

Training-induced plasticity in older adults: Effects of training on hemispheric asymmetry

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Abstract

The extent to which cortical plasticity is retained in old age remains an understudied question, despite large social and scientific implications of such a result. Neuroimaging research reports individual differences in age-related activation, thereby educing speculation that some degree of plasticity may remain throughout life. We conducted a randomized longitudinal dual-task training study to investigate if performance improvements (a) change the magnitude or pattern of fMRI activation, thereby suggesting some plasticity retention in old age and (b) result in a reduction in asymmetry and an increase in age differences in fMRI activation as a compensatory model of performance-related activation predicts. Performance improvements were correlated with an increase in hemispheric asymmetry and a reduction in age differences in ventral and dorsal prefrontal activation. These results provide evidence for plasticity in old age and are discussed in relation to an alternative argument for the role of reduced asymmetry in performance improvements.

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The projected population increase in people over 60 years of age (<http://www.census.gov/>) has prompted an examination of interventions that have the potential to reduce or reverse age-related cognitive and neural decline. A growing number of human and rodent studies suggest that the brain and cognition retain some plasticity into old age [32]. For example, interventions such as aerobic exercise [10–12,24,30], estrogen replacement [15,16], and diets high in anti-oxidants [22] can reduce or reverse cognitive and neural decline in both rodents and humans. Indeed, understanding the neural mechanisms, limitations, and biochemistry associated with plasticity in old age is an imperative practical and scientific endeavor [41].

In addition to these interventions, training procedures have also been shown to enhance cognitive performance over both

short-term and long-term periods for people over 60 years of age [31,49]. Importantly, these training programs offer a potentially inexpensive and effective method for guiding the development of new behaviors while also strengthening existing cognitive functions and skills. Results from training studies have found that the trained skills can sometimes be generalized to other related untrained tasks and skills [28,29] and can also be retained for months or years after the formal training has concluded [1,49] suggesting that training can be used to improve a cognitive process rather than just a stimulus–response association specific to the trained task. Furthermore, in some cases the benefits of cognitive training transfer to real-world skills such as driving performance [42]. Age-related declines in cognition tend to be largest on tasks that heavily rely on executive control (i.e. scheduling, planning, working memory, multi-tasking and interference control), but these same processes are amenable to training

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[2,28,29]. However, despite the plethora of evidence indicating that older adults benefit from cognitive training, the neural correlates and plasticity associated with the changes have been virtually unstudied (see [38] for an exception).

Although the effect of cognitive training on the brain function of older adults is largely unknown, there is a rapidly growing neuroimaging literature on the potential for reorganization and compensation in the older adult brain. For example, a number of memory studies [8,9,40,45] have reported that on tasks in which younger adults show a lateralized pattern of prefrontal activity, older adults often show additional activation in the homologous region of the opposite hemisphere that is correlated with better performance on the task (for exceptions see [13,37]). This reduced asymmetry has been frequently interpreted as representing a compensatory process resulting from dedifferentiation of the areas involved in task-related processing [8,40]. That is, with age, the specificity of the cortical processors become both less effective and less exclusive, resulting in a need to recruit additional regions of cortex to compensate for the reduced specificity of function. Reduced asymmetry patterns in better performing individuals has been interpreted as (a) evidence for plasticity and reorganization of neural circuits in old age [41] and (b) reason to speculate that training procedures that promote bilateral patterns of activation might also result in improvements in behavior [8]. Therefore, this hypothesis predicts that training-induced improvements in performance may result in larger age-related differences (reduced asymmetry) in activation such that training would enhance the capability of other brain regions to compensate for the inability of the primary brain regions to respond effectively to task demands.

At odds with this hypothesis, Logan et al. [34] found that providing older adults with environmental support on a memory task reliably changed the under-recruitment pattern of encoding-related activation in the prefrontal cortex, such that age-related differences in both performance and activation were *reduced* by the support. In addition, Colcombe et al. [13] employing a version of the Eriksen flanker task reported that reduced asymmetry in the prefrontal cortex was associated with worse performance on the task, while a unilateral pattern of activation similar to that of the young adults was associated with better task performance (also see [37] for a similar finding in a go/no-go task). The authors suggested that reduced asymmetry might only be compensatory to the extent that the additional region(s) can subserve a complementary role in task performance [13]. According to this hypothesis, additional age-related cortical activation may obstruct task performance and impede task processing if the additional regions do not aid performance on the task. For example, control of verbal processes tends to be left lateralized in the prefrontal cortex and nonverbal processes lateralized to the right prefrontal cortex [6]. However, the right prefrontal cortex can play a role in monitoring the output of verbal processes, but the left prefrontal cortex does not seem to play a role in nonverbal processes [26,43,44]. Thus, according to the complementary hypothesis, bilateral recruitment in ver-

bal tasks may be beneficial for performance, but bilateral recruitment in a nonverbal task may not benefit performance because the left hemisphere plays no known role in the control of nonverbal processes. In sum, the complementary hypothesis states that reduced asymmetry in older adults may not be universally beneficial to task performance, but is dependent on the role that the active regions have in task processing. This hypothesis predicts that performance improvements engendered by training may result in increased asymmetry, or a reduction in the age-related differences in activation if the additional cortical regions do not effectively support task processing.

We conducted a longitudinal dual-task training study with older adults to assess (a) the degree of plasticity within the attentional and executive control neural circuits in older adults, and (b) whether behavioral improvements in performance were related to increased or decreased hemispheric asymmetry. Importantly, the compensation hypothesis [8] and complementary hypothesis [13] make different, but not necessarily mutually exclusive predictions about the outcome from a cognitive training study. The compensation hypothesis proposes a training-induced reduction in asymmetry and greater age differences in activation at post-training, whereas the complementary hypothesis proposes a training-induced reduction in asymmetry only if the regions play a complementary role in task performance, otherwise increased asymmetry and a reduction in age differences in activation will be found at post-training.

In a previous study we have shown [17] that a comparison of randomly and unpredictably intermixed dual-task trials and single-task trials elicits activation in brain regions that are specific to dual-task processing while minimizing potential confounds between single- and dual-tasks. Because dual-task trials often show a larger degree of performance improvement than single-task trials [4,28,29], we expected that the training protocol would affect the brain regions that appear to support the management and coordination of multiple tasks (e.g. ventral and dorsal prefrontal cortex [7,14,27]) to a greater extent than other areas unassociated with dual-task processing.

In sum, there is evidence that reorganization of function and plasticity is possible in old age [12,41], but the extent of the plasticity and the role of the additional cortical processors in performance remains in question. The central focus of this study was to examine the nature of the cortical changes that support dual-task training-induced improvements in the performance of older adults.

1. Methods

1.1. Participants

We recruited 34 older adults between the ages of 55 and 80 (mean = 66.11; range = 55–76). All participants were screened for claustrophobia, metallic implants, previous head surgery, psychiatric and neurological illnesses and were

excluded from the study based on these criteria. All participants were required to score above a 51 on a modified version of the mini-mental status examination (mMMSE; highest score = 57) for inclusion in the study. Participants were randomly placed into either a control group that did not receive any formal training or a training group that received five sessions of behavioral training. Within the control group, two participants dropped out of the study before completion due to an illness in the family and two participants were excluded from analysis due to excessive head motion. In addition, within the training group, two participants were dropped from the study because of failing to show up regularly to the training sessions, one person dropped out because of claustrophobia during the MRI, and one person was excluded due to excessive head motion. This left a total of 26 participants (13 control and 13 training). All participants signed a consent form approved by the Institutional Review Board at the University of Illinois.

We also collected data on 31 young participants in both training (16 participants) and control (15 participants) groups. These participants were also randomly assigned to a control group and training group. A full report of results from the young participants are described elsewhere [18]. However, we use a subset of the results from the young adults in order to make age-related comparisons in this manuscript.

1.2. Task

Both behavioral training and MRI trials were conducted in the following manner: the fixation point (*) was presented in the middle of the screen for 500 ms at the beginning of each trial. Participants were instructed to attend to the fixation point at all times. The stimuli were then presented on the screen and the participant was asked to respond to the stimuli by using their index and middle fingers of the right or left hand for each task. Response hand mapping was counterbalanced across subjects and was maintained throughout the training and MRI protocol. In the behavioral training sessions, the next trial was begun by the depression of the space bar. In the fMRI sessions, the next trial began after a fixed interval (2.5 s).

One of the single-tasks presented the letter 'X' in either the color yellow or the color green against a black background directly above a fixation cross located in the middle of the screen. Participants were asked to respond as quickly and accurately as possible, via a button press, to the color of the 'X', one button if yellow, another button if green. A placeholder star (*) was simultaneously presented below the fixation cross at the same position as the second single-task. The second single-task presented the letter 'B' or the letter 'C' on the screen in white against a black background and directly beneath a fixation cross. Similar to the first single-task, a star (*) was presented simultaneously above the fixation cross in the same position as the first single-task. The stars (*) served to equate the total number of visual stimuli on the screen for both single- and dual-task conditions. Participants were asked to respond via a button press, to the letter, one button

if 'B', another button if 'C'. Different buttons and different hands were used to respond to each of the single-tasks. Similar paradigms have been employed previously for studying the effects of randomly presenting single-tasks with dual-tasks in a mixed block [4,17,18].

The task consisted of two conditions: (a) a single-mixed (SM) condition in which both single-tasks were randomly presented, and (b) a dual-mixed (DM) condition in which both single-tasks were presented simultaneously (0 ms stimulus onset asynchrony (SOA)) on the screen. The DM and SM trials were presented randomly and unpredictably within the same block such that participants were required to be prepared to respond to both types of tasks on any given trial. Because of this design we were able to make comparisons between the DM and SM trials in which processes such as task-preparation were minimized in order to isolate areas involved in dual-task processing.

Participants were instructed to respond as quickly and accurately as possible and not to withhold any responses. Participants were not instructed to respond to the stimuli in a particular sequence, but most participants responded to the color discrimination task first immediately followed by the letter discrimination task. The sequence of the trial order was unpredictable. This mixed block of trials has shown to reliably reduce potential confounds such as differential levels of task-preparation between single- and dual-task trials [17].

1.3. Training procedure

Subjects (both control and training) received a 1-h pre-training session in which they were familiarized with the single- and dual-tasks. Next, a battery of neuropsychological tests was administered in order to characterize the control and training group participants. Tests were administered to measure the following constructs: IQ (K-BIT), psychomotor speed (Boxes, Digit Copy and Digit Symbol), working memory (Digit Forward, Digit Backward and C-Span), and switching speed (Trails-A and Trails-B). Functional and structural MRI data were then obtained from each participant on the single- and dual-task trials described above.

After the first fMRI session, participants in the control group had a 2- to 3-week break. The training group received five 1-h sessions of formal training on the tasks with continuous and adaptive performance feedback over a 2- to 3-week interval. The feedback (response times only) were reported to participants by a histogram located in the top left corner of the screen. A line at the top of the histogram showed the threshold criterion for good performance, which was continuously updated based on the participants response times to the single-mixed trials. This criterion required participants to respond faster than the 63rd percentile of their previous block of single-task trials. Importantly, these feedback histograms were individualized and adaptive since they depended on the individual subjects performance. After five training sessions, participants had completed 1600 SM trials and 1600 DM trials. Once the training (or break interval for the control group)

was over, both groups participated in a post-training/interval fMRI session in which they were run in the same protocol as the pre-training session.

1.4. fMRI procedure

We used an MR compatible fiber optic goggle system (Magnetic Resonance Technologies) to present visual stimuli. Responses were collected via a four-button response pad. Visual acuity was corrected to 20/30 with lenses that fit into the goggles. The stimulus onsets were fixed at an interval of 4.5 s and each stimulus remained on the screen for 2 s, which left an interstimulus baseline of 2.5 s. In addition, an 18 s fixation period was introduced after every eighth trial. The trial order within a block of trials was pseudo-random with 60 SM trials and 60 DM trials being presented. The button mappings for each stimulus condition were counterbalanced across participants. Similar types of hybrid paradigms have been used previously to investigate the effects of task-switching [5] and Stroop tasks [36] on brain function.

1.5. MRI parameters and preprocessing

A 3T Siemens Allegra MRI scanner was used for structural and functional MRI measures. For the fMRI protocol, we employed a fast echo-planar imaging (EPI) sequence with blood oxygenation level dependent (BOLD) contrast and collected a total of 1760 T2*-weighted images per participant (TR = 1.5; TE = 26; flip angle = 60) for pre-training and post-training sessions. Sixteen slices (5 mm thickness; 3.75 mm in plane resolution; 0 gap) were collected in an ascending interleaved fashion parallel to the anterior and posterior commissures.

Two sets of anatomical images were also collected during both pre-training and post-training MRI sessions: a high-resolution T1-weighted MPRAGE (0.96 mm × 0.96 mm × 1.3 mm) and a lower resolution T1-weighted image collected in the same plane as the EPI data. Both sets of anatomical images were skull-stripped using a brain extraction technique [47] and subsequently used for registration purposes.

After reconstruction, the first six images were removed in order to allow the magnet to reach steady state. The data from the pre-training and post-training sessions for every participant were preprocessed separately using FSL Version 3.1. Images were slice-time corrected, motion-corrected, temporally filtered with a Gaussian high pass cut-off of 50 s and a low pass cut-off of 1.5 s, and spatially smoothed with a 7 mm full-width half-max 3D Gaussian kernel.

1.6. Data analysis

We analyzed the behavioral data (response time and accuracy) collected in the MRI machine with a repeated measure ANOVA with Time (pre-training and post-training) and Condition (SM and DM) as within-subject factors and Group

(control and training) and Age (old and young) as between subject factors. In addition, we conducted post hoc analyses to assess the effects of Time, Group, Time × Group, and Time × Group × Age in order to determine the conditions that were most affected by the training manipulation as well as the direction of the changes. In addition, we assessed differences between the control group and training group for each condition at post-training with a one-way ANOVA with the factor of Group (control and training) at two levels (SM and DM). This was done to examine whether the two groups reliably differed by the end of training. Finally, we conducted a one-way ANOVA between the young and the old training groups to examine if any differences existed between the two age groups at the end of training. All behavioral data was analyzed using SPSS 11.02 for Mac.

The neuroimaging data was analyzed separately for the pre-training and post-training sessions. The data was first convolved using a double-gamma function with temporal derivatives using the six-motion correction vectors and error trials as covariates in the model. Errors were recorded in the DM condition when participants incorrectly responded to one or both of the stimuli. We averaged the activation for each condition over the different blocks and calculated the contrasts and direct comparisons of interest within subject separately for pre-training and post-training sessions. A single parameter estimate for each variable and each contrast were obtained for every participant from this first level analysis for the pre-training and post-training data. We then performed a whole-head higher-level analysis to locate regions that were significant in the Time × Group interaction. The parameter estimates from these regions were then extracted and examined for the direction of the effects and interactions with Condition and Age. Importantly, using the regions from the Time × Group interaction as regions-of-interest does not bias the probability of finding higher level interactions. Since the questions that we were addressing in this manuscript relate specifically to the Time × Group interaction, Time × Group × Condition interaction, Time × Group × Age interaction, and Time × Group × Condition × Age interaction, we will focus on these results.

In addition, similar to the one-way ANOVA described in the behavioral results section, the parameter estimates from the post-training session were examined separately to investigate whether there were any group differences in levels of activation after training. Furthermore, a similar one-way ANOVA was conducted between the young training group and old training group to examine whether the two age groups differed after training. Finally, to examine the relationship between the behavioral improvements with training and the changes in neural activation associated with performance on the task, we conducted correlations between change in performance and change in the degree of activation for each of the regions.

Analysis was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.1, part of FSL (FMRIB's Software

Library, <http://www.fmrib.ox.ac.uk/fsl>). Higher level analyses were carried out using FLAME stage 1 only (i.e. without the final MCMC-based stage) [3]. All results from the final whole-head analysis resulted in Z statistic images that were thresholded using clusters determined by $Z > 3.1$ and a (corrected) cluster significance threshold of $p = 0.01$ [20,21,50]. All images were rendered in Mri3DX Version 5.

2. Results

The analyses described here are primarily for older adults in the control and training groups. A complete report of results from younger adults in this task and training protocol has been previously described [18]. However, we include a subset of results from younger adults reported in Erickson et al. [18] here in order to assess age-related differences in performance and brain activation.

2.1. Reaction time

The results (see Table 1) from the repeated measures ANOVA revealed a significant main effect of Time ($F(1,24) = 125.42; p < 0.001$) such that there was a decrease in RT from pre-training to post-training for the older adults. Importantly, there was also a significant Time \times Group interaction ($F(1,24) = 44.22; p < 0.001$) such that the training group showed a significantly greater improvement in RT than the control group. We also found a significant Time \times Condition \times Group interaction ($F(2,23) = 8.06; p < 0.002$) resulting from a greater improvement for the DM than the SM condition for the training group than the control group. When we added the younger adult sample into the analysis we found a main effect of Age ($F(1,53) = 6.02; p < 0.01$) such that older adults on average were reliably slower than the younger adults. There was also a trend for a Time \times Age interaction ($F(1,53) = 3.83; p < 0.056$), but no Time \times Group \times Age interaction ($F(1,53) = 1.74; p < 0.19$) suggesting that both the young and old training groups showed the same degree of performance improvement with training.

2.2. Accuracy

The results from the repeated measures ANOVA revealed a significant main effect of Time ($F(1,24) = 13.59; p < 0.001$) such that there was an increase in accuracy from pre-training to post-training. There was also a significant Time \times Group interaction ($F(1,24) = 6.67; p < 0.01$) such that the training group showed a significantly greater improvement in accuracy than the control group. We also found a significant Time \times Condition \times Group interaction ($F(2,23) = 3.45; p < 0.05$) resulting from a greater improvement for the DM than SM condition for the training group compared to the control group. When we included Age into the model we found no main effect of Age and no significant interactions with Age.

Table 1
Mean reaction times (RT) and accuracy for the control group and training groups at both pre-training and post-training sessions for all three conditions

| | Old-training | | Old-control | | Young-training | | Young-control | |
|----------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| | Pre-training | Post-training | Pre-training | Post-training | Pre-training | Post-training | Pre-training | Post-training |
| RT | | | | | | | | |
| Single | 1249.65 (237.55) | 952.27 (224.89) | 1216.49 (136.64) | 1130.12 (137.48) | 1074.61 (168.79) | 877.59 (187.25) | 1080.47 (158.52) | 1032.18 (93.53) |
| Dual | 1454.52 (266.79) | 1057.34 (242.58) | 1433.11 (157.05) | 1370.34 (133.88) | 1364.80 (209.28) | 1059.66 (222.96) | 1320.32 (151.24) | 1237.23 (184.95) |
| Accuracy | | | | | | | | |
| Single | 0.940 (0.075) | 0.980 (0.035) | 0.941 (0.057) | 0.941 (0.045) | 0.937 (0.04) | 0.989 (0.02) | 0.931 (0.02) | 0.955 (0.02) |
| Dual | 0.909 (0.055) | 0.968 (0.035) | 0.898 (0.062) | 0.912 (0.050) | 0.881 (0.05) | 0.984 (0.03) | 0.902 (0.05) | 0.918 (0.04) |

Standard deviations are represented in parentheses.

Table 2
Neuropsychological and demographic variables for both control and training groups

| Measure | Old-training | Old-control | Young-training | Young-control |
|----------------|--------------------|--------------------|---------------------|--------------------|
| Sex | 4 males; 9 females | 6 males; 7 females | 5 males; 11 females | 6 males; 9 females |
| Education | 15.15 (3.99) | 14.27 (1.89) | 17.29 (3.25) | 14.15 (2.34) |
| Health | 4.30 (0.48) | 4.15 (0.69) | 4.58 (0.71) | 4.73 (0.59) |
| mMMSE | 54.69 (1.37) | 55.75 (1.42) | X | X |
| Digit Forward | 7.54 (1.76) | 8.16 (1.86) | 9.64 (2.06) | 9.33 (2.16) |
| Digit Backward | 6.92 (2.25) | 7.83 (2.41) | 9.11 (2.26) | 9.06 (2.94) |
| K-BIT | 117.00 (10.06) | 114.33 (8.43) | 108.92 (10.07) | 112.5 (9.19) |
| Boxes | 38.31 (14.51) | 33.08 (10.01) | 42.94 (12.65) | 49.66 (11.63) |
| Digit Copy | 60.92 (11.11) | 54.91 (9.22) | 72.82 (12.79) | 74.8 (10.82) |
| Digit Symbol | 33.46 (5.31) | 32.25 (3.89) | 47.70 (6.77) | 42.33 (5.39) |
| C-Span | 3.00 (0.91) | 3.25 (1.16) | 5.00 (1.54) | 4.40 (1.59) |
| Trails-A | 34.00 (9.24) | 40.16 (9.56) | 24.53 (7.80) | 27.86 (7.64) |
| Trails-B | 76.84 (32.34) | 77.33 (17.55) | 51.94 (11.72) | 56.33 (17.12) |

Standard deviations are represented in parentheses. Health status was measured on a 5-point scale. mMMSE scores have a high value of 57 and a cut-off at 51. Boxes, Digit Copy, and Digit Symbol values represent the number of items completed within a given time limit. C-Span scores represent the number of items held in working memory while successfully completing the calculations. The values for Trails-A and Trails-B are in seconds.

2.3. Neuropsychological testing

We performed one-way ANOVAs on the neuropsychological measures to test for any differences between the control and training groups on measures of general cognitive functioning (see Table 2). None of the tests showed a reliable difference between the training and control groups.

2.4. Neuroimaging

The results from the Time \times Group interaction in the whole-head analysis for the older adult sample revealed a significant interaction in several prefrontal regions, but only for the DM condition. These regions were located in the ventral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC) in both hemispheres. In order to examine the direction of the effects, an interaction with condition type, interactions with age, interactions between the hemispheres, and correlations with performance, we extracted the parameter estimates for both conditions from the regions showing a Time \times Group interaction for the DM condition and performed the remaining analyses of interest in SPSS.

After extracting the parameter estimates, we found that the Time \times Group interaction for the DM condition in the left VLPFC resulted from a significant increase in activity for the training group relative to the control group (see Figs. 1 and 2). This DM condition specific effect was evident by a significant Time \times Group \times Condition interaction ($F(2,23) = 5.83; p < 0.001$) indicating that this region changed more for the DM condition than the SM condition. Importantly, we found that this same VLPFC region was also active for the DM condition for the young adults but did not show any training-induced changes. When including the young adults in the analyses, we found a significant main effect of Age ($F(1,53) = 13.15; p < 0.001$) such that older adults showed less activation on average in this region compared to young adults. However, we found no significant interactions between Age and the other factors indicating that the

training-related changes were statistically equivalent for both age groups. Importantly, the improvement in performance for the older adult training group was significantly correlated with the increase in activity in this region ($r = -0.68; p < 0.01$) indicating a clear relationship between behavioral improvement and the change in the magnitude of activity.

Although the results from the repeated measures ANOVA indicates that the training group showed more change in activity than the control group, the ANOVA does not indicate whether the two groups reliably differed by the end of training. Therefore, as a post hoc analysis we compared the activity in the left VLPFC between the training and control older adults. We found that although the two groups did not reliably differ at pre-training for the DM condition ($F(1,25) = 0.02; p < 0.89$) the training group showed significantly greater activity in this region than the control group at post-training ($F(1,25) = 9.51; p < 0.005$). We conducted a similar analysis to assess whether the older adult training group reliably differed from the young adult training group. We found that the two age groups were reliably different at pre-training ($F(1,28) = 4.30; p < 0.05$), but did not show a reliable difference at post-training ($F(1,28) = 0.224; p < 0.64$). These results clearly indicate that the dual-task training paradigm reliably reduced the age-related differences in dual-task activation in the left VLPFC.

The right VLPFC activation also showed a Time \times Group interaction for the DM condition, however we found that this interaction resulted from a *reduction* in activity for the training group compared to the control group (see Figs. 1 and 2). Therefore the direction of the effect was opposite from that found for the homologous region in the left hemisphere. Moreover, we found that although the Time \times Group interaction was only significant for the DM condition ($F(1,24) = 23.39; p < 0.001$), there was only a trend for a Time \times Group \times Condition interaction ($F(2,23) = 3.04; p < 0.06$) suggesting that the DM and SM conditions did not reliably differ in the degree of change in activation from pre-training to post-training. Interestingly, the young adults who

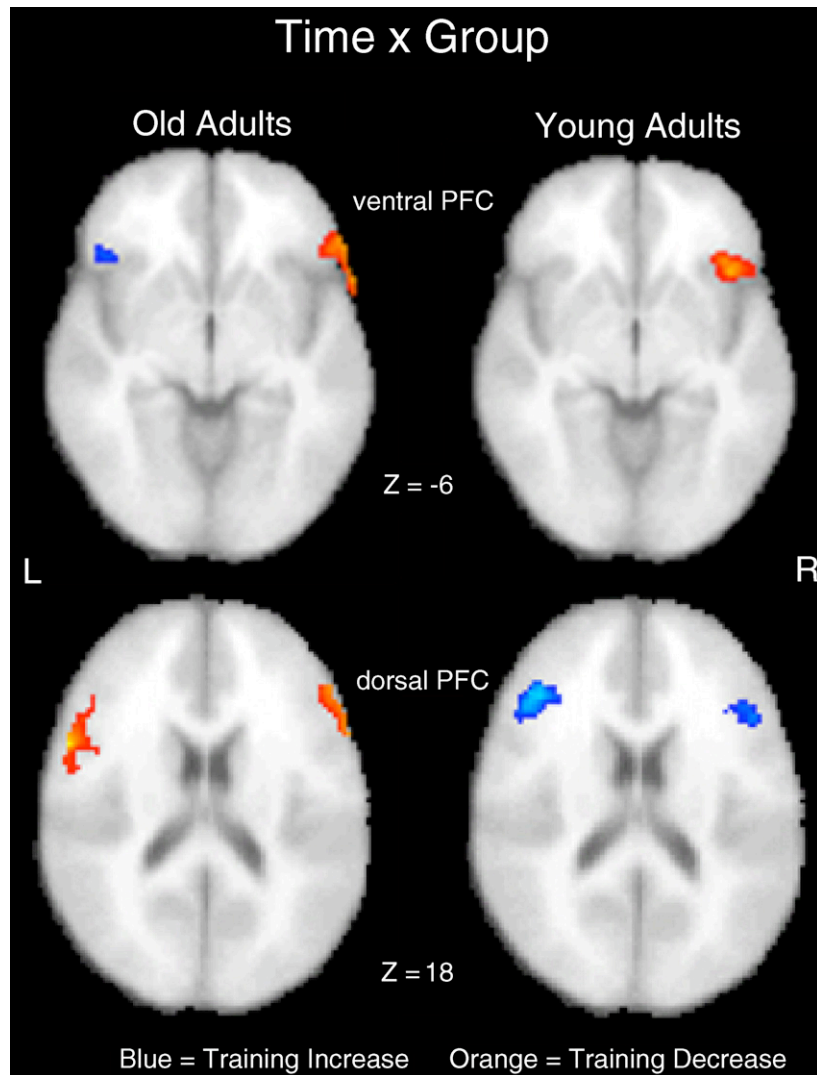


Fig. 1. Ventral prefrontal cortex (top) and dorsal prefrontal cortex (bottom) regions showing an increase (blue) in activation and a decrease (orange) in activation for the DM condition for the training group relative to the control group (Time \times Group interaction) for older (left side) and young (right side) adults. The older adults showed a Time \times Group \times Hemisphere interaction for the dorsal prefrontal cortex (see Section 2). Images are displayed in neurological convention (left on the left) at a threshold of $Z > 3.1$ and a (corrected) cluster significance threshold of $p = 0.01$.

were trained on the task also showed a significant reduction in activity from pre-training to post-training in this region when compared to a control group. When we incorporated Age into the model, we found a significant main effect of Age ($F(1,53) = 12.41$; $p < 0.001$) such that older adults had less activation in this region than the younger adults. However, similar to the left VLPFC, we found no interactions with Age on any of the factors in the model. In other words, none of the training effects affected one age group more than the other in this region. When we performed the correlation analysis for the old training group we found a significant correlation between the change in activation and change in performance for the right VLPFC for the DM condition ($r = 0.62$; $p < 0.02$).

In addition, we ran a post hoc analysis to examine whether the level of activation for the training group reliably differed from the control group in the right VLPFC at pre- and post-training. We found no differences in activation between

the training and control groups for the DM condition at pre-training ($F(1,25) = 0.06$; $p < 0.80$), but the DM condition showed reliably less activation for the training group than the control group ($F(1,25) = 14.56$; $p < 0.001$) at post-training. Furthermore, we tested whether the older adult training group differed from the young adult training group. At pre-testing, there was a trend for the two groups to reliably differ in activation ($F(1,28) = 3.02$; $p < 0.09$) for the DM condition, but by post-training there was no significant difference between young and older adults ($F(1,28) = 1.21$; $p < 0.28$). Similar to the left VLPFC, this result suggests that the age difference in activation was considerably reduced after the training regimen.

Because the direction of the training effect in the left VLPFC was opposite that from the right VLPFC, we assessed whether this resulted in a significant Time \times Group \times Hemisphere interaction for the older adults.

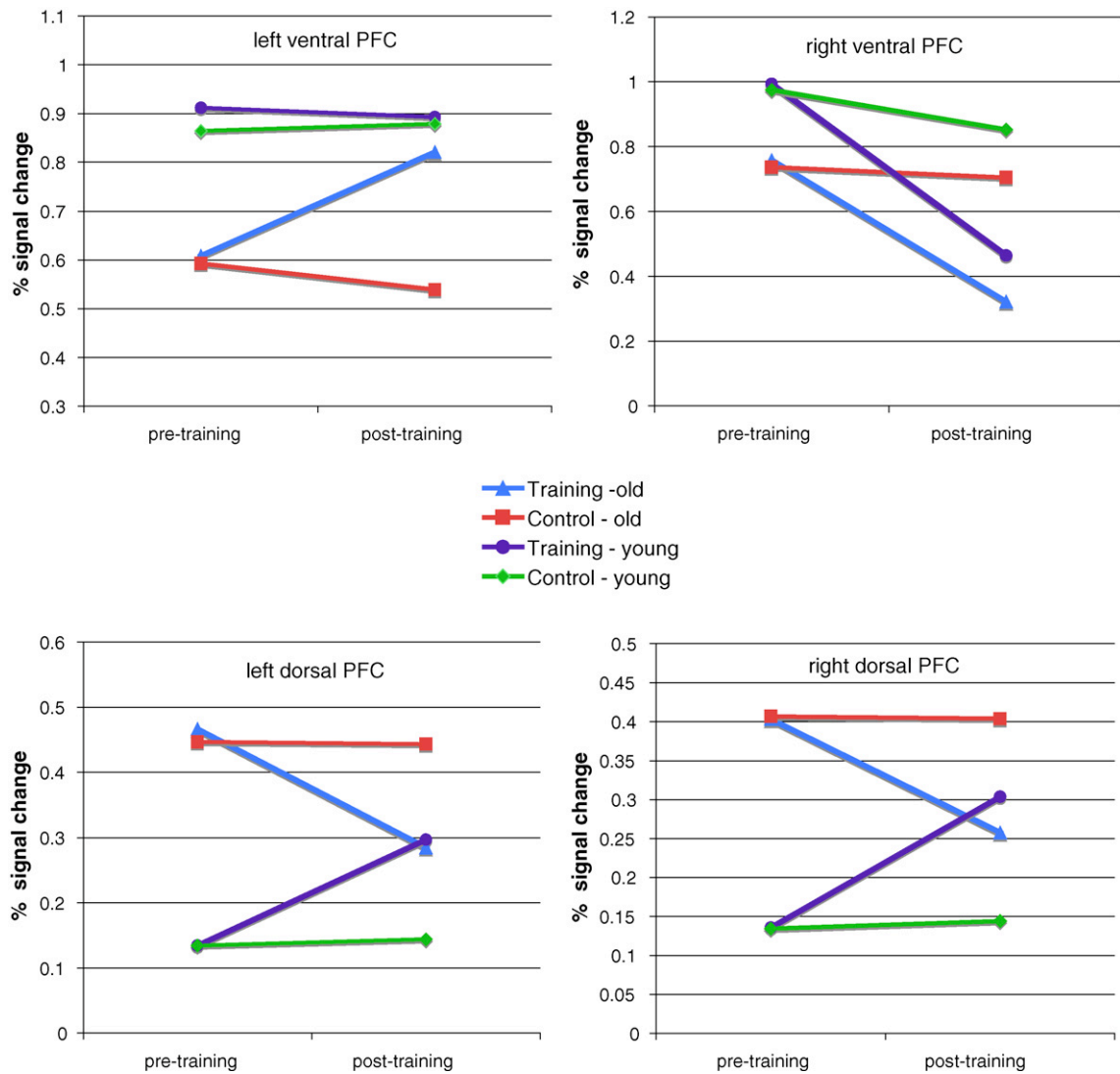


Fig. 2. Percent signal change for the left and right ventral prefrontal cortex (top) and dorsal prefrontal cortex (bottom) for the DM condition for all four groups (training-old (blue), control-old (red), training-young (purple), control-young (green)) for the pre-training session and the post-training session.

We found that although there was no main effect of Hemisphere ($F(1,24)=0.04$; $p<0.85$), there was a significant Time \times Group \times Hemisphere interaction ($F(1,24)=46.10$; $p<0.001$) suggesting that the hemispheres were differentially affected by training. Since the right hemisphere was decreasing while the left hemisphere was increasing in activity, this suggests that in this task and in this region, increased asymmetry was related to an improvement in performance.

Finally, we found that both the left ($F(1,24)=9.56$; $p<0.005$) and right ($F(1,24)=10.87$; $p<0.003$) DLPFC showed a Time \times Group interaction for the older adults. We found that this interaction resulted from a training-induced reduction in activation for both regions. Importantly, the Time \times Group interaction was modified by a significant Time \times Group \times Condition interaction in both the left ($F(2,23)=12.18$; $p<0.001$) and right ($F(2,23)=36.71$; $p<0.001$) hemisphere. Post hoc comparisons revealed that the change in activation was only significant for the DM

condition for both the left ($F(1,24)=33.42$; $p<0.001$) and right ($F(1,24)=87.53$; $p<0.001$) hemispheres. Importantly, both of these DLPFC regions also showed training-induced changes in activity for the young adults, but in that population the training resulted in an increase in activity. As a result, when we added Age into the model, we found a significant main effect of Age for the left hemisphere ($F(1,53)=80.05$; $p<0.001$) and right hemisphere ($F(1,53)=18.79$; $p<0.001$) such that the older adults showed more activity in both of these regions than the younger adults. We also found a significant Time \times Group \times Condition \times Age four-way interaction in the left ($F(2,52)=27.06$; $p<0.001$) and right ($F(2,52)=34.73$; $p<0.001$) hemisphere. This effect resulted from a disproportionate change for the DM condition relative to the SM condition for both age groups and an age difference in the direction of the training-induced change (olders decreasing and youngers increasing). Importantly, we also found that for the older adult training group the change in

both the left ($r=0.69$; $p<0.01$) and right ($r=0.62$; $p<0.02$) regions were correlated with improved performance for the DM condition.

Similar to the VLPFC regions, we wanted to assess whether the training program resulted in a reduction in the age differences in activation as well as an increase in the difference between control and training groups. Our post hoc analyses found that the training group did not reliably differ from the control group at pre-training for the DM condition in either the left ($F(1,25)=0.53$; $p<0.47$) or right ($F(1,25)=0.07$; $p<0.78$) hemisphere. However, we found that for the DM condition, the two groups were significantly different from each other in both the left ($F(1,25)=38.82$; $p<0.001$) and right ($F(1,25)=68.06$; $p<0.001$) hemisphere following training. In addition, we found that the older adult training group reliably differed from the younger adult training group for both the left ($F(1,28)=225.45$; $p<0.001$) and right ($F(1,25)=344.61$; $p<0.001$) hemispheres before training. However, at post-training the two groups did not reliably differ for the left ($F(1,28)=0.40$; $p<0.53$) hemisphere, but continued to show a significant difference in the right ($F(1,28)=7.37$; $p<0.01$) hemisphere. Importantly, these results indicate that although both age groups showed a different direction of the training-induced effects, the end result was a reduction in the age differences in activation.

Finally, we found no interactions with Hemisphere in the DLPFC regions for the older group (Time \times Group \times Hemisphere: ($F(1,24)=0.97$; $p<0.33$)). This result indicates that both hemispheres showed a similar degree of reduction.

3. Discussion

We conducted a dual-task training study to examine: (a) the degree of plasticity in regions involved in the management and coordination of performing multiple tasks in older adults and (b) whether training-induced dual-task performance improvements results in increased or reduced age differences in activity and hemispheric asymmetry. In short, our results provide evidence inconsistent with current views of compensation models of reduced asymmetry, but consistent with the complementary hypothesis [13] suggesting that better task performance in older adults is not universally associated with a pattern of reduced asymmetry.

First, we found that cognitive training reliably improves behavioral performance and alters age-related patterns of cortical functioning thereby indicating a potential for plasticity in aged individuals. This training also transfers to other untrained dual-task paradigms [4] indicating that the training was not stimulus–response specific. Furthermore, the training-induced changes in activation occurred in cortical areas commonly associated with the largest age-related atrophy, that is the dorsal and ventral prefrontal cortex [10,39,48]. This suggests that age-related functional decline in these regions is not an inevitable process of aging, but can be

reliably reduced and possibly reversed with training. These relatively inexpensive interventions could prove to be critical methods to reduce age-related cognitive and neural decline.

Our results are also interesting in the context of recent research on repetition priming and implicit memory in non-demented and demented older adult populations. The results from these studies have shown relatively intact behavioral responses and neural substrates of priming in these populations [23,35]. Priming related reductions in prefrontal activation were present for both older and younger adults and correlations between reductions in activity and response times were found for all groups [35]. Indeed, Lustig and Buckner [35] suggest that training procedures that reduce the need for controlled, or frontally based, processes may benefit both non-demented and demented individuals. The results from our study support these claims and indicate that some neuronal plasticity remains in old age and can be modified by experience on the task. Importantly, our results support these prior studies and extend the observations to a longitudinal cognitive training paradigm.

Our results are also relevant in relation to one previous neuroimaging study on the effects of training in an older adult population. Nyberg et al. [38] reported that a visual–spatial mnemonic improved memory performance in both older and younger adults, but only younger adults showed increased activity in both occipito-parietal and frontal regions after learning the mnemonic and only the older adults who benefited from the mnemonic showed increased activity in occipito-parietal regions. These results differ from our study in that we find training-related changes in activation in prefrontal regions and not in occipito-parietal regions. There are a number important differences between the two studies that may contribute to the different pattern of results. These differences include different amounts of training (one session in [38]; five sessions in the current study), different cognitive processes being trained (memory in [38]; dual-task performance in the current study), and the type of training (mnemonic in [38]; adaptive, individualized and continuous feedback in the current study). In short, the effects of training on the cortical circuitry in older adults should take into account the regions involved in the tasks, the type and amount of training, and the type of cognitive process being trained.

We found an increase in activity in the left VLPFC region. It is likely that this increase in the left VLPFC (near Broca's area) represents an increased reliance on verbal or inner speech strategies during performance of the dual-task. Previous studies have suggested that verbalization of goal-directed behavior reduces task-switch costs [25]. In addition, recent task-switching studies have found that older adults benefit from verbalization during preparation of a task-switch [33]. Therefore, older adults may utilize a verbal strategy because they are more efficient, comfortable, and effective at using verbal and semantic processes. The increase in activity in language production regions suggests that this ability may be able to be refined with adaptive feedback and training.

The decrease in right VLPFC was also found for the young-training group and may represent a reduced dependence on response selection strategies that are often associated with the right prefrontal cortex [36] or it may represent a decreased reliance on task-retrieval strategies that have also been associated with right prefrontal processing [46]. In any case, the decrease in activity represents either a reduced need or more efficient use of this brain region in dual-task performance. However, the fact that both age groups showed similar reductions in activity in this region suggests that this change is an important correlate of training-related improvements in behavior and is not an age-specific effect.

Importantly, the increased asymmetry in the VLPFC regions indicated by the significant hemisphere interaction, and reduction in the age-related differences in activation conflicts with the compensatory model of reduced asymmetry, which predicts that performance improvements should be associated with an increase in bilateral activa-

tion. In fact our VLPFC results reveal that *both* age groups show a similar training-related increase in lateralization (no Time \times Group \times Age interaction) indicating that older and younger adults respond in a similar way to dual-task training. Our results, however, are consistent with research showing that environmental support, in the present case in the form of individualized adaptive performance feedback, reduces age differences in performance and activation [34] and fMRI and event-related potential studies reporting that greater age differences in activation can be associated with poorer performance [13,19,37]. Importantly, this study provides the first longitudinal evidence for the relationship between behavioral performance and the cortical processors involved in dual-task processing—and fails to support compensation predictions of reduced asymmetry.

The direction and degree of change in DLPFC regions were also inconsistent with a compensatory view of reduced asymmetry. Although the old adults showed a decrease in

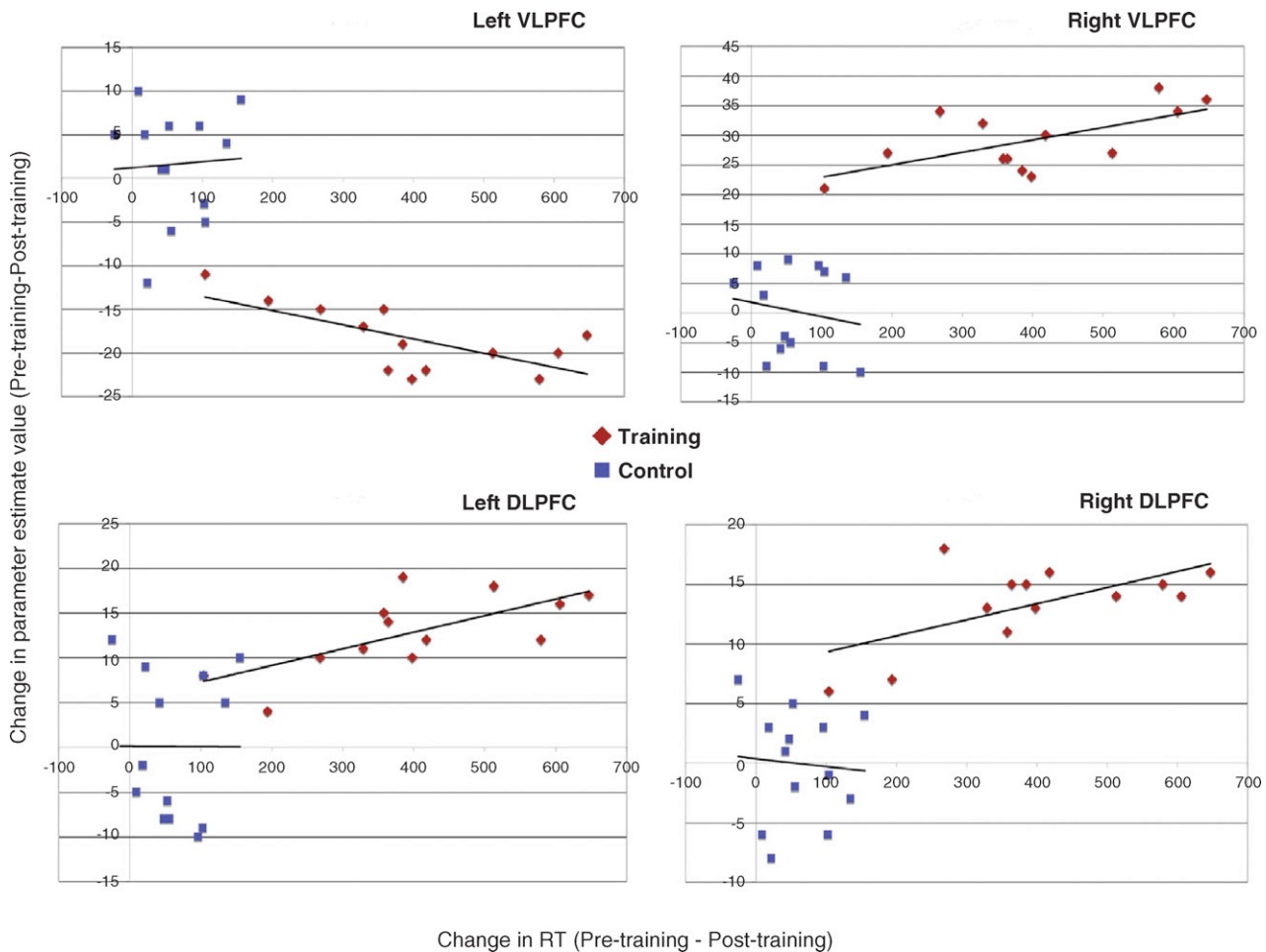


Fig. 3. Depicted are scatterplots and trendlines from the correlations between the change in response time from pre-training to post-training and the change in activation from pre-training to post-training for the older adult participants. The old training group is represented by red diamonds and the old control group is represented by blue squares. We found significant correlations for the old training group for the left VLPFC (-0.68), right VLPFC (0.62), left DLPFC (0.69), and right DLPFC (0.62). It is important to note that the positive correlations actually represent decreases in activation from pre-training to post-training (because of the difference measures) and negative correlations represent increases in activation from pre-training to post-training. It is also notable that the control group participants failed to show any correlation between behavior and activation.

this region and the young adults showed an increase, age differences were reliably reduced with training. Although speculative, the convergence in the activation for older and younger adults after training suggests that older adults may learn to more effectively use this region in cognitive control and task coordination; whereas younger adults may learn to more extensively apply this region to dual-task demands and reduce the burden on other regions.

Importantly, we found that the changes occurring in VLPFC and DLPFC regions were correlated with improved performance on the task and were therefore not an irrelevant derivative of training (see Fig. 3). Furthermore, these effects and correlations were specific to the DM condition, which happens to be (a) the condition shown to be most amenable to training [29], (b) the condition requiring executive functioning processes such as managing and coordinating multiple concurrent tasks, and (c) the condition that shows the largest age-related performance differences prior to training. Therefore, we can conclude that similar to training effects in young adults [18], older adults show the largest changes in activation on the more challenging condition and the condition most amenable to a cognitive training intervention, that is the dual-task condition.

In sum, we find that the functioning of the brain retains some degree of plasticity well into older adulthood. Furthermore, we find that improvement in task performance results in an increased asymmetry in VLPFC regions and a reduction in age differences in activation in both VLPFC and DLPFC regions. Our results conflict with current views of compensation-related bilateral activation [8] and express important limitations in the compensation model. In addition, our results suggest that the training-induced patterns of age-related activation cannot be explained according to simple monotonic increases or decreases in activation and that training studies must account for the task being studied, the region being examined, and the ages of the participants.

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