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Neural correlates of training-related working-memory gains in old age

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ABSTRACT

Working memory (WM) functioning declines in old age. Due to its impact on many higher-order cognitive functions, investigating whether training can modify WM performance has recently been of great interest. We examined the relationship between behavioral performance and neural activity following five weeks of intensive WM training in 23 healthy older adults ($M = 63.7$ years). 12 participants received adaptive training (i.e. individually adjusted task difficulty to bring individuals to their performance maximum), whereas the others served as active controls (i.e. fixed low-level practice). Brain activity was measured before and after training, using fMRI, while subjects performed a WM task under two difficulty conditions. Although there were no training-related changes in WM during scanning, neocortical brain activity decreased post training and these decreases were larger in the adaptive training group than in the controls under high WM load. This pattern suggests intervention-related increases in neural efficiency. Further, there were disproportionate gains in the adaptive training group in trained as well as in non-trained (i.e. attention, episodic memory) tasks assessed outside the scanner, indicating the efficacy of the training regimen. Critically, the degree of training-related changes in brain activity (i.e. neocortical decreases and subcortical increases) was related to the maximum gain score achieved during the intervention period. This relationship suggests that the decreased activity, but also specific activity increases, observed were functionally relevant.

Working memory (WM) involves maintaining and manipulating information without the presence of external cues (Baddeley, 2003). WM is critical to several higher-order cognitive abilities, such as fluid intelligence, planning, problem solving, reasoning, and language comprehension (Baddeley, 1992; Engle et al., 1999). Neuronally, WM functioning is dependent on activity in a widespread network, including fronto-striatal, premotor, parietal, and temporal brain regions (D'Esposito et al., 1999; Linden, 2007; Reuter-Lorenz and Sylvester, 2005; Smith and Jonides, 1997; Wager and Smith, 2003; D'Esposito et al., 1999; Linden, 2007; Smith and Jonides, 1997; Wager and Smith, 2003).

WM performance, particularly visuospatial WM, declines markedly in old age (Jenkins et al., 2000; Park et al., 2002). This age-related deficit is accompanied by anatomical and neuromodulatory changes, as well as alterations in functional brain activity patterns (Bäckman et al., 2010; Bäckman et al., 2006; Erixon-Lindroth et al., 2005; Nagel et al., 2009, 2010; Rajah and D'Esposito, 2005; Raz, 2005; Reuter-Lorenz, 2000; Reuter-Lorenz and Sylvester, 2005).

In recent years, there has been increasing interest in the extent to which WM performance may be enhanced through systematic training. This research demonstrates training-related WM gains in children and younger adults, as well as in persons with acquired brain injuries (Holmes et al., 2009; Jaeggi et al., 2008; Jolles et al., 2010; Klingberg, 2010; Klingberg et al., 2002; Olesen et al., 2004; Thorell et al., 2009; Westerberg et al., 2007). Potential intervention-related benefits in WM and executive functions among older adults have also been examined (Bherer et al., 2006; Dahlin et al., 2008a, 2008b; Erickson et al., 2007; Karbach and Kray, 2009; Li et al., 2008; Mozolic et al., 2009). In general, these studies demonstrate performance improvements in the trained tasks. However, transfer of training gains is typically limited to non-trained tasks from the same domain and not generalizable to tasks tapping non-trained abilities (Buschkuehl et al., 2008; Dahlin et al., 2008a, 2008b; Li et al., 2008, but see Karbach and Kray, 2009; Mahncke et al., 2006; Mozolic et al., 2009). In addition, in these studies a group receiving WM training was compared to a no-contact control group or to a group participating in activities not directly related to WM (e.g., watching movies, walking, listen to educational lectures; e.g., Buschkuehl et al., 2008; Mahncke et al., 2006; Mozolic et al., 2009). This fact makes it difficult to disentangle the effects of the training itself from those that may result from other factors (e.g., motivation, test familiarity, performance anxiety, stimulus–response mappings).

With regard to neural correlates of training-related WM gains, an important point concerns whether the intervention results in increases or decreases of brain activity. Whereas increases are thought to reflect individuals' latent potential by recruiting additional brain regions (i.e., additional cortical units or increasing the level of activity within a

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specific region), decreases in brain activity are often discussed in terms of processing being more efficient (Kelly and Garavan, 2005; Lustig et al., 2009; Mattay et al., 2006; Poldrack, 2000). In intervention research on higher-order cognitive functions such as WM, practice has been associated with both decreases (Beauchamp et al., 2003; Dahlin et al., 2008a, 2008b; Garavan et al., 2000; Jansma et al., 2001; Landau et al., 2007; Sayala et al., 2006) and increases (Hempel et al., 2004; Moore et al., 2006; Olesen et al., 2004; Wexler et al., 2000) of brain activity (for review, see Klingberg, 2010) in task-relevant brain regions. The relation between these activation changes and performance is still an open issue.

In this study, a group of healthy older adults received five weeks of adaptive WM training, following the procedure devised by Klingberg et al. (2002). To our knowledge, our study is the first in the aging domain that included an active control group where subjects worked on the same material as the experimental group, the only difference being that task difficulty was fixed at a low level during practice. Thus, the study design allows for determining training-specific performance gains, accounting for influences of other performance-relevant factors (e.g., test familiarity, performance anxiety). An off-line cognitive battery tapping various non-trained abilities (e.g., interference, episodic memory, reasoning) was administered before and after the WM training to investigate potential transfer effects. A key objective was to investigate whether adaptive WM training leads to increases or decreases of brain activity in task-relevant regions among older adults, and if potential BOLD activation changes are related to the degree of training-related performance improvement. Therefore, fMRI was assessed before and after training while participants performed a visuospatial WM task.

Methods

Participants

24 older adults (aged 60–70 years, $M = 63.6$, 12 female) were recruited through a newspaper advertisement. Individuals were screened for claustrophobia, left-handedness, color-blindness, metal implants, previous head surgery, psychiatric and neurological diseases, and were excluded based on all these criteria. The study was approved by the local ethics committee at the Karolinska Hospital, Stockholm, Sweden. Individuals gave written informed consent to participate in the study and were paid SEK 5000 (approximately 600 USD) for participation. After baseline fMRI assessment, individuals were randomly assigned to either an adaptive training group or an active control group that received low-level practice on the same WM tasks. One older woman in the active control group left the study during training, due to health problems. Hence, the effective sample consisted of 12 adults receiving adaptive training and 11 adults receiving low-level practice. The two intervention groups did not differ significantly in age, years of education, or gender distribution ($ps > .05$).

Design and procedure

All individuals participated in three consecutive parts of the study, including (1) cognitive testing and fMRI examination while performing a visuospatial WM task under two load conditions before training; (2) five weeks of intervention; and (3) cognitive testing and fMRI examination while performing the same WM tasks as in (1) after training (see Fig. 1).

Cognitive assessment at baseline and post training

Before and after the five weeks of intervention, all individuals were examined with a set of eight cognitive tests to assess training-related performance gains in *criterion* tasks very similar to those practiced for five weeks (i.e. Span Board forward, Digit Span backward; Wechsler, 1981), *near-transfer* tasks (i.e. Span Board backward, Digit Span forward; Wechsler, 1981), as well as *far-transfer* tasks tapping non-trained cognitive abilities (i.e. sustained attention (PASAT; Gronwall, 1977)), interference control (Stroop; Dodrill, 1978), episodic memory (RAVLT; Lezak, 1983), and non-verbal reasoning (RAVEN; Raven, 1990). For a more detailed description of the tasks, see Klingberg et al. (2002) and Westerberg et al. (2007).

Five weeks of cognitive intervention

Adaptive training

All participants completed 25 sessions of computerized WM training. In each session, they worked on four visuospatial and three verbal WM tasks (Table 1). In total, they trained for 90 WM trials per day and needed, on average, 25 min to complete a training session. They trained at home using their personal computers, which had to meet minimum requirements to ensure equivalence of presentation times (PC with a Pentium II processor, 266 Mhz (400 Mhz recommended), containing Windows ME, Windows 2000, or Windows XP software, internal memory of 64 MB (128 recommended) and 150 MB free space on the hard drive). Individuals were introduced to the training program beforehand and were instructed to find some quiet time of the day (e.g., not being disturbed by phone calls or visitors)

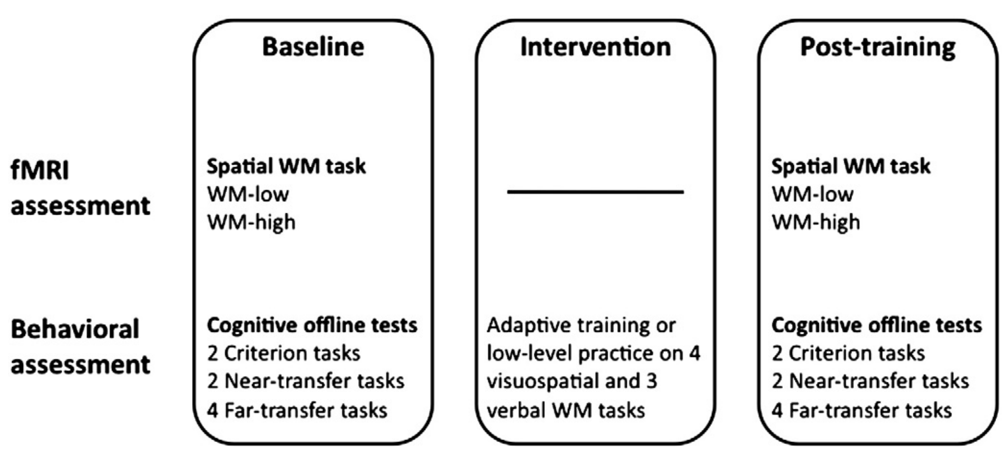


Fig. 1. Study design. For further information on (a) the spatial WM tasks performed during fMRI assessment, see Fig. 2; (b) the offline cognitive test battery, see Table 2; (c) the WM tasks used during training, see Table 1.

Table 1
Description of the seven WM tasks used during training.

Task	Description
Visuospatial	
Grid	A grid with four by four dots is shown and a sequence of dots lights up. Participants have to reproduce the sequence by clicking the dots in the same order as they lit up.
3D grid	A three-dimensional grid (projected in two dimensions) consisting of four sides and a bottom (viewed from above) is shown, each side consisting of four squares. A sequence of squares lights up. Participants have to reproduce the sequence by clicking the squares in the same order they lit up.
Rotating dots	Ten dots placed in a circle. As the circle rotates, a sequence of dots lights up. Participants have to reproduce the sequence by clicking the dots in the same order as they lit up.
Rotating grid	This task is identical to the above described Grid task with one exception: after the to-be-remembered sequence is shown, the grid is rotated 90°, and participants are to reproduce the sequence by clicking the dots, which will now be in a new position.
Verbal	
Numbers	A panel with the digits one through nine is shown. A sequence of numbers is presented auditory and light up on the panel simultaneously. Participants are to click the numbers on the panel in the reversed order of presentation.
Hidden numbers	This task is identical to the above described Numbers task with one exception: the digits are only presented auditory, and the digit panel appears only after the full sequence is presented. Participants are to click the numbers on the panel in the reversed order of presentation.
Letters	A circle of dots is shown. A sequence of letters is presented auditory and for each letter a dot in the circle lights up. The participants are then presented with one of the letters from the sequence and are to click the dot, which lit up when that letter was previously presented.

and create a relaxed environment for themselves before starting the program.

In the first session, individuals started each task at the same low difficulty level, namely remembering two items. As training proceeded, task difficulty was individually adjusted by increasing/decreasing the number of items individuals had to remember, such that they reached approximately 60% correct per day for each task (for details about the adaptive training algorithm, see Cogmed QM; www.cogmed.com; Klingberg et al., 2002). Each training session started at the task difficulty level where the participant ended in the previous session. Individuals could not train more than once a day and were instructed to train for five days a week. Their performance and reaction time data were continuously recorded while they were on task and these data were sent automatically to the test leader after each session. The test leader provided feedback on the training data once a week via e-mail and controlled the data for potential breaks, interruptions, and unusual performance fluctuations. No problems were observed for any of the participants.

Low-level practice

Individuals in the control group also completed 25 sessions of the same computerized WM training as the adaptive training group. The main differences between the two groups were that (a) task difficulty remained at the same low starting level, namely remembering 2 items for the control group, and (b) to adjust for time differences on task due to an increased number of items per task in the adaptive training group, the controls worked on 120 trials on each task and day. As with the adaptive training group, to confirm compliance, performance during training was continuously recorded and feedback was provided via e-mail once a week. For motivational reasons, individuals in the control group were told that they were to participate in speed training that may have a positive impact on cognitive functioning.

In-scanner tasks

In scanner, participants performed a spatial delayed-matching task modeled after Klingberg et al. (2002) under two load conditions (low vs. high). A blocked design was used, with semi-randomized order of WM-low, WM-high, and two appearance-adjusted control tasks (see Fig. 2).

WM tasks

On a display, either 4 (WM-low load) or 6 (WM-high load) red filled circles appeared sequentially in a 4×4 grid during an 11,650 ms time interval. After a 200 ms delay, each cue was presented for 900 ms followed by an ISI of 1100 ms (WM-low load) or 500 ms (WM-high load). Participants were asked to remember the locations in which the cues were presented. After another delay of 1400 ms (WM-low load) or 1000 ms (WM-high load), a response phase of 1750 ms followed. During this phase, an unfilled probe circle appeared on the 4×4 grid and participants had to indicate whether the probe was in the same location as any of the previously presented cues. Responses were made by pressing a button with the right index finger to indicate "yes" or the right middle finger to indicate "no". The next trial started after a 300 ms delay.

Control tasks

Participants saw 4 (CON-low) or 6 (CON-high) green filled circles that were always presented sequentially in a 4×4 grid. Thus, the color of the circles (i.e. red or green) indicated if the trial was a target trial or a control trial. In addition, the control trials were always presented in the corners of the grid. In the response phase, a green unfilled circle (probe) appeared in the middle of the grid and participants had to press any button when the probe appeared.

Stimuli were presented using E-prime (Psychology Software Tools), which also recorded behavioral performance. Stimuli were projected via a Philips LCD projector (Philips Corp, Netherlands) onto a mirror mounted on top of the head coil and in good view for the

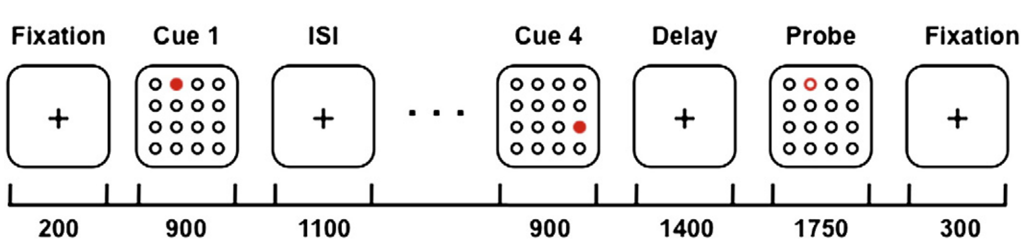


Fig. 2. Design of the WM-low task condition performed in scanner. Individuals were asked to remember the location of four cues in a 4×4 grid. After a delay, individuals had to indicate if a probe cue location was matched by one of the locations of the cues shown before. Numerical values below the line denote ms.

participants. Before entering the scanner, participants practiced the task between one and three times to be acquainted with the experimental situation.

During scanning, participants performed five 35-s blocks in each condition (WM-high, WM-low, CON-high, CON-low), alternated in counterbalanced order, and split across two runs of 5 min 50 s. Each block contained three trials, yielding a total of 15 trials per condition.

MRI protocol

Whole brain MRI data were collected with a 1.5 T system (Signa Excite HD Twinspeed, General Electrics Medical Systems, USA), using a standard circular one-channel head coil.

Functional scans

Blood-oxygen-level-dependent (BOLD) fMRI images were generated with a gradient-echo-planar-imaging (EPI) pulse sequence (TR/TE = 2500/40 ms, flip angle = 90°, matrix = 64 64, FOV = 22 cm 22 cm, 32 slices, slice thickness 4 mm, 0.5 mm interslice spacing), that yielded 3.44 3.44 4 mm^3 voxels. Slices were acquired interleaved, in axial orientation. Each of the two runs yielded a total of 140 volumes. Four dummy scans were performed prior to the image acquisition to eliminate signals arising from progressive saturation.

Structural scan

In the first MRI session a T1-weighted image (TR/TE = 24/6 ms, flip angle = 35°, FOV = 22 cm × 22 cm, slice thickness 1.5 mm) was acquired and used to co-register with the functional scans.

Data analyses

Cognitive off-line tasks

To examine potential baseline differences between the two experimental groups, one-way ANOVAs were conducted separately for the eight off-line cognitive tasks before training. In addition, potential group differences in intervention-related performance changes were investigated using mixed ANOVAs with group (adaptive training vs. active control) as a between-subjects factor and time (baseline vs. post training) as a within-subjects factor for the eight cognitive off-line tests separately.

Performance gains during training

All participants who received adaptive training completed 25 training sessions. Performance was operationalized as the task difficulty level individuals reached across the five weeks of training (i.e. number of items individuals were able to remember). Performance of the first two sessions was excluded from analysis due to lack of variability, as the starting point was identical for all individuals. For the remaining 23 sessions, mean daily performance was *t*-standardized ($M = 50$, $SD = 10$) across the 25 training sessions for all individuals, separately for each of the seven trained tasks. Individual composite scores for the visuospatial and verbal WM tasks were created. Due to the facts that these composite scores were highly correlated ($r = .74$, $p = .006$), and changed similarly across the five weeks of training, the two scores were aggregated into one WM performance score. Weekly scores were computed based on mean performance of three training sessions for week 1 and five training sessions for weeks 2 through 5, respectively. A repeated-measures ANOVA was conducted with time (weeks 1–5) as within-subjects factor to investigate the pattern of performance gains during training. This analysis was restricted to the adaptive training group, due to the fact that the performance level of the control group was held constant at a low-level across the five weeks of intervention, and hence, no performance changes could be observed for the controls.

Table 2
Offline cognitive assessment.

Cognitive tests	Adaptive training group		Active control group	
	Baseline	Post training	Baseline	Post training
Span Board Forward	5.29 (1.42)	5.79 (1.27)	5.36 (0.78)	5.32 (1.12)
Span Board Backward *	4.77 (0.63)	5.54 (0.86)	5.18 (0.87)	5.18 (0.64)
Digit Span Forward	6.67 (1.03)	7.21 (1.01)	6.32 (1.12)	6.36 (0.78)
Digit Span Backward	5.08 (1.43)	5.88 (1.88)	5.00 (1.38)	5.32 (1.31)
PASAT *	46.25 (7.07)	53.58 (6.65)	50.55 (7.54)	51.36 (5.68)
RAVEN	6.00 (3.69)	6.42 (3.55)	5.45 (2.70)	6.82 (3.46)
RAVLT *	11.75 (2.26)	12.75 (1.55)	12.00 (1.55)	11.91 (2.59)
Stroop	113.33 (24.20)	108.67 (18.55)	123.64 (34.96)	120.09 (23.77)

Note. Values indicate means (and standard deviations). PASAT = Paced Auditory Serial Addition Task, RAVEN = Raven's Progressive Matrices, RAVLT = Rey Auditory Verbal Learning Test. For tests marked with an *, a significant group × time interaction effect was observed, indicating that the adaptive training group improved more than the active control group. This effect was only marginally significant for the RAVLT.

In-scanner WM task

To examine potential performance differences between the two experimental groups at baseline, two-way ANOVAs were conducted with group (adaptive training vs. control) as a between-subjects factor and load (WM-low vs. WM-high) as a within-subjects factor. In addition, potential performance differences after training were investigated using mixed ANOVAs with as between-subjects factor, and load (WM-low vs. WM-high) and time (baseline vs. post training) as within-subjects factors, separately for accuracy and response latencies.

Functional brain activity

Functional images were analyzed with FEAT (FMRIBs Expert Analysis Tool Version 5.92), available as part of FSL (FMRIBs Software Library; Smith et al., 2004).

Before images were subjected to pre-processing, BET (Brain Extraction Tool; Smith, 2002) was used to strip away the skull and other non-brain parts of the images. Images were motion corrected using rigid body transformation as implemented in MCFLIRT (Motion Correction using FMRIBs Linear Image Registration Tool; Jenkinson et al., 2002), and smoothed using an isotrophic 8.0 mm FWHM Gaussian filter kernel to remove low-frequency noise.

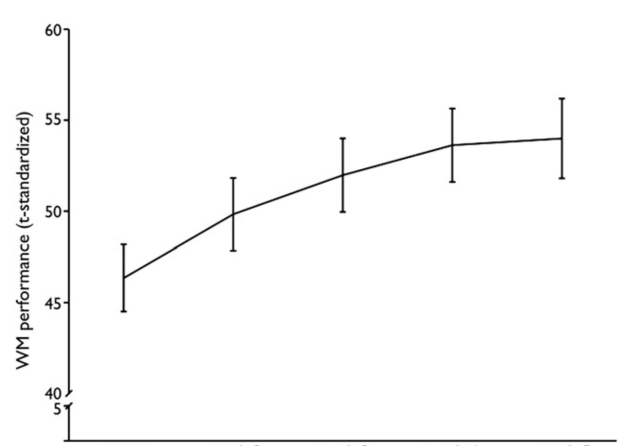


Fig. 3. Mean working-memory (WM) performance across 5 weeks of adaptive training. Error bars represent standard errors around the means.

Table 3
Behavioral in-scanner working-memory (WM) performance.

Group	WM-high		WM-low	
	Baseline	Post training	Baseline	Post training
Accuracy (max. = 15)				
Adaptive training	12.36 (2.01)	13.64 (1.43)	11.91 (1.58)	12.82 (2.79)
Active control	12.45 (1.51)	11.73 (3.82)	11.55 (2.07)	11.55 (3.67)
Reaction times				
Adaptive training	1118.05 (127.61)	1043.15 (156.75)	1081.30 (133.95)	1087.48 (139.02)
Active control	1097.63 (134.76)	1106.19 (179.97)	1120.50 (160.35)	1147.70 (190.55)

Note. Values indicate means (and standard deviations) for task accuracy (max. 15 trials) and reaction times (ms) for the two task difficulty levels. WM-low refers to memory for four different spatial locations and WM-high to six spatial locations.

Table 4
Activation changes in the working memory (WM)-low and WM-high conditions.

Brain area		# voxel	BA	x	y	z	Z max
WM-low: intervention-general activation decreases							
Inferior frontal	R	168	47	36	18	−18	3.22
Anterior cingulate	L/R	546	24	0	0	32	3.14
Lingual gyrus	R	210	18	8	−80	−2	3.47
WM-high: intervention-general activation decreases							
Anterior cingulate	L	86	24	−2	−4	38	2.92
Inferior parietal	R	245	40	62	−32	28	3.22
Hippocampus	L	299		−22	−6	−14	3.74
	R	140		24	−12	−20	3.31
WM-high: intervention-specific activation decreases							
Superior frontal	R	134	8	32	18	32	3.21
Superior temporal	R	101	22	44	−36	8	3.09
Lingual gyrus	L/R	2466	18	10	−74	0	3.92

Note. Coordinates x, y, z are reported in MNI space.

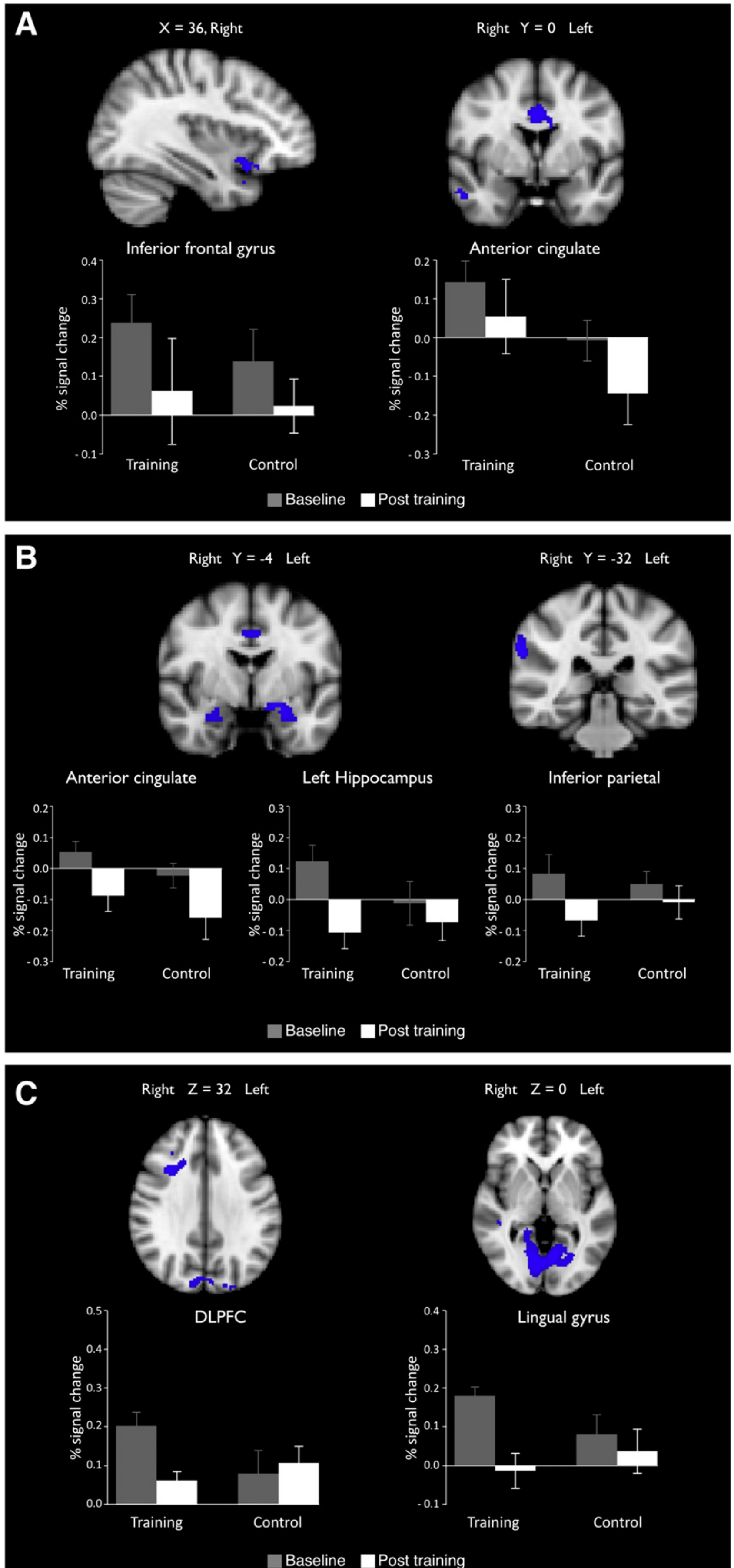
Statistical analysis was performed according to the general linear model. The first-level individual analysis modeled the four conditions (WM-low, WM-high, CON-low, CON-high) as explanatory variables, separately for each run and MRI session (baseline, post training). In a second set of individual analyses, the resulting contrasts of interest (WM-low–CON-low and WM-high–CON-high) from the first-level analysis were averaged across runs within each session using fixed effects. To estimate activation changes across time, these contrasts were then compared between baseline (T1) and post training (T2), again on an individual level and using fixed effects. The individual contrast images were then used for mixed-effect group analyses. FLIRT was used to register functional images to the respective high-resolution structural images and then to the MNI152 standard brain (2 mm resolution) for anatomical reference of the group results. First, we identified the WM network under two load conditions [WM-low − CON-low] and [WM-high − CON-high] in all 23 older adults at baseline, and examined whether there were any effects of the task load manipulation [(WM-high − CON-high) − (WM-low − CON-low)]. Based on an earlier study of Dahlin et al. (2008a, 2008b), intervention-related activation changes across time were analyzed for the adaptive training group for the two task load conditions separately [activation increases = (WM − CON post training) − (WM − CON at baseline); activation decreases = (WM − CON at baseline) − (WM − CON post training)]. Group was modeled as an explanatory variable and percent signal change from ROIs (3-mm spheres placed around the peak activation in MNI152 space) in regions showing pre-post changes for the adaptive training group were used for further analysis. Percent signal changes were calculated using the featquery tool provided by FSL.

Percent signal changes were analyzed in group (adaptive training vs. control) × time (baseline vs. post training) repeated measure ANOVAs. To qualify as a region showing an *intervention-general* effect, the activity level of the adaptive training and control groups had not to be significantly different in the baseline session, along with a main effect of time in the absence of a time × group interaction. To qualify as a region showing an *intervention-specific* effect, the activity level of the adaptive training and control groups had also not to be significantly different at baseline, along with a more pronounced change in activation level for the adaptive training group in the second session (i.e., a main effect of time and a group × time interaction).

To examine the potential relationship between behavioral performance gains and training-related changes in BOLD activity, follow-up analyses were conducted for the adaptive training group only. For this purpose, individuals' maximum gain score during the five weeks of WM training was calculated by subtracting baseline performance (mean of the first two sessions) from the maximum score that individuals reached during training. These individual maximum gain scores were calculated separately for each of the trained tasks, *t*-standardized, and averaged to form a composite gain score (for details of the trained tasks, see Table 1). These composite scores were included as regressors in the intervention-related activation change analyses separately for the two load conditions [activation increases = (WM − CON post training) − (WM − CON at baseline); activation decreases = (WM − CON at baseline) − (WM − CON post training)]. Due to positive correlations ($r = .62$, $p = .03$) between baseline performance and maximum gain scores (individuals with higher baseline performance improved more from training than individuals with lower baseline performance), baseline performance was included as a second regressor in the analysis and individual maximum gain scores were orthogonalized with respect to baseline performance. This allows for identifying those voxels at which the signal contains variance elicited by the individual maximum training gain after controlling for variance related to baseline performance.

To illustrate BOLD-behavior relations, ROI analyses were conducted. ROIs were created in MNI152 space as a 3 mm sphere around the respective group's peak activations. Percent signal changes for WM-CON at baseline and post training were extracted for each individual and load condition separately. The difference in signal change between baseline and post training was plotted against individual maximum training gain scores and linear trends were fitted. This follow-up analysis was by necessity restricted to the adaptive training group due to the fixed performance level of the active control group across the five weeks of intervention.

Fig. 4. A. Select regions showing *intervention-general* activation decreases (comparable decreases for both experimental groups) in the WM-low condition from baseline to post-training assessment. B. Select regions showing *intervention-general* activation decreases in the WM-high condition from baseline to post-training assessment. C. Select regions showing *intervention-specific* activation decreases (more decreases in the adaptive training group than in the cognitive control group) in the WM-high condition from baseline to post-training assessment. The intervention-general and intervention-specific effects refer to regions showing no baseline differences between the two experimental groups. Anatomical reference is MNI152 space and images are displayed in radiological orientation.


A
X = 36, Right
Right Y = 0 Left
Inferior frontal gyrus
Anterior cingulate
% signal change
Training
Control
Baseline
Post training
B
Right Y = -4 Left
Right Y = -32 Left
Anterior cingulate
Left Hippocampus
Inferior parietal
% signal change
Training
Control
Baseline
Post training
C
Right Z = 32 Left
Right Z = 0 Left
DLPFC
Lingual gyrus
% signal change
Training
Control
Baseline
Post training

All contrasts were thresholded at $Z>2.33$ (equivalent to an uncorrected probability threshold of $p<.01$). Only clusters with a minimum number of 50 contiguous voxels were reported.

Results

Behavioral data

Cognitive off-line performance

The two experimental groups did not differ on any of the cognitive tests at baseline ($ps>.17$; see Table 2). Regarding intervention-related changes, main effects of time were observed for the following tests: Span Board Backward ($F(1, 21)=4.62$, $p=.04$, $\eta_p^2=.18$), Digit Span Backward ($F(1, 21)=4.66$, $p=.04$, $\eta_p^2=.18$), PASAT ($F(1, 21)=9.12$, $p=.01$, $\eta_p^2=.30$), and RAVLT ($F(1, 21)=8.12$, $p=.02$, $\eta_p^2=.24$). In addition, group × time interaction effects were found for Span Board Backward ($F(1, 21)=4.62$, $p=.04$, $\eta_p^2=.18$), PASAT ($F(1, 21)=5.83$, $p=.02$, $\eta_p^2=.22$) and at trend level for RAVLT ($F(1,21)=4.14$, $p=.06$, $\eta_p^2=.17$). The interaction effects reflected the fact that the adaptive training group showed reliable gains in these trained and non-trained tasks ($ps<.05$), whereas the controls did not ($ps>.10$). Although the interaction effect did not approach conventional significance for Digit Span Backward ($p>.05$), the controls did not show an improvement across time for this task either ($p>.30$). No other effects reached significance ($ps>.19$).

Performance gains during training

Whereas the performance of the control group was held constant across the five weeks of intervention (i.e., no performance-changes could be investigated), the adaptive training group improved their performance across training, $F(1, 11)=50.67$, $p<.01$, $\eta_p^2=.82$. Follow-up analyses showed that performance increased continuously from week 1 through week 4 ($ps<.01$), and remained stable from week 4 to week 5 ($F<1$; see Fig. 3).

WM performance in-scanner

During scanning, the two experimental groups did not differ in accuracy or response times in the WM tasks (WM-low, WM-high) at baseline ($Fs<1$, see Table 3). No intervention-related behavioral changes were observed for the two experimental groups, neither for accuracy nor reaction times ($Fs<1$). In general, individuals remembered more items in the WM-low load condition than in the WM-high load condition, as indicated by a significant main effect for task load, $F(1, 20)=7.58$, $p=.01$, $\eta_p^2=.28$. None of the other effects reached significance ($ps>.16$).

Imaging data

Baseline activation

The comparison of the WM and control conditions across the two experimental groups revealed activation in a widespread frontal-parietal-occipital WM network, as has been routinely observed among older adults during WM performance (e.g., Emery et al., 2008; Grady et al., 1998; Nagel et al., 2009, 2010; Reuter-Lorenz, 2000). Although individuals remembered more items in the WM-low load condition than in the WM-high load condition, there were no baseline differences between load conditions in activation patterns [(WM-high − CON-high) − (WM-low − CON-low)].

Intervention-related activation changes

In general, we observed only reductions in brain activity after the five weeks of intervention. No brain activation increases were observed. The intervention-related results are separated into (a) *intervention-general* activation changes, indicating comparable changes from baseline to post training for both groups in regions without baseline activation differences, and (b) *intervention-specific* activation changes, where the adaptive training group changed more than the controls, again based on comparable baseline activation patterns. The analyses were done separately for the two task load conditions.

WM-low load condition. Intervention-general activation changes for the two groups revealed deactivation in frontal (i.e., inferior frontal gyrus, anterior cingulate) and occipital (i.e., lingual gyrus) regions (Table 4 and Fig. 4A). No *intervention-specific* activation changes were observed in the WM-low load condition.

WM-high load condition. Intervention-general activation changes for the two experimental groups were observed as activity decreases in frontal (i.e., anterior cingulate), parietal (i.e., inferior) and limbic (i.e., hippocampus) regions (Table 4 and Fig. 4B). In addition, *intervention-specific* effects were observed, such that the adaptive training group showed larger activity decreases in frontal cortex (i.e., dorsolateral prefrontal cortex (DLPFC)), temporal (i.e., superior), and occipital (i.e., lingual gyrus) regions compared to the control group (Table 4 and Fig. 4C).

Due to higher baseline activation in the adaptive training group than in the active controls in some neocortical regions, we refrain from interpreting larger decreases in activity in the adaptive group for these regions.

Brain-behavior relations

Follow-up analysis, including the maximum gain score reached during the adaptive training period as a covariate, revealed performance-related activity decreases in a widespread network of frontal, parietal, temporal, subcortical, and occipital regions in the WM-low load condition (see Table 5 for full information and Fig. 5A for selected regions). Performance-related activity decreases for the WM-high load condition were more focused including right inferior frontal and right inferior parietal cortex, left fusiform gyrus as well as insula (see

Table 5
Performance-related activation changes from baseline to post training separately for the working memory (WM)-low and WM-high conditions.

Brain area		# voxel	BA	x	y	z	Z max
WM-low: performance-related activation decreases							
Superior frontal	L	97	11	−28	36	−10	3.18
	R	84	10	16	72	8	2.93
Middle frontal	R	60	46	50	36	16	2.88
Inferior parietal	R	294	40	66	−32	30	3.21
Superior parietal	L	129	39	−30	−64	34	3.02
Superior temporal	L	62	38	−40	6	−18	3.00
Hippocampus	R	579		30	−14	−22	3.29
	L	340		−18	−20	−14	3.16
Lingual gyrus	L	960	18	−26	−100	−2	3.97
	L	371	18	−6	−74	−6	3.06
	L	133	18	0	−92	0	2.93
Cuneus	R	223	18	28	−72	20	2.87
Inferior occipital	R	166	19	32	−86	−10	2.81
Cerebellum		156		−2	−80	−34	2.89
WM-low: performance-related activation increases							
Thalamus	L	216		−10	−24	18	3.05
	R	70		12	−18	14	2.83
Middle frontal	L	64	8	−40	16	48	2.73
Cerebellum		56		−12	−46	−34	2.67
WM-high: performance-related activation decreases							
Inferior frontal	R	121	45	54	18	20	2.94
Inferior parietal	R	95	40	30	−50	28	2.97
Occipital	L	84	18	−28	−96	−12	2.89
Insula	R	69	48	36	−10	−4	2.82
Brainstem	R	66		0	−14	−16	2.97
WM-high: performance-related activation increases							
Caudate	L		55	16	−16	20	2.58
Caudate	R		47	−14	−20	22	2.62

Note. Coordinates x, y, z are reported in MNI space. Activation changes were based on maximum performance gain across the five weeks of training. Performance-related BOLD changes were controlled for individual differences in baseline activation.

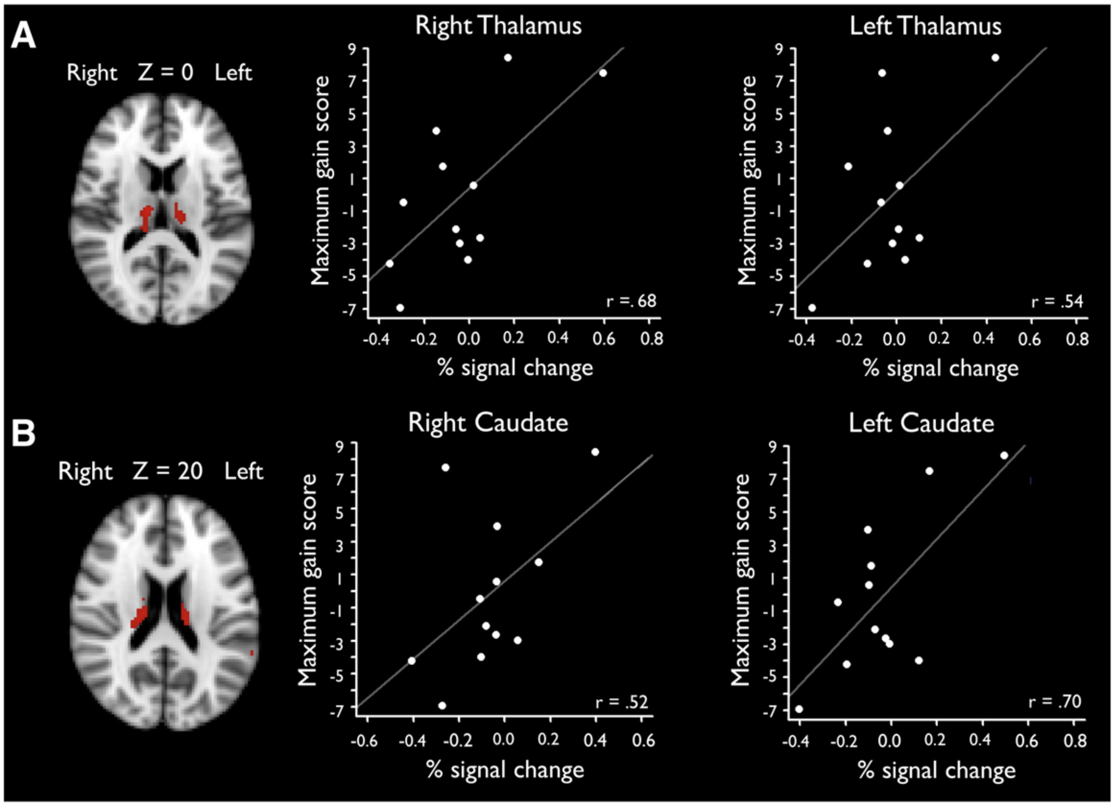


Fig. 5. A. Performance-related activation increases from baseline to post training in the WM-low condition. B. Performance-related activation increases from baseline to post training in the WM-high condition. Select regions are plotted where the degree of improvement during the five weeks of adaptive training is correlated with BOLD signal increase from baseline to post training. Scatter plots depict individuals' maximum gain scores (demeaned and orthogonalized to baseline performance) during the five weeks of WM training and mean percent signal change for each subject from a 3 mm spheric ROI around the peak voxel of regions showing activation decreases from baseline to post training. For a complete list of performance-related activation decreases, see Table 5. Anatomical reference is MNI152 space and images are displayed in radiological orientation.

Table 5 for full information and Fig. 5B for selected regions). Interestingly, in addition to activity decreases, activity increases were observed bilaterally in thalamus as well as a left middle frontal region in the WM-low condition and bilaterally for the caudate in the WM-high condition. These results indicate that individuals who gained the most from training showed the largest activity decreases in various memory- and attention-related regions, but also subcortical activity increases.

In addition to brain regions showing a change from baseline to post-training assessment, we also examined brain-behavior relations in regions showing stable activation before and after training. We created a mask including all voxels that were activated above threshold at baseline as well at post-training assessment separately for both conditions (i.e., WM-high>CON-high and WM-low>CON-low) in the adaptive training group. We then re-analyzed the performance-related activation-change analysis restricted to these regions to investigate if individual differences in performance gains were related to any of the regions being active both before and after the intervention. Activation increases as well as activation decreases were investigated here. After excluding those regions showing a change from baseline to post-training assessment, no region showed functionally relevant relations to performance.

Limitations in BOLD activity change analysis

The present study did not include an implicit baseline condition, but all recorded activations refer to any of the four explicitly modeled regressors (WM-high, WM-low, CON-high, CON-low). Hence, it was not possible to investigate the individual effects of any of the four regressors separately, without running into the problem of rang deficiency. Although more detailed analysis of the activation changes would be of interest, it should be noted that the control conditions were extremely simple and only included to control for differences in visual complexity of the stimulus material between the WM task-load conditions. Collectively, the low demands in the control conditions along with the strong behavioral training gains, the intervention-specific activation decreases, and the performance-related activation changes suggest that the training-related BOLD activations were driven by activation changes in the WM conditions rather than by changes in the control conditions.

Discussion

Behavioral and neural effects of five weeks of WM training in older adults were examined. An adaptive training group was compared to an active control group receiving low-level practice on the same WM tasks. Before and after training, individuals were examined on an offline cognitive test-battery as well as performed a WM task (under two load conditions) while being scanned. The performance level for the in-scanner WM task was high at baseline and indistinguishable in the two experimental groups (WM-low: 83% correct; WM-high: 78% correct). In addition, no significant training-related performance changes were observed for the two experimental groups during the fMRI assessment. This behavioral null effect is in line with earlier studies (e.g., Hempel et al., 2004; Olesen et al., 2004; Sayala et al., 2006), and has the advantage that differences in performance level can be excluded as a confound of possible training-induced BOLD changes (Klingberg, 2010; Poldrack, 2000).

Importantly, however, the five weeks of WM training affected performance assessed outside the scanner (i.e. gains across the five-week training period and performance in the offline cognitive battery assessed before and after training). Regarding the training gains across the intervention period, individuals improved their performance quite substantially (see Fig. 3). With respect to the effects in the offline cognitive battery, the nature of our control group should first be highlighted. To our knowledge, this is the first study in the aging domain using an active control group where individuals worked on the same task material as the experimental group, the only difference being that task difficulty was fixed at a low level. Using an active control group (as opposed to no-contact controls) provides a conservative assessment of training effects, because the influence of various unspecific factors (e.g., stimulus–response mappings, motivation, test familiarity, performance anxiety) is attenuated (Shipstead et al., 2010; Zehnder et al., 2009).

The off-line data showed selective gains for the adaptive training group in the Span Board Backward and Digit Span Backward tests, as well as for transfer tests assessing non-trained abilities (i.e. sustained attention, EM). Even though we used a conservative assessment of the effects of our training program by comparing performance gains of an adaptive training group to an active control group, we observed similar, albeit limited, transfer effects to other non-trained WM tasks and to a test of sustained attention as previous studies (e.g., Mahncke et al., 2006; Mozolic et al., 2009). In addition, the transfer effect to the EM test is particularly interesting. WM capacity has emerged as a strong predictor of EM performance in behavioral studies (e.g., McCabe et al., 2010; Park et al., 1996, 2002). In addition, BOLD patterns partly overlap during WM and EM performance (Braver et al., 2001; Cabeza et al., 2002; Marklund et al., 2007; Nyberg et al., 2002, 2003a, 2003b) and activation in overlapping brain regions between tasks has been found to foster transfer effects (Dahlin et al., 2008a, 2008b). However, behaviorally, transfer effects from WM training to EM have been difficult to demonstrate (Buschkuehl et al., 2008; Dahlin et al., 2008a, 2008b; Mozolic et al., 2010; Westerberg et al., 2007). The reason for the positive effect of WM training on EM found in this study remains unclear, because of lack of an in-scanner EM transfer task and further studies are needed to confirm this result.

In general, the pattern of cognitive data indicates that adaptive training confers a benefit over an active control group in terms of gains in both criterion and transfer tasks. Thus, the offline cognitive tests assessed before and after training were more sensitive to gains from the five weeks of training than the WM task performed inside the scanner. A likely reason thereof is that the in-scanner task was relatively simple requiring mostly maintenance of information, whereas the WM tasks assessed offline were more similar to the training program involving the manipulation and processing of information in addition to pure maintenance.

Regarding training-related neural effects, the main finding was that adaptive training as well as low-level practice resulted in reduced brain activity in various neocortical regions (i.e., frontal, parietal, temporal and occipital). In the WM-low load condition, similar activity decreases were observed after adaptive training and low-level practice (*intervention-general* effects) in frontal and occipital regions. Relatedly, in the WM-high load condition, both groups showed BOLD decreases in frontal and parietal regions as well as in hippocampus. In both load conditions, intervention-general decreases in anterior cingulate cortex were observed, suggesting that less attention and effort were required to perform the in-scanner task after training in both groups (e.g., Kelly and Garavan, 2005; Mattay et al., 2006; Poldrack, 2000). In addition, adaptive training led to selective BOLD decreases in frontal, temporal and occipital regions (*intervention-specific* effects) compared to low-level practice. Thus, in general, the imaging data paralleled the behavioral data, indicating intervention-related effects in both groups, although these effects were more pronounced among those receiving adaptive training.

Note that greater activation decreases for the adaptive training group compared to the controls were only observed for the WM-high load condition, indicating that the benefits of adaptive WM training unfold only under more challenging conditions. Note also that our finding that cognitive training is associated with reduced BOLD activity in neocortical areas is in line with several previous studies (e.g., Dahlin et al., 2008a, 2008b; Garavan et al., 2000; Hempel et al., 2004; Landau et al., 2007).

Of critical importance, the BOLD changes associated with the maximum gain score that reached during training involved not only mostly decreases but also increases: individuals who gained the most from training were those showing the largest BOLD decreases in a large memory-attention network. Although the performance-related network showing decreases in the WM-low condition was relatively widespread, including various frontal, parietal, temporal, and occipital regions as well as hippocampus, the performance-related regions showing activation decreases in the WM-high condition were confined to inferior frontal, inferior parietal and occipital regions as well as insula. In addition, to these activation decreases, performance-related BOLD increases were observed in thalamus and a middle frontal region (WM-low) and caudate (WM-high). The thalamus activations are interesting in light of functional (Callicott et al., 1999; Nyberg et al., 2009) and molecular (Christian et al., 2006) imaging findings implicating this structure in WM.

To our knowledge, this is the first time in aging research that BOLD activation changes have been linked to training-related performance gains (for relationships between training-related performance increases and resting state blood flow, see Mozolic et al., 2010). The patterns obtained indicate that not only the cortical activity decreases, but also the primarily subcortical increases, observed in the present study post training were functionally relevant.

The fact that BOLD activity decreased across training, although there were no in-scanner performance effects, is consistent with an efficiency interpretation, whereby less neural energy needs to be invested to attain the same performance level after training (Kelly and Garavan, 2005; Mattay et al., 2006; Poldrack, 2000). In addition, individuals with the largest training gains also showed the greatest subcortical increases (thalamus and caudate) in BOLD signal as function of training.

Of particular importance is that the magnitude of gains (i.e., maximum gain scores) was related to the degree of training-related BOLD increases during the high-load condition in caudate. First, previous WM training research with younger adults has revealed striatal BOLD increases post training (Dahlin et al., 2008a, 2008b; Olesen et al., 2004). Of further note is that a decrease of neocortical activity along with an increase of striatal activity has also been observed in the context of motor training (Colcombe et al., 2004; Nyberg et al., 2006; Seidler et al., 2002). The pattern of performance-related decreased and increased activity after training observed in this study may reflect the fact that the task becomes less executively demanding and more proceduralized as training proceeds. In addition, neurocomputational models assume that striatal neurons have a key gating function in letting new information enter working memory (O'Reilly, 2006) — a function that indeed would seem to be of critical importance to the current WM tasks.

The difference in activation changes in the group comparison and the performance-related change analyses likely reflects multiple factors. In the former, the activation changes of the adaptive training group were compared to activation changes in the control group (controlling for retest effects, additional performance influencing factors such as motivation, test familiarity, performance anxiety, stimulus–response mappings, as well as for baseline differences between the groups). Hence, this analysis was more restricted than the performance-related change analysis, where only the adaptive training group was investigated, due to the fact that the control group worked at a fixed low difficultly level with no performance gains. It is arguable that performance-related changes are more meaningful than changes obtained in the group comparison, because the former types of changes are directly linked to the degree of training-related improvement. However, in future research, a direct comparison between training and control groups on performance-related changes is warranted, investigating functionally meaningful activation changes and at the same time controlling for additional performance-influencing factors. This may be accomplished by allowing some performance variation also in the controls either by using a more difficult in-scanner task, so that performance changes from baseline to post-training assessment can be included as regressor in the BOLD-change analysis or by using a less stringent training regime for the controls, which does not restrict the performance level to a fixed low level.

This study could not address whether the observed activation changes might partly reflect task-related deactivations rather than training-related decreases in activity. Future studies should investigate this aspect further, especially in relation to current ideas on task-specific WM activations versus default-mode-network deactivations (Hampson et al., 2010; Sambataro et al., 2010). That said, the performance-related subcortical BOLD increases can be interpreted regardless of the "absolute" baseline and are in line with previous research (Dahlin et al., 2008a, 2008b; Olesen et al., 2004).

In addition, an important avenue for future research would be to distinguish training-related effects on WM encoding and retrieval from WM maintenance more clearly. The design of the current study did not allow for distinguishing between these WM processes.

In sum, older adults improved their WM performance through training and there was transfer of gains to non-trained WM tasks tapping sustained attention and episodic memory. Adaptive training as well as low-level practice resulted in BOLD decreases in frontal, parietal, and temporal regions. In addition, the higher neural efficiency of the adaptive training group was most apparent under high-task difficulty conditions (i.e. greater frontal, temporal, and occipital activity decreases). Neocortical activity decreases as well as subcortical increases were related to the size of training gains after adaptive training, which underscores their functional relevance. Two features of this research that deserve special mention are the nature of the age-matched active control group and the observed link between training-related changes in brain and behavior.

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