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Practice effects in the brain: Changes in cerebral activation after working memory practice depend on task demands

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ABSTRACT

Several studies have examined the neural effects of working memory practice, but due to different task demands, diverse patterns of neural changes have been reported. In the present study, we examined neural effects of practice using a task with different working memory demands within a single practice paradigm. Fifteen adults practiced during 6 weeks with a task that required maintenance and manipulation of information under low and high working memory loads. Functional magnetic resonance imaging (FMRI) data were acquired in the first week and last week of the practice period. Results were compared with results of a control group who did not practice the task. We demonstrated that practice was beneficial for both working memory maintenance and manipulation processes but that these processes were supported by different neural changes. While maintenance trials showed increased activation (i.e., less deactivation) in default-mode regions after practice, manipulation trials experienced increased activation in the striatum. Changes were also observed in left ventrolateral prefrontal cortex (VLPFC), bilateral dorsolateral prefrontal cortex (DLPFC) and left superior parietal cortex (SPC). However, for bilateral DLPFC and left SPC, these changes were not specific to the practice group. These findings illustrate the importance of controlling for test–retest effects in training or intervention studies. Behavioral follow-up tests demonstrated that practice effects lasted over a 6-month period, but the absence of transfer effects indicated that the acquired skills were specific for the practiced working memory task.

Introduction

Working memory, or the ability to temporarily store or manipulate information, is crucial for complex cognitive tasks such as reasoning, problem solving, and learning (Baddeley, 1992; Baddeley, 2003). Neuroimaging studies have repeatedly demonstrated that working memory demands are associated with increased activation of a frontoparietal network (Owen et al., 2005; Wager and Smith, 2003). However, it has been suggested that working memory is not a fixed trait with a stable pattern of neural activation (e.g., Olesen et al., 2004). Practice with a working memory task can improve performance and modify underlying patterns of neural activation. Yet, previous studies of working memory practice have reported inconsistent patterns of neural changes (Chein and Schneider, 2005). Whereas some studies have reported increased activation of the frontoparietal network, others have found decreased activation (Kelly et al., 2006; Dahlin et al., 2008a; Garavan et al., 2000; Hempel et al., 2004; Jansma et al., 2001; Kirschen et al., 2005; Landau et al., 2004; Olesen et al., 2004; Sayala et al., 2006). A better understanding of these neural effects of practice is warranted as the plasticity of brain function and performance lies at the foundation of understanding brain–behavior relations.

When people practice a task, their performance often improves, either because they become more efficient at applying their initial strategy or because they learn to employ a new strategy (Jonides, 2004). These types of learning most likely have different neural substrates. On the one hand, when individuals acquire a greater skill using their initial strategy, they will recruit a similar network of brain regions after practice, but they will show changing levels of activation *within* that network (Chein and Schneider, 2005; Kelly and Garavan, 2005). It has been suggested that the direction of these neural changes depends on the task domain (Kelly and Garavan, 2005). That is, practicing sensory or motor tasks is typically associated with increased activation in primary sensory or motor cortex (e.g., Grafton et al., 1992; Karni et al., 1995). In contrast, decreased activation is often reported after practice with complex

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cognitive functions such as working memory (Garavan et al., 2000; Jansma et al., 2001; Landau et al., 2004), visual attention (Tomasi et al., 2004), planning (Beauchamp et al., 2003), free recall (Andreasen et al., 1995a; Andreasen et al., 1995b), and interference control (Bush et al., 1998). The decrease of activation on complex cognitive tasks, associated with more effective implementation of strategies or automatic processing, is thought to be related to increased neural efficiency (e.g., Kelly and Garavan, 2005).

On the other hand, when individuals learn to employ a new strategy, they may show increased activation of the frontoparietal network (Bor and Owen, 2007b), associated with a redistribution or functional reorganization of brain activation (Kelly and Garavan, 2005; Petersen et al., 1998; Poldrack, 2000; Poldrack and Gabrieli, 2001). Interestingly, strategies that involve organization or “chunking” of information may result in increased frontoparietal activation, even when task demands decrease while using these strategies (Bor et al., 2003; Bor et al., 2004; Bor and Owen, 2007a; Wendelken et al., 2008). For example, Bor and Owen (2007b) pointed out that increased frontoparietal activation during a working memory task with extensively practiced visual objects (Moore et al., 2006) was possibly associated with chunking strategies. Thus, prior studies that showed increased frontoparietal activation after working memory practice (Hempel et al., 2004; Kirschen et al., 2005; Olesen et al., 2004) may have observed the development of new strategies such as organization or chunking of information.

Taking these findings together, it appears that prior studies of working memory training might have reported contradicting findings because they measured different effects of practice on a cognitive level. To better understand cognitive effects of practice, it is important to pay attention to specific task characteristics and training procedures that are used. For example, the nature of the task demands (e.g., maintenance or manipulation of information in working memory) may determine to which degree task procedures can be automated and whether or not strategies can be used. In addition, changes seem to depend on the time window of practice (Poldrack, 2000). Depending on the length of the practice period, cognitive changes vary from familiarity with the task to improvements of cognitive skills and even generalization to untrained tasks (e.g., Dahlin et al., 2008a; Garavan et al., 2000; Landau et al., 2004; Olesen et al., 2004).

The goal of this study was to compare different working memory demands within a single practice paradigm. In addition, we studied the effects of extended practice versus familiarity by using control participants who did not practice the task. We used a task which required both maintenance and manipulation of information (Crone et al., 2006; Smith and Jonides, 1999) under low and high working memory loads (Nyberg et al., 2009; Rypma et al., 1999). Healthy adults were trained extensively during a 6-week period and were being scanned in the first week (time point 1) and last week (time point 2) using functional magnetic resonance imaging (FMRI) while performing the working memory task. The control group only participated in the experimental sessions at time point 1 and time point 2. To test for transfer effects (i.e., improvement on untrained tests as a result of working memory practice), additional cognitive tasks were administered in a behavioral session during time point 2 (e.g., Dahlin et al., 2008a,b; Jaeggi et al., 2008; Olesen et al., 2004; Westerberg et al., 2007). The consistency of practice and transfer effects was further tested with a behavioral follow-up session 6 months after the experiment (time point 3). We conducted ROI analyses to examine practice-related changes in the frontoparietal network (i.e., in the ventrolateral prefrontal cortex (VLPFC), dorsolateral prefrontal cortex (DLPFC), and superior parietal cortex (SPC); Crone et al., 2006; D'Esposito et al., 1999; Smith and Jonides, 1999; Wager and Smith, 2003). In addition, we tested for practice effects in other regions, signaling a functional reorganization within the brain or changes in effort/task difficulty (Kelly and Garavan, 2005; Poldrack, 2000; Poldrack and Gabrieli, 2001).

Materials and methods

Participants

Twenty-nine healthy volunteers were assigned to two groups. The practice group consisted of fifteen participants (age 19.3–25.3, $M=22.0$ (SD = 1.85); 8 females) and the control group consisted of fourteen participants (age 19.8–24.7, $M=22.3$ (SD = 1.52); 8 females). Age and gender distributions did not differ between groups (age: $t(27)=.36$, $p=.72$; gender: $\chi^2(1, N=29)=0.42$, $p=.84$). The groups did not differ on an estimated intelligence score (practice group: 11.73 (SD = 1.39); control group: 10.96 (SD = 1.59); $t(27)=-1.40$; $p=.18$), which was measured by averaging scores on four subtests (Similarities, Block Design, Digit Span, and Letter–Number Sequencing) of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955; Wechsler, 1981; Wechsler, 2000). The participants were screened for MRI using a comprehensive medical questionnaire. They had normal or corrected-to-normal vision and they were right-handed according to self-report. The volunteers gave written informed consent for participation in the study, and they received a monetary incentive. The experiment was approved by the Medical Ethics Committee of the Leiden University Medical Center.

Practice procedure

Both the practice group and the control group participated in two test sessions, being referred to as time point 1 and time point 2, which were separated by a 6-week period. During these sessions, FMRI data were acquired while the participants performed a verbal working memory task.

During the 6 weeks in between time point 1 and time point 2, the practice group performed the working memory task on average 2.74 times a week. Once a week, the participants performed the task under the supervision of a trained experimenter (first author) in a controlled laboratory setting. The other practice sessions could be completed at home via the internet. The participants could flexibly choose when to practice the task, under the restriction that they had to perform the task on three separate days during a week. They were explicitly instructed to perform the practice sessions by themselves. On average, participants performed 10.5 practice sessions at home, with a minimum of 7 practice sessions. Performance during the unsupervised sessions was recorded and monitored. If participants did not practice for two or more days, they received an e-mail to encourage them to start a new practice session. On average, participants performed with an accuracy of 87.0% (SD = 16.4) during the unsupervised practice sessions, compared to 88.3% (SD = 14.7) during the supervised practice sessions, indicating that they were seriously involved in the practice sessions. Practice sessions lasted approximately 25 minutes each. The control group did not receive any instructions during the 6 weeks in between time point 1 and time point 2.

During time point 2, all participants performed the Digit Span task of the WAIS again to assess whether improvement of working memory performance transferred to an unpracticed working memory task. In addition, they performed a set of five transfer tasks that they had not seen before, consisting of a spatial variant of the working memory task that was practiced and four tasks of the executive functions test battery developed by Huizinga et al. (2006). The following executive function tasks were used: 1) the Mental Counters task to assess updating in working memory, 2) the Local–Global task to assess cognitive flexibility and inhibition, 3) the Wisconsin Card Sorting Task (WISC), and 4) the Tower of London (TOL) as complex executive function indices. The details about these transfer tasks are presented in the Supplementary material.

Six months after time point 2, there was a follow-up session in which the verbal working memory task and all transfer tasks were administered again (time point 3). One participant of the control group and one participant of the practice group did not participate in the session at time point 3. One additional participant of the control group only performed the verbal working memory task at time point 3.

Tasks and stimuli

Verbal working memory task: scanner version

The task involved a modified version of the working memory task that was previously used by Crone et al. (2006), with the addition of a parametric manipulation of working memory load which allowed for elaborative examination of practice effects. The task is referred to as "verbal working memory" because participants were explicitly instructed to use a verbal strategy. The visual stimuli consisted of two sets of 150 black and white pictures of simple objects taken from the Max Planck Institute's picture database (www.mpi.nl). The selection of stimuli used for time point 1 and for time point 2 was randomized across subjects.

Before each scanning session, participants were shown all objects that were used in the task and they were asked to name each object out loud. They were instructed that there was no right or wrong answer, but they should name the objects with one or two-syllable words. Thus, before scanning, participants were familiar with all objects in the scanning session.

Each trial started with a 250-ms fixation cross, followed by three, four, or five sequentially presented objects in the centre of the screen (i.e., the parametric manipulation of working memory load; presented in separate blocks). Each object was shown for 850 ms with a period of 250 ms in between. After the last object, the instruction "forward" or "backward" was presented for 500 ms. On forward trials, participants were instructed to remember the objects in the presented order during a 6000 ms delay, representing maintenance processes. On backward trials, participants were instructed to remember the objects in the reversed order, representing manipulation processes. They were explicitly instructed to name the objects (internally) during this delay period. Finally, one of the target objects was presented for 2850 ms with an instruction underneath to choose number 1, 2, 3, 4, or 5, representing the location of the target object in the forward or backward sequence. Here, participants had to indicate whether the object was presented first, second, third, fourth, or fifth in the forward or backward sequence. They could respond by pressing a button on a left/right response box with their left middle finger (number 1), left index finger (number 2), right index finger (number 3), right middle finger (number 4), or right ring finger (number 5). Interstimulus intervals in which a fixation cross was presented were jittered between trials based on an optimal sequencing program designed to maximize the efficiency of recovery of the blood oxygenation level-dependent (BOLD) response (Dale, 1999). There were six different versions of the task, in which the order of maintenance (forward) and manipulation (backward) trials was determined by the same program. In these six versions, sequences consisted of a different combination of objects.

The task consisted of three runs of 30 trials each, in which 15 forward and 15 backward items were intermixed. In one run, the trial sequences consisted of three objects to be memorized ('load 3'); in a second run, the trial sequences consisted of four objects ('load 4'); and in a third run, the trial sequences consisted of five objects ('load 5'). The order of runs was counterbalanced across participants, but it was the same for each participant at time point 1 and time point 2. Every object could appear only once during each run.

At time point 1, before the first scan, the participants were trained on the experimental task to make sure that they understood the task instructions. There were five prescan blocks which were presented in the following order: one block with four maintenance trials, one block with four manipulation trials, and then three blocks with eight trials in which maintenance and manipulation trials were mixed. In the mixed task blocks, the first block consisted of sequences of three objects, the second block consisted of sequences of four objects, and the third block consisted of sequences of five objects.

Verbal working memory task: practice version

The working memory task that was used for the practice sessions was the same as the task that was used during scanning except that there were no jittered periods of fixation in between the trials. To make sure that the participants were improving their task skill and not learning the stimuli or sequences of stimuli, we used two different sets of stimuli for the practice sessions, which were alternated every week (a description of the pictures is presented in the Supplementary material). To further reduce familiarization effects, the task was designed so that every sequence of objects was a unique combination of stimuli. Similar to the scanning session, participants were asked to name all objects before their first appearance in the task.

Each practice session consisted of three blocks of 30 trials each, in which 15 forward and 15 backward items were intermixed; one run with load 3 sequences, one run with load 4 sequences, and one run with load 5 sequences. The order of the blocks, the presentation of maintenance or manipulation trials within a block, and the selection of objects within a trial were randomly determined. Each object could appear only once during each block. Participants could respond by pressing one of five keys (X, C, B, N, or M) on the keyboard that corresponded to numbers 1, 2, 3, 4, and 5, respectively.

Image acquisition

Scanning was performed with a standard whole-head coil on a 3-T Philips Achieva MRI system (Best, The Netherlands) in the Leiden University Medical Center. A total of 222 (load 3), 241 (load 4), and 260 (load 5) T2*-weighted whole-brain EPIs were acquired, including two dummy scans preceding each scan to allow for equilibration of T1 saturation effects ($TR = 2.2$ sec; $TE = 30$ msec, flip $angle = 80°$, 38 transverse slices, $2.75 \times 2.75 \times 2.75$ mm (+10% interslice gap)). Visual stimuli were projected onto a screen that was viewed through a mirror at the head end of the magnet. After the functional runs, a high-resolution EPI scan and a T1-weighted anatomical scan were obtained for registration purposes (EPI scan: $TR = 2.2$ msec; $TE = 30$ msec, flip $angle = 80°$, 84 transverse slices, $1.964 \times 1.964 \times 2$ mm; 3D T1-weighted scan: $TR = 9.717$ msec; $TE = 4.59$ msec, flip $angle = 8°$, 140 slices, $.875 \times .875 \times 1.2$ mm, $FOV = 224.000 \times 168.000 \times 177.333$). In addition, a T2*-weighted 160 volume resting state FMRI scan was made, as well as a DTI scan. Results of analyzing these scans will be described elsewhere. In accordance with Leiden University Medical Center policy, all anatomical scans were reviewed and cleared by a radiologist from the Radiology department. No anomalous findings were reported.

FMRI data analysis

Data analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.FMRIb.ox.ac.uk/fsl; (Smith et al., 2004). The following prestatistics processing was applied: motion correction (Jenkinson et al., 2002), non-brain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 8.0 mm, grand-mean intensity normalization of the entire 4D data set by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $sigma = 50.0$ s). Functional scans were registered to high-resolution EPI images, which were registered to T1 images, which were registered to standard MNI space (Jenkinson et al., 2002; Jenkinson and Smith, 2001).

In native space, the FMRI time series were analyzed using an event-related approach in the context of the general linear model with local autocorrelation correction (Woolrich et al., 2001). Within each run (load 3, load 4, and load 5), cue period, delay period, and target/response period were modeled separately. Each effect was modeled on a trial-by-trial basis as a concatenation of square-wave functions. The cue period started with the presentation of the first memory item and lasted until the last memory item disappeared (3050 ms, 4150 ms, or 5250 ms); the delay period started with the instruction and lasted until the target item appeared (6500 ms); and the target/response period started with the presentation of the target item and lasted until the participant made a response (<2850 ms). Delay and target/response periods of maintenance and manipulation trials were modeled separately. Each of these five square-wave functions was then convolved with a canonical hemodynamic response function and its temporal derivative. The model was high-pass-filtered (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). If present, error trials were included in the model (delay and target/response periods separately) but were excluded from the contrasts of interest.

Because we were specifically interested in working memory maintenance and manipulation processes, the contrasts of interest only involved delay period activation. For each run, in each participant, the following contrasts were assessed: (1) 'delay > fixation' (i.e., both maintenance and manipulation > fixation), (2) 'maintenance > fixation', (3) 'manipulation > fixation', and (4) 'manipulation > maintenance'. The contrasts were combined across the three runs on a subject-by-subject basis using fixed-effects analyses (Beckmann et al., 2003; Woolrich et al., 2004) creating the following contrasts at the subject level:

- *contrast A*: delay > fixation
- *contrast B*: maintenance > fixation
- *contrast C*: manipulation > fixation
- *contrast D*: manipulation > maintenance (and the reverse contrast)
- *contrast E*: 'manipulation > maintenance (load 3)' > 'manipulation > maintenance (load 5)' (and the reverse contrast).

These second-level contrast images were submitted to third-level mixed-effects group analyses (see below). Contrasts B, C, and D were conducted for each load separately and for all loads combined.

Time point 1: task effects (whole-brain analysis)

To identify regions involved in working memory processes, time point 1 second-level contrast images were submitted to third-level mixed-effects analyses (Beckmann et al., 2003; Woolrich et al., 2004). Analyses were performed for each load separately and for all loads combined. Data from both groups were included. In addition, we also tested for between group differences on these contrasts with a practice group versus control group comparison. The statistical parametric images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$ (Worsley, 2001).

Time effects in VLPFC, DLPFC and SPC (region of interest analysis)

A region of interest (ROI) analysis was performed to investigate practice related changes in activation of a priori specified regions that were related to working memory in prior research (i.e., VLPFC, DLPFC, and SPC; Crone et al., 2006). The locations of the regions of interest were functionally defined using time point 1 delay period activation of both groups (i.e. *contrast A*; thresholded at $p < 0.01$, cluster corrected using clusters determined by $Z > 2.3$), masked by anatomical ROIs from the Harvard–Oxford cortical atlas (FMRIb.ox.ac.uk/fsl/data/atlas-descriptions.html#ho). The VLPFC ROI(s) were defined by activation that fell within the opercular part of the inferior frontal gyri, the DLPFC ROI(s) were defined by activation that fell within the middle frontal gyri, and the SPC ROI(s) were defined by activation that fell within the superior parietal cortici. Because there was no overlap between the right inferior frontal gyrus and the delay period activation map, we did not create an ROI for the right VLPFC. For each of the five remaining ROIs, (left VLPFC, left and right DLPFC, left and right SPC), mean Z-values were calculated for load 3, load 4, and load 5 'maintenance > fixation' and 'manipulation > fixation' contrasts of time point 1 and time point 2 for each participant (using Featquery; FMRIb.ox.ac.uk/fsl/feat5/featquery.html). Results were entered in a repeated-measures ANOVA with time, load, and condition (maintenance and manipulation) as within-subjects variables and with group as a between-subjects factor.

Time effects in other regions (whole-brain analysis)

To examine the effects of time on maintenance, manipulation, and 'manipulation versus maintenance' conditions, second-level results of both groups at both time points were entered in third level mixed-effects analyses. For each of these second-level contrasts (i.e., *contrast B*, *C*, and *D*), we set up a GLM to test for a group (between-subject) by time (within-subject) interaction. A second set of third-level mixed-effects analyses was performed to test for group differences at time point 2 only. For all analyses, data were combined across the three working memory loads. The statistical parametric images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$ (Worsley, 2001).

Brain–behavior correlations

We tested whether there were significant correlations between (change of) accuracy and (change of) level of activation in the five a priori selected ROIs. Given the large number of possible brain–behavior analyses, we chose to only analyze trials with the largest individual differences in performance. Individual differences were largest for load 5 trials, where standard deviations were highest, while mean percentages of accuracy were lowest. In addition, brain–behavior correlations were also investigated by using the behavioral variables as covariates in the whole-brain analyses. Specifically, we examined correlations between performance and activation on load 5 maintenance and manipulation trials of time point 1 and time point 2.

Results

Behavioral results

Working memory performance was examined in terms of accuracy (quantified as the percentage of correct responses within each condition) and response time (RT) on correct trials. All effects survived Greenhouse–Geisser correction in case of violations of the sphericity assumption.

Working memory performance at time point 1

We examined participants' performance before the start of the practice period to determine whether task manipulations were effective and to test for initial group differences. Repeated-measures ANOVAs were performed for accuracy and RT, with load (load 3, load 4, and load 5) and condition (maintenance and manipulation) as within-subjects variables and group (practice group and control group) as between-subjects factor. The results of the working memory task in the first week replicate the findings of previous research. Accuracy decreased for increasing working memory load and manipulation demands (load: $F(2,54) = 79.65$, $p < .001$; condition: $F(1,27) = 48.46$, $p < .001$; load × condition interaction: $F(2,54) = 14.10$, $p < .001$). RTs increased for increasing working memory load and manipulation demands (load: $F(2,54) = 69.76$, $p < .001$; condition: $F(1,27) = 58.18$, $p < .001$; load × condition interaction ns). There were no group differences on accuracy and RT (all p values > .062) and there were no interactions between group and load and/or condition (all p values > .251). These results confirm that groups were comparable at the outset of the experiment and set the stage of examining practice effects.

Practice effects over 6 weeks (practice group)

To test for practice effects, accuracy and RT of the supervised weekly practice sessions of the practice group (8 in total; including those from time point 1 and time point 2) were entered in a set of repeated-measures ANOVAs. Within-subjects variables were time (8 levels), load (3 levels), and condition (2 levels). Participants performed more accurately and faster after practicing the working memory task for 6 weeks (Fig. 1A; $F(7,98)=10.19$, $p<.001$ and $F(7,98)=15.97$, $p<.001$ for accuracy and RT, respectively). Accuracy increased more on trials with higher working memory loads and on manipulation trials compared to maintenance trials (time × condition interaction: $F(7,98)=4.42$, $p<.001$; time × load interaction: $F(14,196)=5.31$, $p<.001$; time × load × condition interaction: $F(14,196)=2.77$, $p=.001$). Post hoc tests that were performed for each load separately revealed that accuracy increased only for load 4 and load 5 and more in the manipulation condition than in the maintenance condition (main effect of time; load 3: $F(7,98)=.664$, ns; load 4: $F(7,98)=9.25$, $p<.001$; load 5: $F(7,98)=10.95$, $p<.001$; time × condition interaction: load 3: $F(7,98)=2.08$, ns; load 4: $F(7,98)=4.62$, $p<.001$; load 5: $F(7,98)=3.38$, $p<.005$). RTs decreased more on trials with higher working memory loads and on manipulation trials compared to maintenance trials (time × condition interaction: $F(7,98)=5.38$, $p<.001$; time × load interaction: $F(14,196)=2.94$, $p<.001$; time × load × condition interaction: $F(14,196)=1.03$, ns). Post hoc tests that were performed for each load separately revealed that RT decreased for all working memory loads. For load 3 and load 4, this decrease was larger in the manipulation condition than in the maintenance condition (main effect of time; load 3: $F(7,98)=7.90$, $p<.001$; load 4: $F(7,98)=16.05$, $p<.001$; load 5: $F(7,98)=8.39$, $p<.001$; time × condition interaction: load 3: $F(7,98)=4.18$, $p<.001$; load 4: $F(7,98)=4.79$, $p<.001$; load 5: $F(7,98)=.597$, ns). Performance increases were largest in the first 2 weeks.

Time effects in the practice group compared to the control group

Group differences in time effects were examined using a 2 (time points) × 3 (load) × 2 (condition) × 2 (group) ANOVA. Results showed that participants of the practice group improved more than participants of the control group (Fig. 1A; $F(1,27)=8.76$, $p<.01$ and $F(1,27)=14.63$, $p=.001$ for accuracy and RT, respectively). For accuracy increases, these effects depended on working memory load (time × load × group interaction: $F(2,54)=6.71$, $p<.005$). Post hoc tests that were performed for each load separately, revealed that time × group differences were specific to load 4 and load 5 (load 3: $F(1,27)=.221$, ns; load 4: $F(1,27)=4.98$, $p<.05$; load 5: $F(1,27)=$

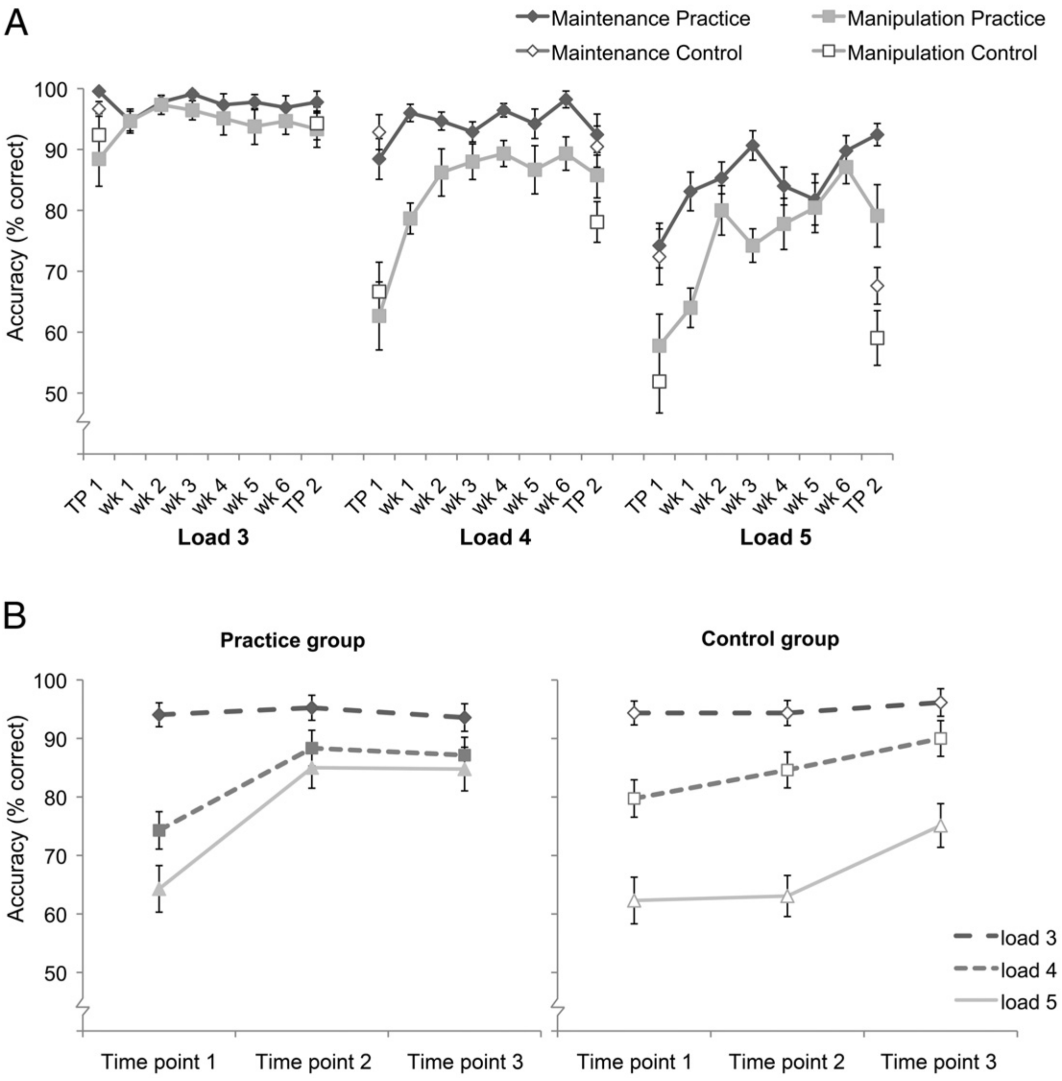

Fig. 1. A. Percentage of correct responses on the working memory task for load 3, load 4, and load 5, maintenance and manipulation trials during the eight supervised weekly practice sessions (including the sessions at time point 1 and time point 2). TP = time point; wk = week. B. Percentage of correct responses for load 3, load 4, and load 5 trials during time point 1, time point 2, and time point 3, collapsed across maintenance and manipulation trials. Results are presented for the practice group (left) and the control group (right).

14.97, $p = .001$). RT effects were not influenced by working memory load. There were no interactions between time, group, and condition.

Follow-up effects in the practice group compared to the control group

Fourteen participants of the practice group and thirteen participants of the control group took part in the follow-up test, 6 months after time point 2. Fig. 1B shows that accuracy remained stable after time point 2 in the practice group. Participants of the control group improved further from time point 2 to time point 3. A 2 (group) × 2 (time points) × 2 (condition) × 3 (load) ANOVA confirmed larger accuracy increases in the control group from time point 2 to time point 3 (time × group interaction: $F(1,25) = 14.12$, $p = .001$). Time × group interactions were not affected by condition or load (all p values > .117). A 2 (group) × 2 (condition) × 3 (load) ANOVA at time point 3 illustrated that the practice group performed relatively better at higher working memory loads than the control group (load × group interaction; $F(2,50) = 4.15$, $p < .05$). RTs did not change for either of the groups from time point 2 to time point 3 (all p values > .200). A 2 (group) × 2 (condition) × 3 (load) ANOVA at time point 3 did not reveal any RT differences between groups at time point 3 (all p values > .061).

Transfer effects at time point 2 and time point 3

Both groups did not improve their backward or forward digit span from time point 1 to time point 2 and time point 3 (Tables 1S and 2S, Supplementary material). For the other five transfer tasks which were only administered at time point 2 and time point 3, we did not find any group differences (Tables 3S to 5S, Supplementary material), indicating that improvements were task-specific, and there was no evidence for transfer of skills acquired during the verbal working memory task.

FMRI results

Time point 1: task effects (whole-brain analysis)

The first set of analyses was performed for time point 1 only, across all participants. During the delay period compared to fixation (i.e., *contrast A*, *B*, and *C*; Table 6S, Supplementary Material), a frontoparietal circuit was recruited, which included the left VLPFC, bilateral DLPFC, bilateral SPC, supramarginal gyrus/lateral occipital cortex, bilateral anterior cingulate cortex, and bilateral supplementary motor area. The frontoparietal circuit showed greater activation for manipulation > maintenance (i.e., *contrast D*). Separate contrasts for each load revealed activation in the frontoparietal network for both maintenance and manipulation trials across loads (Fig. 2). Load 3 and 4 trials showed increased activation for manipulation > maintenance. For load 5 trials, there was little difference between maintenance and manipulation trials, related to increased activation on load 5 maintenance trials (compared to load 3 maintenance trials). Increased activation for 'manipulation > maintenance (load 3)' > 'manipulation > maintenance (load 5)' (i.e., *contrast E*) confirmed that there was an interaction between working memory load and condition in the frontoparietal circuit. At the same statistical threshold, there were no differences between the practice group and the control group.

Time effects in the VLPFC, DLPFC, and SPC (ROI analysis)

We conducted ROI analyses to examine time effects in the left VLPFC, bilateral DLPFC, and bilateral SPC, based on an unbiased delay > fixation contrast across groups at time point 1 (Fig. 3). A 2 (time points) × 3 (load) × 2 (condition) × 2 (group) ANOVA showed a three-way interaction between time, load, and condition in bilateral DLPFC (left DLPFC: $F(2,54) = 7.99$, $p = .001$; right DLPFC: $F(2,54) = 4.36$, $p < .05$) and a four-way interaction between time, load, condition, and group in the left VLPFC (time × load × condition interaction: $F(2,54) = 4.80$, $p < .05$; time × load × condition × group interaction: $F(2,54) = 3.74$, $p < .05$). For bilateral SPC, no significant effects of time and/or group were found (all p values > .071). Post hoc tests were performed for each load separately. At load 3 and load 4, activation was increased for manipulation trials relative to maintenance trials in all ROIs (all p values < .001). These effects were not influenced by time and/or group (all p values > .131). Load 5 showed a different pattern. For most ROIs, activation differences between load 5 manipulation and maintenance trials increased over time (time × condition interaction, left VLPFC: $F(1,27) = 8.37$, $p < .01$, left DLPFC: $F(1,27) = 9.54$, $p = .005$, right DLPFC: $F(1,27) = 5.27$, $p < .05$, and left SPC: $F(1,27) = 5.15$, $p < .05$; but not in right SPC: $F(1,27) = .975$, ns). For left VLPFC, the time × condition interaction was stronger for the practice group than for the control group (time × condition × group interaction; $F(1,27) = 7.89$, $p < .01$). Post hoc tests were also performed for load 5 trials in each group separately. These analyses revealed time × condition effects in left VLPFC, bilateral DLPFC, and left SPC for the practice group (left VLPFC: $F(1,14) = 38.54$, $p < .001$, left

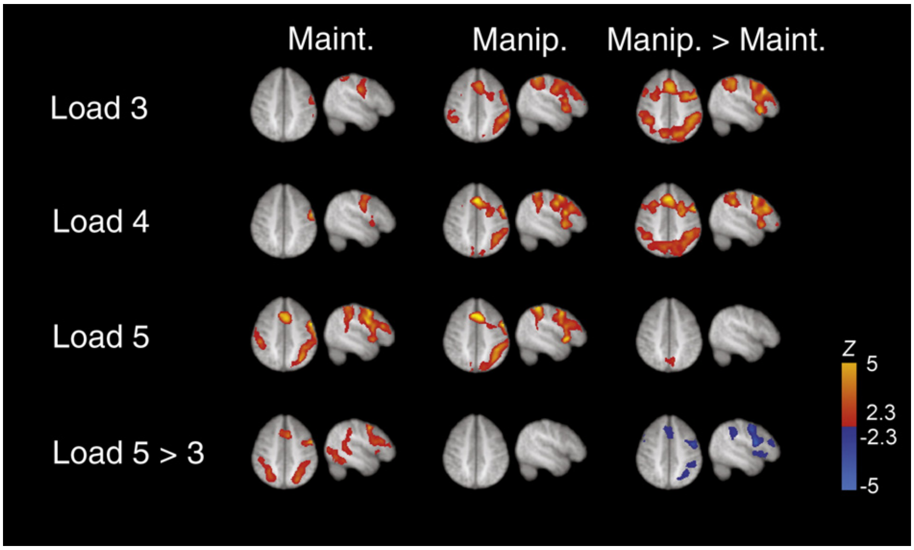

Fig. 2. FMRI activation foci for maintenance (Maint.), manipulation (Manip.), and manipulation versus maintenance (Manip. > Maint.) at all loads during time point 1 for both groups combined. In addition, activation for load 5 > load 3 is presented in red/yellow and activation for load 3 > load 5 is presented in blue. Images are overlaid on axial and sagittal slices ($z = -6$ and $x = -48$) of a standard anatomical image. The left side of the image is the right side of the brain. Results are thresholded at $p < .05$, cluster corrected (using clusters determined by $Z > 2.3$).

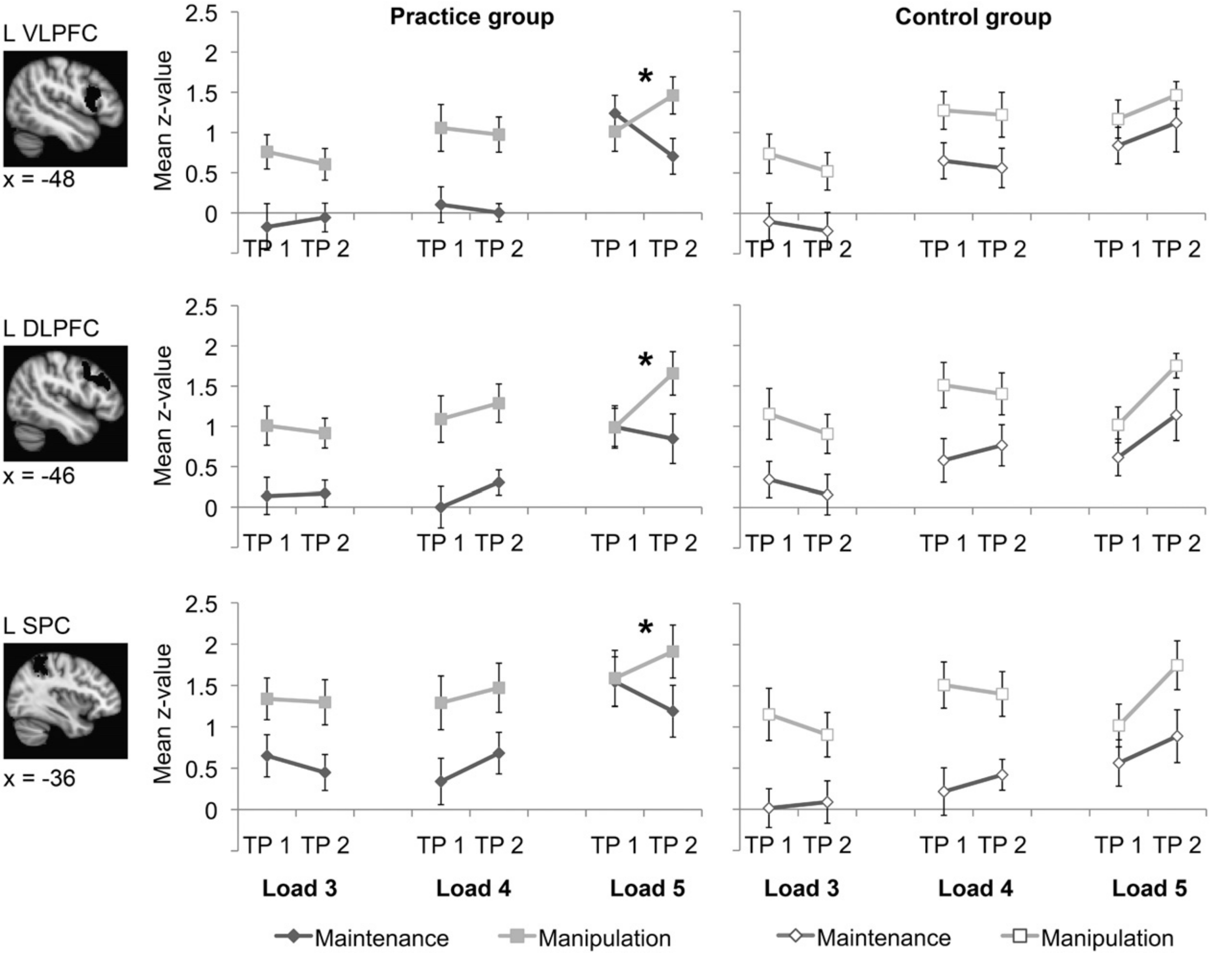

Fig. 3. Mean *Z*-values in left VLPFC, DLPFC, and SPC for load 3, load 4, and load 5 maintenance and manipulation contrasts of time point 1 and time point 2, for practice group (left) and control group (right). For the practice group, all areas showed a time × condition interaction at load 5 (the time × load × condition effect in the SPC failed to reach significance, see text for further details). TP = time point; * = time × condition interaction (load 5 only), $p<.05$.

DLPFC: $F(1,14)=24.22$, $p<.001$, right DLPFC: $F(1,14)=4.58$, $p=.050$ and left SPC: $F(1,14)=4.62$, $p=.050$; right SPC: $F(1,14)=1.23$, ns). In the control group, none of the ROIs showed a time × condition effect (all p values>.274), but a main effect of time was found in bilateral DLPFC and left SPC (left DLPFC: $F(1,13)=9.37$, $p<.01$, right DLPFC: $F(1,13)=6.62$, $p<.05$, left SPC: $F(1,13)=5.12$, $p<.05$). Left VLPFC and right SPC did not show an effect of time in the control group (left VLPFC: $F(1,13)=2.28$, ns, right SPC $F(1,13)=4.33$, ns).

Time effects in other regions (whole-brain analysis)

For maintenance trials, we found a time × group interaction in medial prefrontal cortex/ paracingulate cortex/frontal pole and lingual gyrus (thresholded at $p<.05$, cluster corrected; Fig. 4; Table 7S, Supplementary material). Separate analyses of time effects in each group revealed that the practice group, but not the control group, showed increased activation in these areas over time. This was confirmed by a group comparison at time point 2, which revealed increased activation in the practice group relative to the control group. Because these regions were mainly deactivated before practice (Table 6S, Supplementary material), these effects can be interpreted as less deactivation over time in the practice group relative to the control group.

For manipulation trials, we found a time × group interaction in right striatum, extending into the temporal lobe and amygdala (thresholded at $p<.05$, cluster corrected; Fig. 4; Table 7S, Supplementary Material). This interaction was related to increased activation over time in the practice group but not the control group. This was also confirmed by a group comparison at time point 2 which revealed increased activation in the practice group relative to the control group. In addition, these analyses showed increased activation in the lingual gyrus.

At the same statistical threshold, we did not find time × group effects for the manipulation versus maintenance contrast. When we lowered the threshold to $p<.001$ (uncorrected) we found time × group effects for maintenance>manipulation in bilateral lateral occipital cortex/angular gyrus (Fig. 4). When the practice group was analyzed separately, time effects were also found in precuneus and frontal pole. Most of these regions were deactivated before practice, suggesting less deactivation over time. No effects of time were found in the control group. In addition, we found time × group effects for manipulation>maintenance in right striatum (Fig. 4). When the practice group was analyzed separately, time effects were also found in left striatum. Small clusters were also found in left DLPFC/ precentral gyrus (11 voxels) and left precentral gyrus/ postcentral gyrus (7 voxels). The control group did not show any changes over time.

Brain–behavior correlations

Brain–behavior correlations were only found for the left VLPFC ROI. Time point 1 accuracy on manipulation trials was associated with higher activation during time point 1 ($r=.518$, $p<.005$). Accuracy increases from time point 1 to time point 2 were associated with low time point 1 activation and with activation increases from time point 1 to time point 2 ($r=-.493$, $p<0.01$ and $r=.383$, $p<0.05$ for time point 1 and change-scores respectively), although the correlation

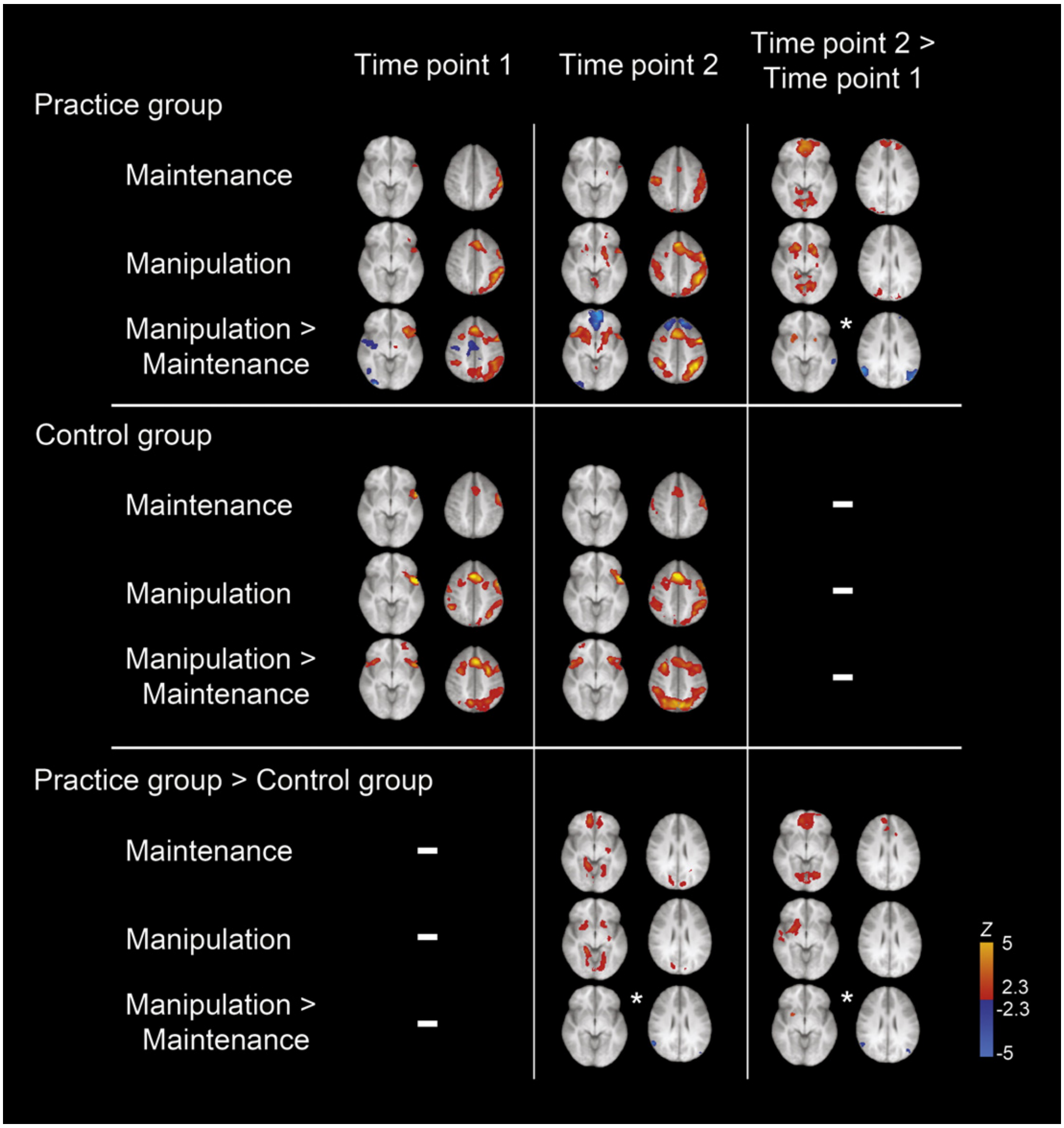

Fig. 4. FMRI activation foci for maintenance, manipulation and manipulation versus maintenance (across working memory loads) during time point 1, time point 2, and time point 2 versus time point 1 for the practice group, control group, and practice group versus control group. Activation for manipulation>maintenance is presented in red/yellow and activation for maintenance>manipulation is presented in blue. Images are overlaid on axial slices ($z=-6$ and $z=46$ or $z=28$) of a standard anatomical image. The left of the image is the right of the brain. Results are thresholded at $p<.05$, cluster corrected (using clusters determined by $Z>2.3$), except for images indicated with *. These images are thresholded at $p<.001$ (uncorrected).

between low time point 1 activation and accuracy increases from time point 1 to time point 2 did not survive Bonferroni correction for the number of correlations per ROI. When controlling for group, the brain–behavior correlations in left VLPFC were still significant (correlations between time point 1 accuracy and time point 1 activity: $r=.540$, $p<.005$; between accuracy increases over time and decreased activity at time point 1: $r=-.495$, $p<.01$; and between accuracy increases over time and activity increases over time: $r=.379$, $p<.05$). There were no brain–behavior correlations for maintenance trials.

When behavioral variables were entered as covariates in the whole-brain analyses, we found a significant relation between performance and activation on load 5 manipulation trials at time point 1. Regions that showed increased activation in participants with higher accuracy involved left supramarginal gyrus/parietal operculum, extending into the lateral occipital cortex, and right supramarginal gyrus/postcentral gyrus, extending into right VLPFC (cluster corrected at $p<.05$).

Discussion

In the present study, we investigated how neural effects of working memory practice were influenced by different working memory demands. Fifteen adults practiced during 6 weeks with a working memory task that required maintenance and manipulation of information under low and high working memory loads. We showed that participants improved on the task, and neural activation changed as a result of practice, depending on the task demands. Most of these changes could not be attributed to test–retest effects. However, results of the control group showed that performance and activity changes are influenced by task familiarity as well.

Prior studies did not consistently find performance benefits after practice (Kelly et al., 2006; Landau et al., 2004). The present experiment showed that participants who practiced a working memory task for 6 weeks responded faster and more accurately after practice. Performance improvements were larger for manipulation trials compared to maintenance trials. Analyses of the follow-up test at time point 3 demonstrated that the practice effects lasted over a 6-month period. The control group showed less improvement, but accuracy still increased from time point 2 to time point 3, indicating that even a small amount of practice can improve performance (Garavan et al., 2000). In addition, these findings show that practice improves performance even when there is a long period between two practice sessions. Notably, at time point 3, the practice group still performed relatively better at the highest working memory load.

The frontoparietal working memory network

As expected, maintenance and manipulation of information in working memory activated a frontoparietal network including the left VLPFC, bilateral DLPFC, and bilateral SPC. In line with prior studies, activation within the network was larger for the manipulation condition compared to the maintenance condition (Crone et al., 2006; Curtis and D'Esposito, 2003; D'Esposito et al., 1999; Owen, 2000; Sakai and Passingham, 2003; Smith and Jonides, 1999; Wagner et al., 2001). Interestingly, this effect was restricted to trials with low working memory loads (3 or 4 items). For trials with a high working memory load (5 items), there was little additional difference between manipulation trials and maintenance trials. This effect was the result of load related increases during maintenance trials (Rypma et al., 1999; Rypma et al., 2002; Veltman et al., 2003). Performance was lowest for load 5 maintenance trials, and participants reported to have used strategies to keep information in mind. Possibly, the increased activation during load 5 maintenance trials was therefore related to strategy use (Bor and Owen, 2007a; Wendelken et al., 2008). On manipulation trials, we did not find load related increases of activation. Presumably, capacity limits were reached already during trials with a lower working memory load, preventing a further increase of activation (Callicott et al., 1999; Goldberg et al., 1998; Mattay et al., 2006; Nyberg et al., 2009).

Neural effects of practice within the frontoparietal network

ROI analyses were performed to examine changes of neural activation from time point 1 to time point 2 within the VLPFC, DLPFC, and SPC. For load 3 and load 4, activation patterns did not change over time. The fact that, at time point 2, activation for manipulation trials was still increased compared to maintenance trials suggests that controlled processing was still required after practice. Perhaps participants could not automatically reverse stimulus sequences because the sequences did not remain consistent over the course of practice (Chein and Schneider, 2005; Jansma et al., 2001; Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977).

Load 5 showed a different pattern. From time point 1 to time point 2, activation on load 5 manipulation trials increased *relative to* activation on maintenance trials in left VLPFC, bilateral DLPFC, and left SPC. On the one hand, this interaction effect might have been associated with more efficient maintenance processes at time point 2. This could be related to the sharpening of responses in the neural network, a reduction in time of processing, and/or reduced need for control processes or strategy use (Poldrack, 2000). On the other hand, the interaction effect might have been associated with increased control during manipulation trials at time point 2. Perhaps participants were better able to keep lateral PFC regions engaged for manipulation processes (Nyberg et al., 2009), for example, by using reorganizing or chunking strategies (Bor and Owen, 2007a).

For left VLPFC, the time × condition interaction was significantly stronger for the practice group than for the control group. For bilateral DLPFC and left SPC, there was no difference between groups. Although post hoc tests failed to show time × condition effects in the control group, there was a general increase of activation from time point 1 to time point 2 in bilateral DLPFC and left SPC. Together with performance changes in the control group, these findings suggest that familiarity with the task can be beneficial for working memory performance and lead to activation changes in task-related regions. These results are of particular importance to studies examining the effects of long-term interventions, pointing out the importance of controlling for test–retest effects using a control group.

Whole-brain effects of working memory practice

In addition to our a priori hypotheses, we also tested for time × group interactions in other brain regions using whole-brain interaction analyses over all loads combined. Results of these analyses showed increased activation (i.e., less deactivation) in medial prefrontal regions for maintenance trials after practice and increased activation in the striatum for manipulation trials after practice. When time × group interactions for the maintenance and manipulation conditions were directly compared, similar effects were observed, although at a lower significance threshold ($p<.001$, uncorrected). These results support the hypothesis that neural effects of practice are different for working memory processes that involve manipulation of information and working memory processes that require only verbal rehearsal of information.

Areas that showed increased activation (i.e., less deactivation) for maintenance trials involved the medial prefrontal cortex and to a lesser extent also the precuneus and lateral occipital cortex. These regions are known to be part of the ‘default-mode network’, which is usually deactivated during demanding cognitive tasks (Raichle et al., 2001). It has been shown that the default-mode network is more deactivated when task difficulty increases (McKiernan et al., 2003), and it has been suggested that when performance of a task becomes more automatic after practice, deactivations should be reduced (Poldrack, 2000). In the present experiment, reduced deactivation for maintenance trials indicates that cognitive demands decreased after practice.

Considering the various reported roles of the striatum, there are several possible explanations for the increased striatal activation on manipulation trials after practice. A first hypothesis suggests enhancement of processes directly involved in the task. Several prior studies have confirmed a role for the basal ganglia in working memory (Braver et al., 1997; McNab and Klingberg, 2008; Menon et al., 2000; Postle and D'Esposito, 2003), and specifically in working memory manipulation (Lewis et al., 2004). Although speculative, striatal activation in the present task could have been associated with a strategy that involves mapping of sensory information onto motor codes (Postle and D'Esposito, 2003). Perhaps, during the presentation of the object sequences, participants automatically created a mapping between each object and a button press. When a forward instruction was presented, they simply maintained these stimulus–response mappings in working memory. However, when a backward instruction was presented, they were required to inhibit the previously created stimulus–response mappings and create new associations between the objects and button presses.

An alternative explanation for increased striatal activation after practice relates to habit formation or learning processes itself (Grahn et al., 2008). It has been suggested that the basal ganglia play an important role in several types of skill learning, both in the (visuo-) motor (Doyon et al., 2009; Hartley et al., 2003; Penhune and Doyon, 2002) and in the cognitive domain (Knowlton et al., 1996; Poldrack and Gabrieli, 2001). One might speculate that in the present experiment, activation increases were related to the formation of associations between cue (i.e., the backward instruction) and action (i.e. reversal of stimulus sequences) over the course of practice.

Thus, the increased striatal activation on manipulation trials might have been associated with increased involvement of specific task-related processes, such as the creation and inhibition of stimulus–response mappings on a trial-by-trial basis. Alternatively, it might have been related to processes involved in habit formation or learning itself. These competing hypotheses should be tested in future research.

Transfer effects

Prior studies have shown that practice effects may transfer to an untrained task (e.g., Dahlin et al., 2008a; Jaeggi et al., 2008; Olesen et al., 2004; Westerberg et al., 2007). Because transfer effects should be attributed to specific task elements common to the trained task and the transfer task, transfer effects can inform us about specific procedures that are learned while practicing a task. In the present experiment, we used six transfer tasks that had one or more elements in common with the practiced working memory task, but none of these tasks showed an advantage for participants of the practice group compared to participants of the control group. Although we cannot rule out the possibility that the control group experienced transfer effects as well, transfer effects in the control group are unlikely because of the limited amount of practice. Therefore, it is more likely that practice effects were related to specific task characteristics, rather than a general improvement of the participant's performance skills.

In general, previously reported transfer effects were restricted to tasks that showed much processing overlap with the practiced task (Dahlin et al., 2008b; Dahlin et al., 2008a; Li et al., 2008). In the present experiment, even the spatial version of the verbal working memory task, which involved the exact same procedures, did not show any advantages for the practice group compared to the control group. One explanation for this finding could be that participants were learning the stimuli of the verbal working memory task rather than the procedures (as in Jansma et al., 2001). However, stimuli that were used during time point 2 were different from the stimuli that were used during time point 1 and during practice. A more likely explanation for the lack of transfer to the spatial task is related to the different strategies that were used in both tasks. Almost all participants used a verbal strategy while performing the verbal working memory task, whereas they used a spatial strategy while performing the spatial task. Ericsson et al. (1980) demonstrated that practice effects can be very specific to a particular strategy. After 230 hours of practice, one student increased his digit span from 7 to 79 digits, but this did not have an effect on his memory span for letters of the alphabet.

Prior studies suggested that adaptive training with changing tasks (e.g., Holmes et al., 2009; Klingberg et al., 2005; Westerberg et al., 2007) is most successful in demonstrating transfer effects. Nevertheless, the generalizability of practice effects and its neural underpinnings are yet to be fully understood and will require further investigation using larger study populations.

Conclusion

Together, the current results demonstrate that practice can be beneficial for both working maintenance and working memory manipulation processes, although the absence of transfer effects indicates that the skills that were being trained were specific for the verbal working memory task. Neuroimaging results showed increased activation in the striatum for manipulation trials after practice and increased activation (i.e., less deactivation) in default-mode regions for maintenance trials after practice. This again demonstrates the specificity of neural practice effects. Time × condition effects were also found in left VLPFC, bilateral DLPFC, and left SPC. However, at least for bilateral DLPFC and left SPC, these effects were not specific to the practice group. That is, there were also activation changes in a control group who did not practice the task, pointing out the importance of controlling for test–retest effects in training or intervention studies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.04.028.

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