johnson KA. (2012). Stepwise Connectivity of the Modal Cortex Reveals the Multimodal Organization of the Human Brain. *J. Neurosci.*, *32*(31), 10649–10661. doi:10.1523/jneurosci.0759-12.2012

Shamloo F, Helie S. (2016). Changes in default mode network as automaticity develops in a categorization task. *Behav. Brain. Res., 15*;313:324-33. doi:10.1016/j.bbr.2016.07.029

Shiffrin RM, Schneider W. (1977). Controlled and automatic human information processing: II. Perceptual learning, automatic attending and a general theory. *Psychol. Rev.*, *84*(2), 127–190. doi:10.1037/0033-295x.84.2.127

Shulman GL, McAvoy MP, Cowan MC, Astafiev SV, Tansy AP, d'Avossa G, et al. (2003). Quantitative analysis of attention and detection signals during visual search. *J. Neurophysiol.*, *90*(5), 3384-97. doi:10.1152/jn.00343.2003

Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW, Schacter DL. (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage., 53*(1), 303–317. doi:10.1016/j.neuroimage.2010.06.016

Thompson TW, Waskom ML, Gabrieli JDE. (2016). Intensive Working Memory Training Produces Functional Changes in Large-scale Frontoparietal Networks. *J. Cogn. Neurosci., 28*(4), 575–588. doi:10.1162/jocn_a_00916

Tian L, Ren J, Zang Y. (2012). Regional homogeneity of resting state fMRI signals predicts Stop signal task performance. *Neuroimage., 60*(1), 539–544. doi:10.1016/j.neuroimage.2011.11.098

Van den Heuvel MP, Sporns O. (2011). Rich-Club Organization of the Human Connectome. *J. Neurosci.*, 31(44), 15775–15786. doi:10.1523/jneurosci.3539-11.2011

Van Dijk KRA, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL. (2010). Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization. *J. Neurophysiol.*, *103*(1), 297–321. doi:10.1152/jn.00783.2009

Van Essen DC, Dierker DL. (2007). Surface-Based and Probabilistic Atlases of Primate Cerebral Cortex. *Neuron.*, *56*(2), 209–225. doi:10.1016/j.neuron.2007.10.015

Van Essen DC. (2005). A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. *Neuroimage.*, *28*(3), 635–662. doi:10.1016/j.neuroimage.2005.06.058

Worsley KJ, Evans AC, Marrett S, Neelin P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *J. Cereb. Blood. Flow. Metab., 12*(6):900-18. doi:10.1038/jcbfm.1992.127

Worsley KJ, Taylor JE, Tomaiuolo F, Lerch J. (2004). Unified univariate and multivariate random field theory. *Neuroimage.*, *23*, S189–s195. doi:10.1016/j.neuroimage.2004.07.026

Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol., 106*(3):1125-65. doi:10.3410/f.13521958.14898069

TABLE CAPTIONS

Table 1. Pearson correlation analyses results. The Pearson correlation analysis results between training induced changes in behavior and distant link values in the right dorsolateral prefrontal cortex (rDLPFC) in the pre-training session, post-training session, or the difference between sessions are presented below for each experimental group. The behavioral variable is the difference in reaction time (RT) values between conditions (search condition and control condition) and sessions (pre-training session - post-training session): RT values *[Pre-training session (Trained condition - Control condition)- Post-training session (Trained condition - Control condition)]>0.*

Table 2. Coefficient of determination and slope of the main Pearson correlation analyses results. In relation to the results of the correlation analyses between training induced changes in behavior and distant link values in the right dorsolateral prefrontal cortex (rDLPFC) in the post-training session, the coefficient of determination, the slope of the curve and the confidence interval of the slope have been calculated for each experimental group.

FIGURE CAPTIONS

Fig. 1 Functional connectivity changes after training on VST. (a) It was found increased local and distant connectivity after training on a distributed cortical surface. The degree maps were projected on the cerebral hemispheres of the PALS-B12 surface using CARET. The interpolated voxel algorithm and multi-fiducial mapping of the metrics were used, along with SPM's native space specification and the 2% to 98% scale. A medial wall mask was also included only when projecting the images to cover non-cortical regions (Van Essen, 2005, Van Essen and Dierker, 2007). (b) The brain nodes have been represented according to the number of functional links that depart from each node, the brain hubs are the areas with greatest change. (c) The brain network formed within the hubs has been represented, revealing high connectivity between hubs. The statistical contrast of these results corresponds to: *[Trained group (post-training - pre-training session) - Control group (post-training session - pre-training session)]>0*. Results are $p<0.025$ FWE voxel-corrected (with a minimum t-score = 4.98). The color bar represents t-values. L = left. R = right.

Fig. 2 Cortical networks change after cognitive training on VST. (a) The analysis was based on the 7-network estimate parcellation map of the cerebrum (Yeo et al. 2011). The black lines on **(b)** the local degree map and **(c)** the distant degree map represent the boundary of each network. The percentage of change for each network was estimated and plotted. **(d)** Similar percentages of change were found for the dATN, FPN and DMN in local connections. **(e)** The visual network and the dATN had the greatest changes in distant connections. Network legend: Vis: visual network; Mot: sensorimotor network; dATN: dorsal attention network; vATN: ventral attention network; LMB: limbic system network; FPN: fronto-parietal network; DMN: default mode network

Fig. 3 Correlation analysis results reveal individual differences in task learning. The participants with more connections in the right DLPFC after training had greater performance improvement on the VST from pre-training to the post-training session

TABLES

Table 1

	Pre-training session Distant-links rDLPFC	Post-training session Distant-links rDLPFC	Post minus Pre-training distant-links rDLPFC
Pearson correlation analysis results with training induced changes in behavior			
Trained Group	$r = 0.049$ $p = 0.842$	$r = 0.497$ * $p = 0.031$	$r = 0.364$ $p = 0.126$
Control Group	$r = -0.220$ $p = 0.365$	$r = -0.232$ $p = 0.339$	$r = 0.061$ $p = 0.804$

Table 2

	N	Pearson Correlation coefficient	Corrected Coefficient of determination R^2	Unstandardized slope B (standard error of the estimate)	Unstandardized slope's confidence interval (95%)
Trained Group	19	$r = 0.497$ * $p = 0.031$	0.202	0.401 (0.170)	0.042 – 0.759
Control Group	19	$r = -0.232$ $p = 0.339$	-0.002	-0.334 (0.339)	-1.050 – 0.382

FIGURES

Figure 1
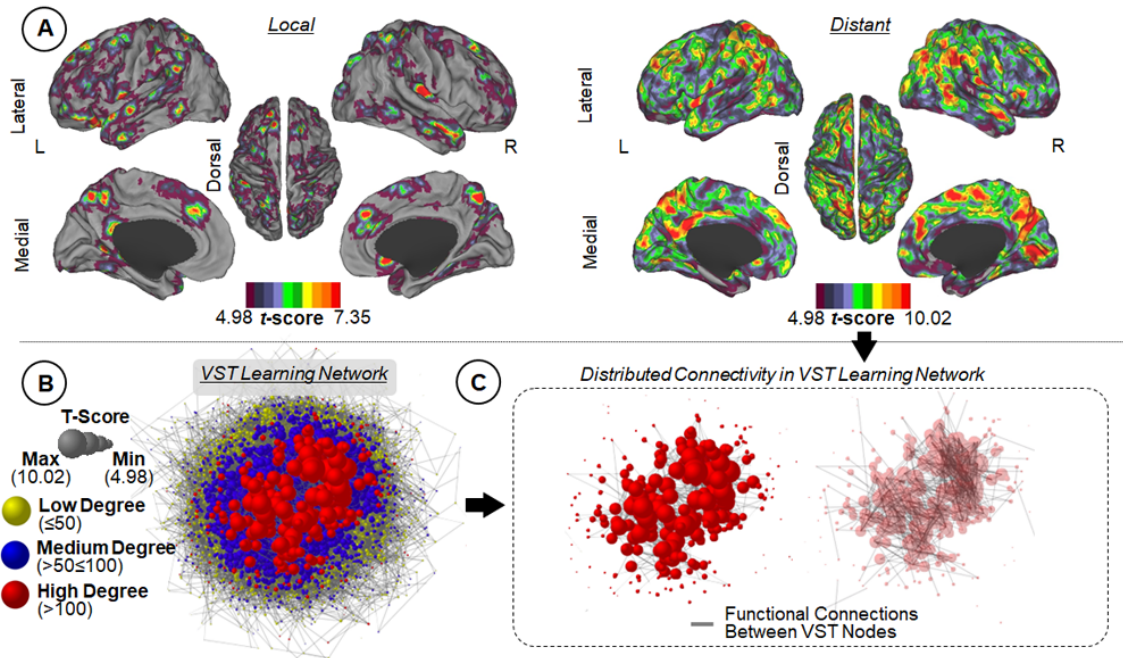
Figure 2
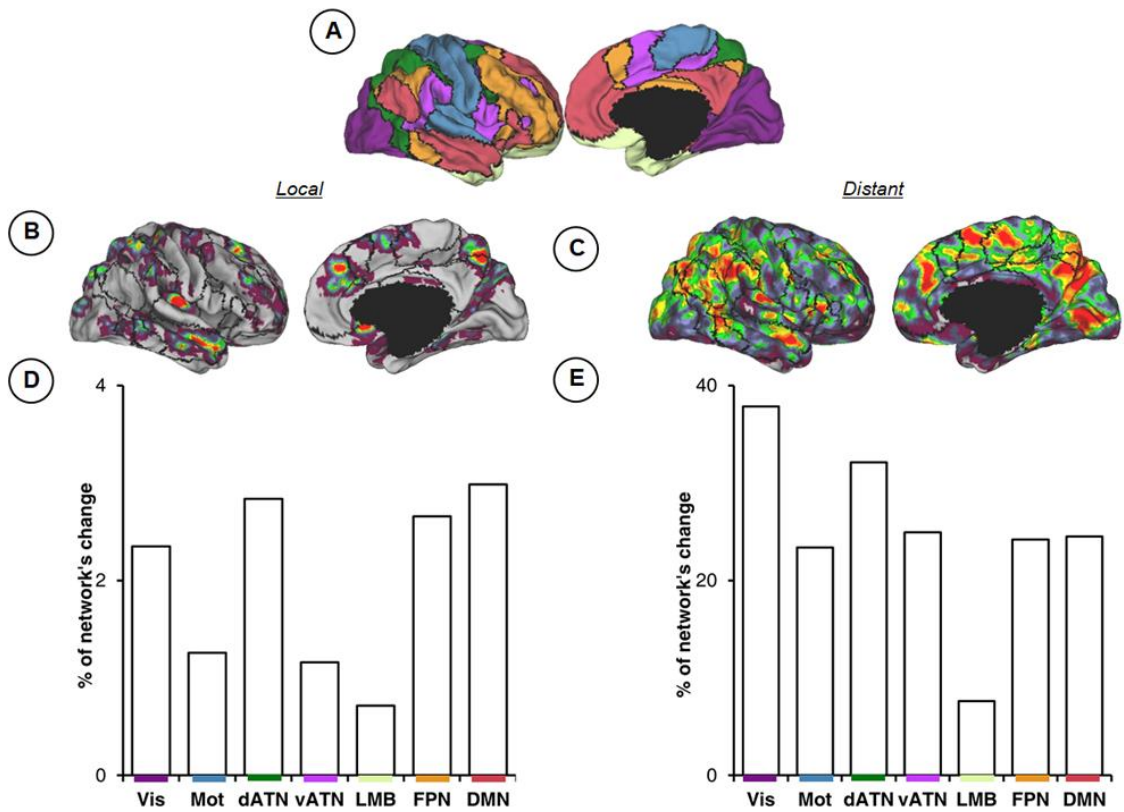
Figure 3
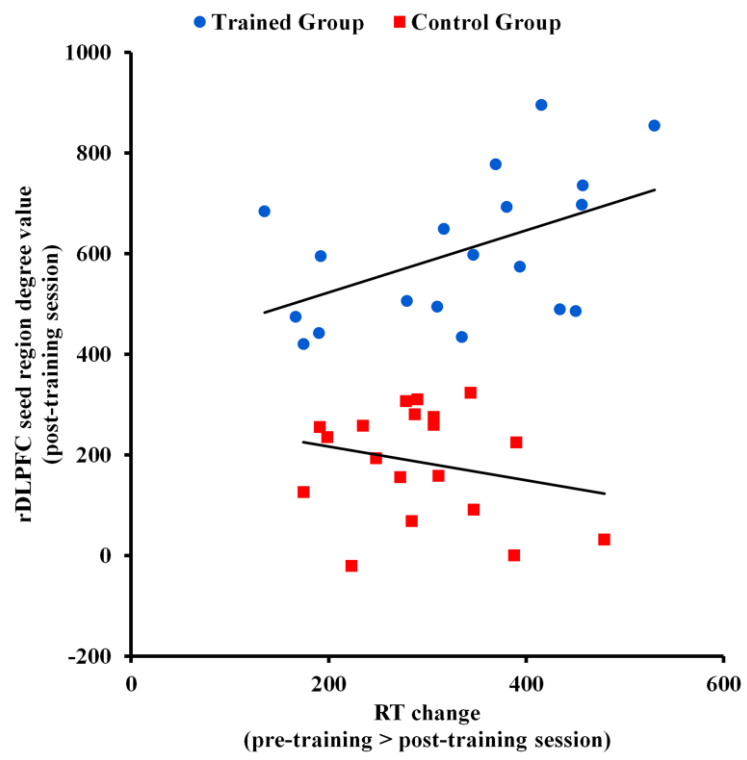
SUPPLEMENTARY MATERIALS

Author responsible for correspondence

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

Supplementary Figure 1. Schematic representation of the experimental procedure. In the top part of the figure, the organization of the experiment has been represented. 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 (squares and lines). Note that only the trained group performed 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). In the bottom part of the figure, the organization of the visual search task 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.

Trained group
Control group

Experiment

45 min

7 min	10 min	25 min	~ 30 min	10 min	25 min
Practice Outside scanner	T1 MRI	task-fMRI	Training	T1 MRI	task-fMRI

Task schema

3000 ms	300 ms	1500 ms	200 ms	8000 ms
B C D F G H		S T Z + V D K		After each block

Trial (x12)

Block (x14)