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Brain structural changes following adaptive cognitive training assessed by Tensor-Based Morphometry (TBM)

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Abstract

Tensor-Based Morphometry (TBM) allows the automatic mapping of brain changes across time building 3D deformation maps. This technique has been applied for tracking brain degeneration in Alzheimer's and other neurodegenerative diseases with high sensitivity and reliability. Here we applied TBM to quantify changes in brain structure after completing a challenging adaptive cognitive training program based on the n-back task. Twenty-six young women completed twenty-four training sessions across twelve weeks and they showed, on average, large cognitive improvements. High-resolution MRI scans were obtained before and after training. The computed longitudinal deformation maps were analyzed for answering three questions: (a) Are there differential brain structural changes in the training group as compared with a matched control group? (b) Are these changes related to performance differences in the training program? (c) Are standardized changes in a set of psychological factors (fluid and crystallized intelligence, working memory, and attention control) measured before and after training, related to structural changes in the brain? Results showed (a) greater structural changes for the training group in the temporal lobe, (b) a negative correlation between these changes and performance across training sessions (the greater the structural change, the lower the cognitive performance improvements), and (c) negligible effects regarding the psychological factors measured before and after training.

Keywords

Working memory training; Brain structural changes; Tensor-Based Morphometry

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1. Introduction

Animal studies have demonstrated plasticity-induced modifications in the brain (see Buonomano and Merzenich, 1998 for an early review of the evidence). In this regard, studying rodents Matzel and Kolata (2010) showed that working memory training changes brain features, reinforcing the sensitivity of dopamine receptors in the frontal lobes, which, in turn, influences far-transfer to performance on general cognitive ability tasks.

Research with humans is mainly based on neuroimaging techniques, which allow observing changes in brain structure resulting from a variety of behavioral interventions. After their review of the published research, Zatorre et al. (2012) noted that behaviorally evoked changes in the brain might involve increases or decreases in the considered biological properties, mainly because the interaction between structural and functional changes in the brain is complex. In addition, neuroimaging data and their underlying biological substrate are not easily related: gray matter changes may involve neuronal morphology, synaptogenesis, or neurogenesis, while white matter changes may implicate fiber density, axon diameter, or myelination. Regarding gray matter, Zatorre et al. suggest that neuroimaging data might be insensitive to neurogenesis, but gliogenesis and synaptogenesis would be proper candidates to explain macroanatomical brain changes. With respect to white matter, these authors suggest that modifications in fibers' paths (tracts geometry) may influence neuroimaging data.

Regardless of which specific microstructural changes take place in response to behavioral interventions, it is assumed that those changes may have an impact on macroscopic brain morphology. Nevertheless, Thomas and Baker (2012a,b) pointed out that methodological flaws are common among structural neuroimaging studies analyzing gray and white matter changes after behavioral training. Studies' designs, methods, and artifacts raise reservations with respect to conclusions derived from training-dependent structural changes in the human brain. Indeed, the changes evidenced by a given training program should analyze the interaction between groups (training versus control) and times (before versus after training). Also, clear hypotheses with respect to brain regions sensitive to training must be stated in advance. These points are frequently overlooked in current research.

The majority of published structural studies have relied on voxel-based morphometry (VBM), but in the present study a related technique, namely, tensor-based morphometry (TBM) will be applied. This technique builds three-dimensional maps of volumetric changes (Jacobian determinants) by matching brain scans acquired at two time points. Thus, TBM is well suited for the automated mapping of brain changes across time (Leow et al., 2009) and it has been successfully applied to track brain diseases (Hua et al., 2011). However, it has been very rarely considered for analyzing short-term longitudinal changes after experimental cognitive training regimes completed by healthy young individuals. In this regard, Ceccarelli et al. (2009) used a TBM approach for analyzing images of one small group of university students following a regular course of anatomy, biology, and physiology during two weeks. Hoekzema et al. (2011) proposed that TBM-based volumetric changes could be detected in a small group of ADHD children that completed a complex cognitive training program

(targeting planning, working memory, attention, cognitive flexibility, and problem solving) across two weeks.

To our knowledge, the study reported in the present article is the first applying TBM to a dataset comprising a group of young adult healthy participants completing a short-term (twelve weeks) challenging adaptive cognitive training program, based on the n-back task, under strict supervision in the laboratory. Note that three months have been suggested as a proper time interval for effectively evoking changes in brain structure, either neuronal dendritic arborization or dendritic spine length and synaptogenesis. In this respect, Cummings et al. (2005) showed that human stem cells do have the potential for building synapses within injured tissue related with locomotor functions in the very short-term. May et al. (2007) reported macroscopic gray matter changes after seven days of delivering transcranial magnetic stimulation towards the superior temporal cortex, concluding that structural plasticity in humans can be observed within very short periods of time.

It must be also noted that previous research has shown that cognitive training regimes based on the n-back task are associated with transfer effects (Au et al., 2014). Therefore, the sustained and adaptive training based on the n-back task is assumed to recruit cognitive processes that overlap those required for psychological factors such as fluid intelligence or working memory. Thus, their common neuroanatomical substrates might be sensitive to the adaptive training regime.

In the current investigation, brain changes (Jacobian determinants) in the training group will be compared to those computed for a matched control group. We expect neuroanatomical changes to be related to (1) variations in the performance level achieved across training sessions, and (2) the standardized change in related psychological factors measured before and after training. We hypothesize changes for the training group in brain regions thought to be involved in the training regime. From a general perspective, working memory tasks involve systematic activations in prefrontal, parietal, cingulate, occipital, and cerebellar areas. Specifically, the n-back task, requiring monitoring and inhibitory processes, usually evokes activations in (frontal) Brodmann areas (BAs) 6, 9, and 46, along with activations in (parietal) BAs 7 and 40. The anterior cingulate seems to be recruited at increased levels of difficulty, and occipital regions are involved in visuospatial working memory tasks (Cabeza and Nyberg, 2000). The meta-analysis on studies of working memory reported by Wager and Smith (2003) identified several regions frequently activated: the superior frontal cortex (BAs 6, 8, and 9) was involved in updating and short-term memory for temporal order; right BAs 10 and 47 were activated during manipulation and dual-task conditions; the posterior parietal cortex (BA 7) supported executive working memory processes; finally, BA 32 was recruited when selective attention was required for information storage in working memory. Yarkoni et al. (2011) reported consistent activations in anterior prefrontal and posterior parietal regions when completing tasks requiring cognitive control, such as the n-back task.

Nevertheless, these findings are based on functional correlates. As noted above, the interaction between structure and function is far from straightforward (Zatorre et al., 2012). The VBM study by Colom et al. (2007) analyzed the common neuroanatomic framework of the general factor of intelligence (g) and working memory span tasks, finding significant

overlaps in the right superior and left middle frontal gyri (BA 10), along with the right inferior parietal lobe (BA 40). These results were interpreted as suggesting that frontal regions support processes devoted to cognitive control, whereas parietal areas are responsible for the capacity limitations of the human brain (Cowan, 2005).

In short, considering the reviewed evidence, differential structural changes are expected mainly in parietal and frontal discrete regions (Burgess et al., 2011; Buschman et al., 2011; Colom et al., 2007; Klingberg, 2010; Rottschy et al., 2012). Furthermore, the cerebellum should also be involved because of the executive updating and skill acquisition requirements of the training program (Ferrucci et al., 2008; Habas et al., 2009; Hautzel et al., 2009; Owen et al., 2005). In this regard, Leggio et al. (2011) underscored the role of the cerebellum in the sequence and feedforward processing related with cognitive abilities. The cerebellum was seen as a booster supporting general processing.

2. Method

2.1. Participants

Two groups of twenty-six females each were recruited from a larger group of 169 university undergraduates. Members of each group were matched for their general intelligence, and the groups overlapped on and represented a range of scores (please see Colom et al. (2013) for details). All participants were right handed, as assessed by the Edinburgh Test (Oldfield, 1971). They also completed a set of questions asking for medical or psychiatric disorders, as well as substance intake. The recruitment process followed the Helsinki guidelines (World Medical Association, 2008) and the local ethics committee approved the study. Colom et al. (2013) analyzed this same sample and reported the observed cognitive results. Further details can be found on this report. Nevertheless, Appendix 1 provides sociodemographic and cognitive data.

2.2. Basic design

169 participants completed a battery of tests and tasks tapping fluid intelligence –Gf, crystallized intelligence – Gc, working memory capacity – WMC, and attention control – ATT—before recruitment. Afterwards, 52 individuals were recruited for MRI scanning and half of these participants (training group) completed the cognitive program based on the n-back task over the course of three months. At the end of the training period, participants from both the training and control groups were scanned and completed a second psychological assessment. The interval between MRI scans was, on average, 117 days (SD = 8 days; range = 99–133) and there were no significant differences ($t = 1.68$; $p = 0.10$) between the training (115 days; SD = 6 days; range = 104–121) and control (119 days; SD = 10 days; range = 99–133) groups in this regard.

2.3. Cognitive training program

The cognitive training program followed the guidelines provided by Jaeggi et al. (2008), but here the training began with four sessions (weeks 1 and 2) with a visual adaptive n-back version and four sessions (weeks 3 and 4) with an auditory adaptive n-back version, before completing the sixteen sessions of the adaptive n-back dual program (weeks 5–12). We

extended the training period from four weeks to three months (12 weeks). There were two training sessions per week lasting around 30 min each and they took place under strict supervision in the laboratory. Participants completed their training within individual cabins. Data were systematically analyzed weekly for checking progress and participants received feedback regarding their performance.

The control group was passive and these participants followed their habits as university students. Note that previous research has shown that there are not remarkable differences between active and passive control groups in this kind of research (Chooi and Thompson, 2012; Redick et al., 2012). This observation is reinforced in the meta-analysis by Klauer and Phye (2008): no differences were found between no-contact and active control groups. The behavioral results reported by Colom et al. (2013) for the same participants analyzed here are fully consistent with this conclusion.

2.4. Psychological factors

Fluid intelligence was measured by screening versions of the Raven Advanced Progressive Matrices Test (RAPM), the abstract reasoning subtest from the Differential Aptitude Test (DAT-AR), and the inductive reasoning subtest from the Primary Mental Abilities Battery (PMA-R). Crystallized intelligence was measured by screening versions of the verbal reasoning subtest from the DAT (DAT-VR), the numerical reasoning subtest from the DAT (DAT-NR), and the vocabulary subtest from the PMA (PMA-V). Working memory capacity was measured by the reading span, the computation span, and the dot matrix tasks. Finally, attention control was tapped by cognitive tasks based on the quick management of conflict: verbal (vowel–consonant) and numerical (odd–even) flanker tasks, along with the spatial (right–left) Simon task. Colom et al. (2013) provide a full description of these intelligence tests and cognitive tasks.

2.5. MRI acquisition

Images were acquired in a General Electric Signa 3T MR Scanner (General Electric Healthcare, Fairfield, CT) using a whole-body radiofrequency (RF) coil for signal excitation and quadrature 8-channel coil for reception. For the structural images analyzed here, a high-resolution 3D T1-weighted Gradient Echo-SPGR was applied, with parameters: TE = 4.1 ms, TR = 9.1 ms, TI = 450 ms, flip angle = 10°, 170 sagittal slices, acquisition matrix = 256 mm × 256 mm, isotropic voxel size = 1 mm³.

2.6. Image preprocessing

When scan pairs were checked, a warping distortion between pre- and post-test scans from the same subject was observed. Specifically, we saw a stretch-expansion in the temporal lobe area and the opposite in the parietal area. This distortion was due to (a) the use of a high-field scanner and (b) the offset of iso-center in the longitudinal scans. Note that the MR scanner software level used to acquire the data in this study only supports 2D distortion correction. In order to reduce the differences in residual distortion to do differences in participant positioning, we corrected all the images to have equivalent 3D distortion correction. Correction for B1-inhomogeneity (shading) artifacts is commonly done – whether it is explicitly stated as separate steps or included as a “bias correction” inside

processing schemes. These corrections were required as we expect subtle changes and any distortion might engulf the signal of interest.

The applied technique for correcting distortions was embedded in the “Grinder” toolbox. This corrects for geometric distortions due to non-uniformities in the magnetic field strength in the scanner. The applied image pre-processing steps for this correction involved Grinder + N3 + bias correction from SPM5 unified segmentation (Jack et al., 2008). The tool chain was identical to the one used to process the Alzheimer's Disease Neuroimaging Initiative T1-weighted MR images. Gradient distortion correction is done based on distortion parameters provided by the MR scanner manufacturers. The correctness of the distortion parameters for supported scanners has been validated using phantoms. For the limited scope of this study, a single scanner was used. B1 inhomogeneity and coil sensitivity shading artifacts are corrected with the “N3” correction of Sled et al. (1998) and by bias correction in SPM5 unified segmentation. The N3 parameters are those outlined in Boyes et al. (2008) and SPM5 unified segmentation is used with a custom template as outlined in Vemuri et al. (2008). Structural analysis of the images did not use the segmentation outputs from SPM5, only the smoothly varying bias correction. These steps were successful for correcting the distortions.

2.7. Tensor-Based Morphometry (TBM)

The TBM protocol followed several standard steps that are detailed next. Firstly, we registered an individual brain to the ICBM space using 7P linear registration to create a registration target for the remaining brains. Secondly, to linearly align the scans to ICBM space, each follow-up scan was linearly registered to its baseline scan with 6-parameter (6p, mritoself function of minctools) and 9-parameter (9p) affine transformation, then both scans were registered to ICBM using the same 9-parameter (9p) transformation, with mutual information as a similarity measure. The mutually aligned baseline and follow-up scans were then linearly registered to the ICBM space, applying the same 9P transformation (baseline to ICBM) to both scans. Intermediate transformation matrices were concatenated into a single transformation file, so that both baseline and follow-up scans were resampled once during the linear registration, to ensure equivalent resampling (Yushkevich, et al., 2010).

All the images were resampled to $220 \times 220 \times 220$ in $-x$, $-y$, and $-z$ dimensions, with a voxel size of $1 \times 1 \times 1$, and a file format of unsigned short. Quality checks were conducted by generating a .png file to display a 3×3 preview of linearly aligned baseline (9p) and follow-up (6p and 9p) scans in coronal, horizontal, and sagittal views. A trained RA visually inspected the preview images. We assumed minimal skull size changes and therefore we used `pretest_icbm9p` (pretest 9p registered to ICBM) and `posttest_icbm6p` (posttest 6p registered to pretest) for mapping the brain changes that might be attributed to the training program.

Thirdly, we created a customized brain template for the study. All the 52 pretest subjects were used to create the MDT. Steps for creating the MDT are described elsewhere (see Hua et al. (2009)). Briefly, an affine average image was created from all pretest images after nine-parameter affine registration to ICBM space. Each scan was nonlinearly registered to

the affine average template using a nonlinear inverse-consistent elastic intensity-based registration algorithm (see Leow et al. (2005)). The deformation field was determined by maximizing the mutual information of the image intensities and by minimizing the elastic energy of the deformation. A nonlinear average was computed by voxel-wise averaging the intensities of the images that had been nonlinearly registered to the affine average template. Finally, the MDT was created adjusting the nonlinear average with inverse geometric centering of the displacement fields. The MDT serves as an average brain template for the study.

The fourth step involved the use of ROBEX (Iglesias et al., 2011) to create brain masks that exclude non-brain tissue. Individual masks were created for each pretest and posttest scans in the ICBM space. After creating the masks, a Matlab program was used for generating displays of the brains with overlaying mask. The linear registration quality was checked, as well as the quality of ROBEX masking, during this step. Afterwards, we created a joint mask based on the union of Robex masks of pretest and posttest scans, and then dilated the union mask 2×. This created a uniform mask for both scans. The pipeline also applied the joint mask to skull strip the pretest-icbm9p and posttest-icbm6p images.

The fifth step corresponded to the cross-sectional nonlinear registration. Here we registered individual pretest scans to the MDT. The transformation matrix was later used to reslice the longitudinal maps in the next step, so that all change maps shared a common space defined by the MDT.

The longitudinal nonlinear registration was the final step. The individual posttest-icbm6p scans were registered to the pretest-icbm9p scans. The deformation field obtained from intrasubject scan pairs represents changes in an individual brain from the pretest to the posttest. The longitudinal Jacobian determinant map was resliced using the displacement field derived from the cross-sectional registration to align the longitudinal Jacobian determinants maps into the common MDT space for voxel-wise analysis. Group comparisons and statistical analyses were based on the Jacobian determinant maps in the MDT space. The image processing steps were executed using the LONI Pipeline Processing Environment (Shattuck et al., 2001).

2.8. Statistical analyses

Firstly, we computed the improvements in the completed training program (achieved average n-back level in the last training session – achieved average n-back level at the first training session). Then, we examined the influence of pre-training cognitive level in the performance during the training program by correlating individual differences in baseline cognitive level (pre-training scores in the psychological factors) with the level of achievement in the training program (the achieved average n-back level in the last session).

Secondly, the Jacobian determinants obtained for the training and control groups were visualized for checking descriptive differences between groups. The computed Jacobian determinants were smoothed using a kernel of 8 mm and submitted to voxel-based independent samples *t*-tests for finding brain regions where the training group differed from controls in the level of changing after training. For ensuring that the interval between MRI

scans did not affect our main findings, we repeated the voxel-based independent samples *t*-tests including this interval as covariate.

Next, the average change in regions distinguishing both groups was correlated with the improvements in the training program.

Finally, transfer effects were tested. These transfer effects were analyzed, at the cognitive level, by correlating improvements in the training program with changes in the psychological factors. At the brain level, the average change in regions distinguishing both the training and control groups was correlated with the standardized changes in fluid and crystallized intelligence, working memory capacity, and attention control.

3. Results

3.1. Cognitive results

The average cognitive performance across training sessions (visual, auditory, and dual), shown in Fig. 1, demonstrates that participants were engaged reaching the required levels at the end of the training sessions. Substantial average improvements were observed, varying from 2.4 in the first session to 5.2 in the last session. Nevertheless, there were remarkable individual differences. Thus, for instance, in the final session four participants performed at 3-back, seven participants performed at 4-back, six participants performed at 5-back, three participants performed at 6-back, three participants performed at 7-back, two participants performed at 8-back, and one participant performed at 9-back.

Regarding the influence of pre-training cognitive level in the improvements due to the training, participants who achieved a higher n-back level in the last session of the training program also showed remarkably better cognitive level at baseline. The computed effect sizes (Pearson's *r* and Cohen's *d*) were: fluid intelligence ($r = 0.53$; $d = 1.3$), crystallized intelligence ($r = 0.42$; $d = 0.92$), working memory capacity ($r = 0.48$; $d = 1.1$), and attention control ($r = 0.14$; $d = 0.29$). Thus, high-achievers in the training program have higher cognitive resources from the beginning for dealing with the training requirements.

3.2. Imaging results

3.2.1. Training versus controls—The top panel of Fig. 2 displays maps representing the between groups mean differences (training – controls) in the Jacobian determinants. There was greater change for the training group in the right cerebellum, bilateral temporal, bilateral prefrontal, and bilateral inferior parietal regions (as denoted by white clusters). However, only a region located in the temporal lobe (red cluster in the bottom panel), survived cluster-based FWE corrections ($p = 0.05$) after independent samples *t*-tests. After a within-group one sample *t*-test, we observed that changes for this temporal cluster correspond to volume reduction in the control group and volume preservation in the training group [$(t_{\text{controls}} = -4.98, p < 0.0005)$; $(t_{\text{training}} = 0.49, p = 0.63)$]. Importantly, we did not find, any region where the control group showed greater changes compared with the training group. Note that similar results were found after controlling for the effect of the interval between MRI scans (please see Supplementary materials).

Hereafter, mean changes computed for the temporal cluster significantly distinguishing both groups were considered in the remaining analyses.

3.2.2. Relationship between brain structural changes and training performance

—Fig. 3 shows the scatterplot regarding the correlation between mean changes (Jacobian determinants) computed for the temporal cluster and cognitive performance differences on the n-back task. A substantial negative value was observed, equivalent to a large effect size (Cohen's $d = -1.01$). Therefore, participants showing greater expansions improved less across the cognitive training sessions.

3.2.3. Transfer effects—Improvements in the completed training program were unrelated to changes in the psychological factors ($r_{Gf} = -0.09$; $r_{Gc} = 0.01$; $r_{WMC} = -0.09$; $r_{ATT} = 0.25$). Thus, there were not transfer effects at the cognitive level. There were not significant correlations between the average Jacobian determinants at the identified temporal cluster and the standardized changes in the psychological factors (see Fig. 4). The observed changes at the brain level were unrelated with changes at the cognitive level in the psychological factors where transfer effects were hypothesized.

4. Discussion

In the present study, we have analyzed brain structural changes in two groups of healthy young participants. The first group completed a challenging cognitive program based on the n-back task across twenty-four training sessions (three months), whereas the second (control) group did not. Both groups were carefully matched in socio-demographic and cognitive factors (please see Colom et al., 2013). High-resolution MRIs were submitted to a processing pipeline designed for computing standard tensor-based morphometric (TBM) analyses. We reported unique findings resulting from the application of this neuroimaging approach for answering three main questions. First, are there differential brain structural changes in the training and control groups? Second, are the observed brain structural changes related to cognitive performance differences in the training program? Third, are standardized changes in a set of psychological factors (fluid and crystallized intelligence, working memory capacity, and attention control) measured before and after training related to the computed brain structural changes?

The cognitive results observed across the completed training program revealed that participants were engaged in the task (Fig. 1). Improvements were large and equivalent to those appreciated in the study by Jaeggi et al. (2008). Also, there were substantial individual differences in training performance. The range in the dual version of the n-back program was between 3-back and 9-back, and therefore, not all participants improved to the same degree.

The applied TBM pipeline allowed computing the Jacobian determinants quantifying changes from the first to the second brain scan. As described above, TBM provides the

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2016.07.034>.

automated mapping of brain changes across time (Hua et al., 2013) and these changes can be used for comparing groups of participants. TBM has been successfully applied for comparing healthy subjects and patients, but it has not been considered for analyzing short-term longitudinal changes after experimental cognitive training regimes completed by healthy young participants.

As noted at the introduction section, Ceccarelli et al. (2009) analyzed a group of 13 students from a medical school completing a two-week learning course and a passive control group comprised by 19 students from the same school. Uncorrected TBM results suggested increments of gray matter volume in the training group. Findings were circumscribed to the dorsomedial frontal cortex, orbitofrontal cortex, and precuneus. These researchers underscored that TBM maximizes within-subject registration, which contributes to overcome presumed biases related with longitudinal comparisons.

On the other hand, Hoekzema et al. (2011) also considered a 2-week program comprising daily 45-min training sessions. The program included printed exercises for stimulating high-order mental processes related with working memory, flexibility, attention, planning, and problem solving. The 18 participants met diagnostic criteria for ADHD. Results showed differences (uncorrected for multiple comparisons) between the training and control groups in the frontal lobes and the cerebellum. The authors hypothesized that the observed structural effects reflect changes in neuronal morphology, especially synaptic remodeling in regions associated with the completed behavioral tasks.

As noted, to our knowledge there are not published reports applying TBM to young healthy individuals facing a challenging cognitive program completed across three months. As discussed above, this time period would suffice for observing macroscopic changes in the brain in response to cognitive training (Cummings et al., 2005; May et al., 2007). The reported results suggested expansions of brain tissue in frontal, parietal, and temporal regions, along with the cerebellum, in the training group (Fig. 2). All these regions have been related with the cognitive operations required by the training regime: monitoring and inhibitory processes, updating and short-term memory for temporal order, manipulation and dual-task requirements, executive working memory processes, cognitive control, sequence and feedforward processing (Cabeza and Nyberg, 2000, Hautzel et al., 2009, Leggio et al., 2011, Wager and Smith, 2003, Yarkoni et al., 2011).

Nevertheless, statistical analyses indicated that only findings for the temporal lobe survive to multiple comparisons. Therefore, the average change computed for this region was correlated with participants' performance in the training regime. Specifically, we correlated the differences in rate of cognitive improvement across sessions with the observed brain structural changes in the temporal region. The obtained value was equivalent to one standard deviation (Cohen's $d = -1.01$). The correlation was negative, meaning that participants with lower rates of improvement across training sessions showed the largest structural expansions (Fig. 4). This finding might be tentatively interpreted from the brain efficiency hypothesis. Neubauer and Fink (2009) noted that this hypothesis is related with the processing resources required for successfully completing a cognitive task. Our finding suggests that participants with high rates of improvement across training sessions do have the required processing

resources, whereas participants with low rates of improvement do not. In the latter case, the sustained effortful processing across sessions might be behind the observed structural changes.

Poldrack (2014) published a critical comment regarding the efficiency hypothesis. The main conclusion was that, as commonly understood, efficiency is not a useful concept in cognitive neuroscience. However, efficiency would be conceptualized as the energy invested for information transmission within a given network in the brain. Also, individual differences in energy requirements for completing similar computations may be useful. This latter approach may help to explain the results reported here. Participants were required to complete one specific and well-defined cognitive task across a relatively large time interval. Systematic challenges were faced and difficulty levels were adaptively adjusted to individuals' performance. Using Poldrack's analogy regarding the hybrid Toyota Prius and the gas-only Porsche Carrera, participants were required to ride their brains/cars from Los Angeles/1-back to Northern California/9-back during the same period of time (twelve weeks). However, some brains/cars traveled far away from the exit line at a low cost, whereas other brains/cars invested a lot of gas for traveling a short distance.

This perspective was substantiated after the analysis of the psychological measures completed by participants of the training group in the first psychological assessment. We computed their scores in fluid intelligence, crystallized intelligence, working memory capacity, and attention control. Afterwards, we tested if high-achievers and low achievers in the training program were different from the outset at the cognitive level. We found large effect sizes denoting that participants with large improvements across the training program showed better cognitive resources from the outset, and, therefore, the required processing would be least challenging for them. Low achievers showed worst processing resources from the outset, and, therefore, their brains might be particularly sensitive to the sustained effort.

The functional study reported by Bassett et al. (2015) is consistent with this interpretation. The recruitment and coordination of neural circuits were analyzed across the learning process associated with a motor task. Their main findings indicated that the sensorimotor brain regions involved were progressively disengaged with increased practice. Furthermore, the differential release of brain regions devoted to cognitive control processes (frontal and cingulate cortices) predicted individual variations in learning rates. Their results were interpreted based on the neural efficiency hypothesis: cognitive resources required in the first stages of learning become progressively less relevant with increased automation (“*the cortical system will tend to economize resources and limit unnecessary communication and transmission to enable automaticity*”, p. 5). This pattern was clearer for individuals showing better cognitive levels at baseline, before training. Negative relationships were found between visual-motor integration levels at baseline and release levels across training sessions.

Moreover, further support to this efficiency interpretation can be found, to a certain extent, in the nonhuman animal literature. Curlik and Shors (2011) noted that animals requiring more trials to learn a given conditioned response (CR) retain more new neurons than animals quickly acquiring the CR. The difficulty of the to be learned task and the learning rate

“*determine how many newborn neurons survive*” (p. 2168). Therefore, effort involved in learning is crucial for observing structural brain changes (Shors, 2014).

Finally, the relationship between the observed brain structural changes and the standardized change in the transfer measures revealed negligible findings. Specifically, there were null correlations between the four psychological factors measured before and after training, namely, fluid intelligence, crystallized intelligence, working memory capacity and attention control. These results indicate that the structural change was not powerful enough to support any appreciable effect over the psychological covariates of interest. This was the case for working memory capacity (a near-transfer factor) and for fluid intelligence (a far-transfer factor). The failure to detect statistically significant changes at the hypothesized brain regions (mainly in frontal and parietal cortices) may account for the lack of results in this regard. Indeed, the large-scale lesion study reported by Barbey et al. (2014) might be consistent with this view. Analyzing the overlap between fluid intelligence (Gf) and four working memory distinguishable cognitive factors (verbal/numeric working memory, spatial working memory, working memory manipulation, and working memory monitoring) meager overlap was found for Gf and monitoring processes (as assessed by 1-back, 2-back, and 3-back tasks): the overlap was circumscribed to a small region within the right inferior parietal cortex.

The type of cognitive training analyzed here may have applicability to clinical practice. In this regard, Klinberg's (2010) review discusses evidence showing that working memory training might help ADHD individuals and stroke patients by decreasing their cognitive symptoms. Subramaniam et al. (2012) demonstrated that cognitive training, based on neuroscience evidence, enhances schizophrenia patients' brain function. Their training regime comprised working memory related cognitive processes. The benefits observed after training, mainly concentrated in reality monitoring, were reflected in better quality of life months after the end of the program itself. Recently, De Giglio et al. (2016) observed improvements in thalamic resting-state connectivity in multiple sclerosis patients after completing a cognitive training program based on video games. The completed cognitive training enhanced communication between the default mode network and the thalamus. Lövdén et al. (2013) extensive review underscores the relevance of improving our understanding of learning-related changes in the human brain; preventing decline in the elderly may be largely different from “eliciting structural plasticity” in old age.

In conclusion, the present TBM study revealed suggestive differences between a control and a training group that completed a challenging cognitive program based on the n-back task in frontal, parietal, and temporal regions, along with the cerebellum. However, only the temporal region survived to correction for multiple comparisons (see Colom et al., 2016, Román et al., 2016). Afterwards, the analyses were focused on this brain region. Structural changes in this area showed a substantial negative correlation with change scores in cognitive performance across training sessions. This was interpreted from the brain efficiency hypothesis, supported by the fact that high performers do have the required resources for successfully copying with the cognitive challenges comprised by the training, whereas low performers do not. We suggest that this lack of processing resources may evoke the greater changes observed in their brain structure in response to the sustained cognitive

challenge. Nevertheless, the observed brain changes were unrelated with changes in a set of cognitive factors assessed before and after training.

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Appendix

See Table A1.

Table A1

Sociodemographic and cognitive data.

	Mean	SD	Min	Max
Age	18.3	1.1	17	22
Height	1.6	0.06	1.5	1.8
Weight	57.07	7.1	44	75
Gf_Pretest	101.6	13.9	64.6	129
Gf_Posttest	110.5	15.2	64.9	137.1
Gc_Pretest	101.5	14.5	69.9	134.9
Gc_Posttest	100.9	13.8	70.3	131.1
WMC_Pretest	240.36	30.4	170	293
WMC_Posttest	253.4	28.3	191	301
ATT_Pretest	44.27	22.75	-15	115
ATT_Posttest	40.13	17.1	-7.7	98.3

Gf = Fluid intelligence, Gc = Crystallized intelligence, WMC = Working memory capacity, ATT = Attention control, SD = Standard deviation.

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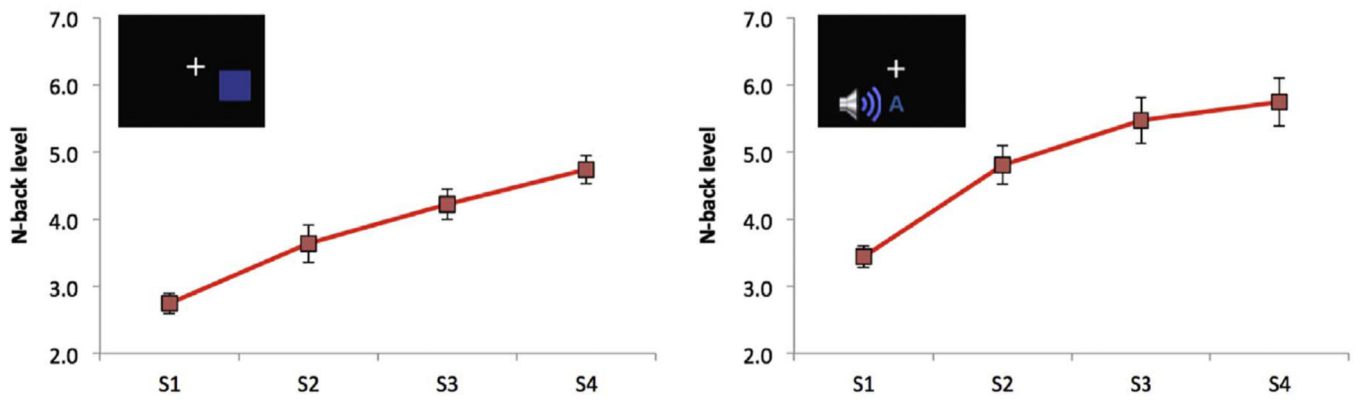
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Single N-back tasks



Dual N-back task

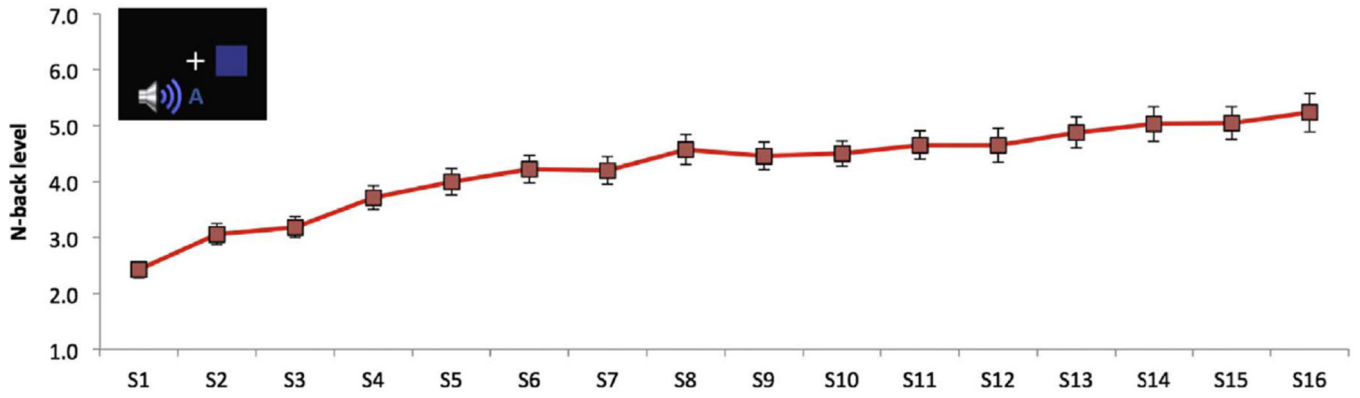


Fig. 1. Average performance across training sessions in the visual, auditory, and dual cognitive programs.

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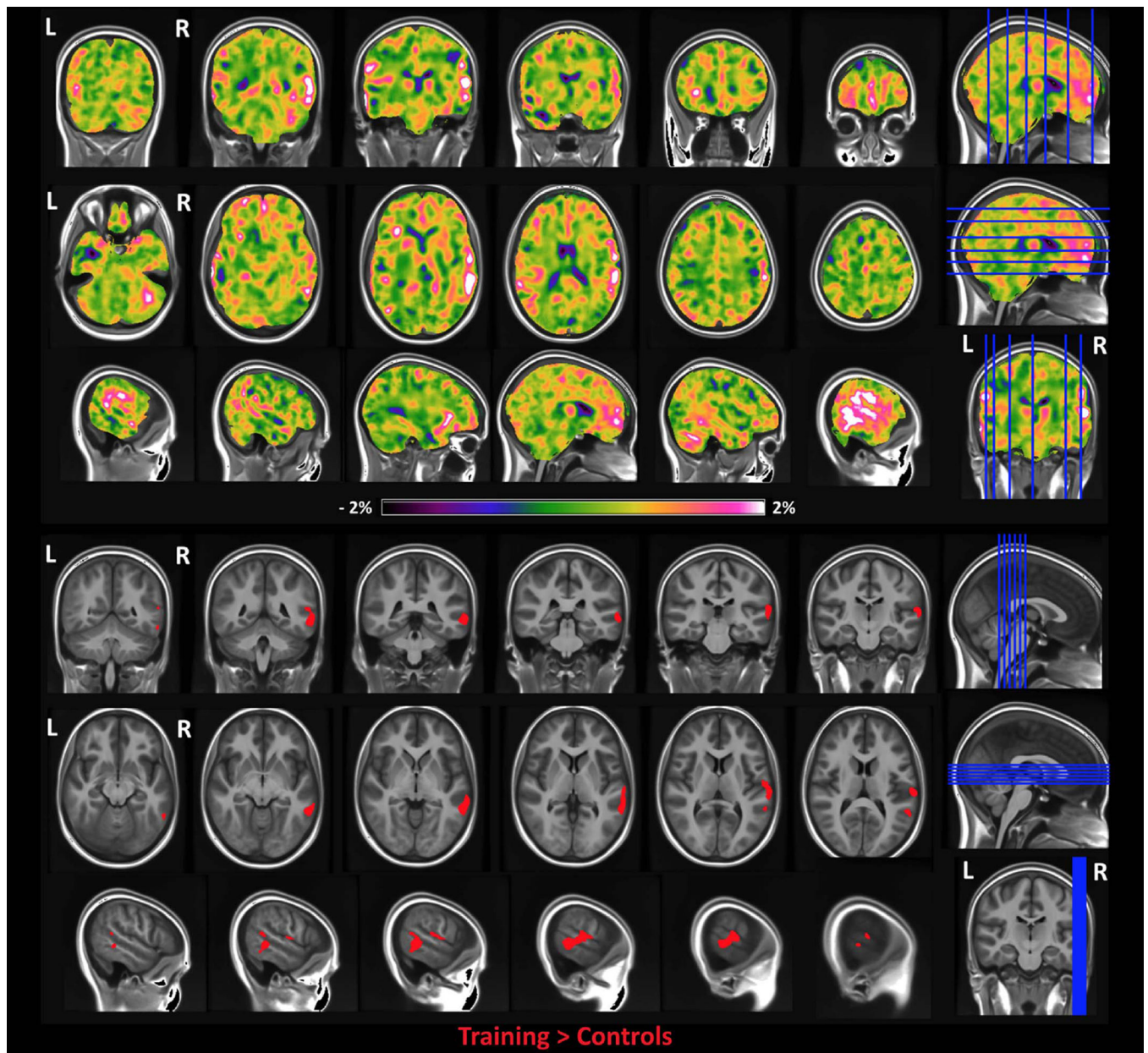


Fig. 2. Mean differences between Jacobian determinants in the training and control groups (Top panel) and the temporal cluster where this difference is statistically significant (FWE < 0.05; Bottom panel). White color in the mean map represents brain regions where the training group showed higher changes compared to the control group.

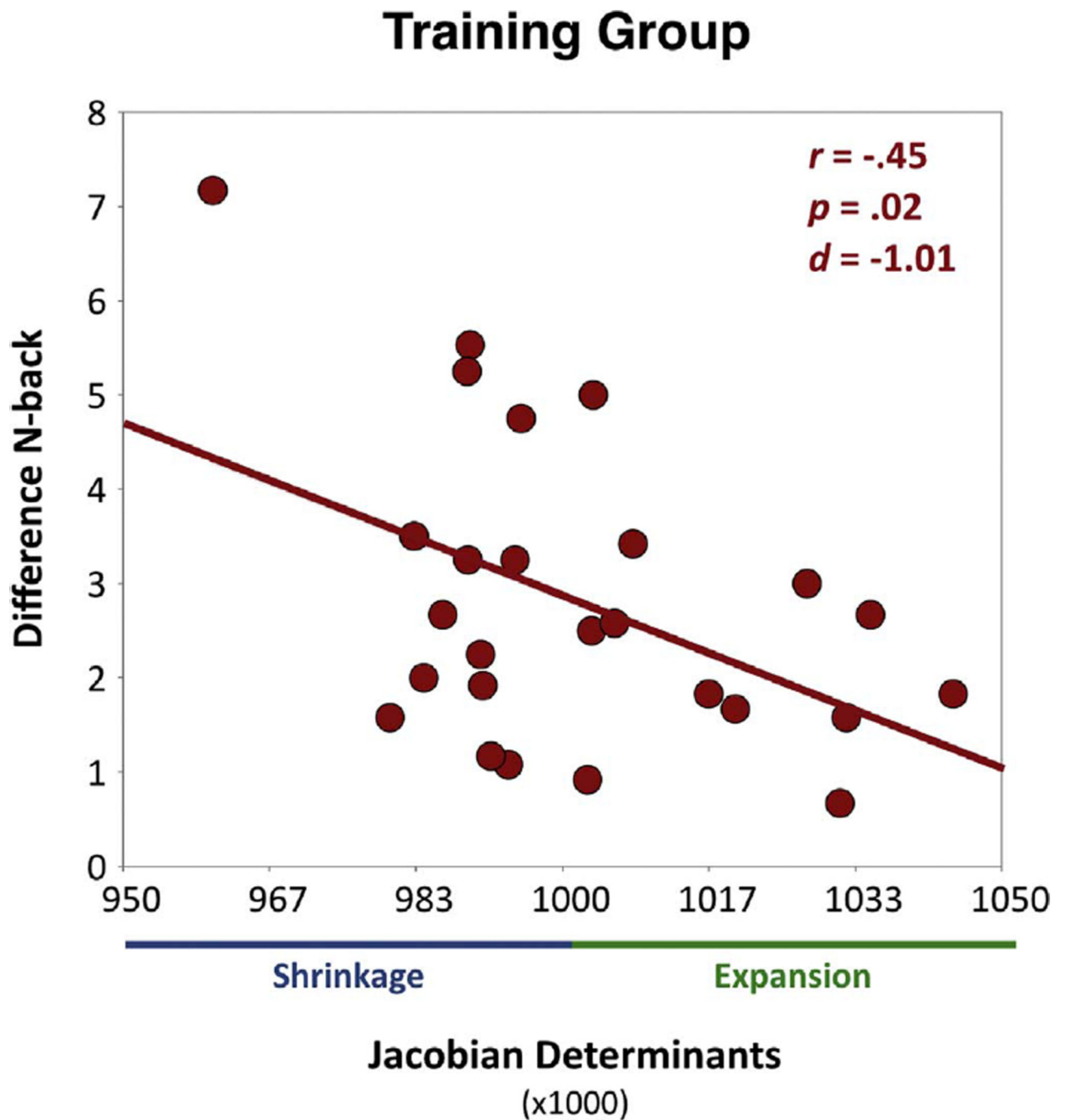


Fig. 3. Scatterplot showing the correlation between brain structural changes in the temporal lobe and the rate of cognitive improvement in the training regime.

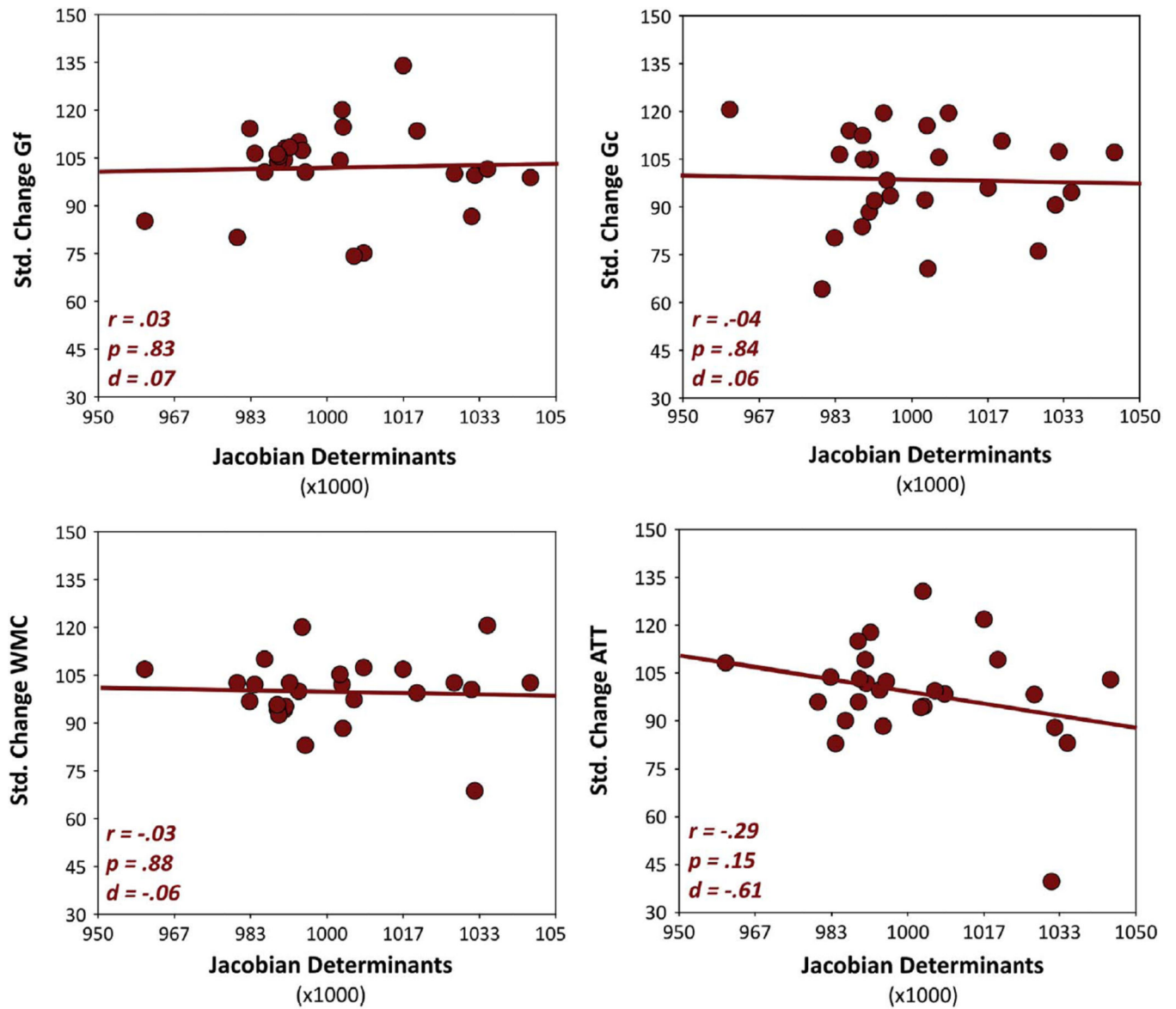


Fig. 4. Scatterplots showing the correlation between brain structural changes in the temporal cluster and changes in the psychological factors: fluid intelligence (top left), crystallized intelligence (top right), working memory (bottom left), and attention control (bottom right).