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Changes in cortical activity after training of working memory — a single-subject analysis

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Abstract

Working memory (WM) capacity is an important factor for a wide range of cognitive skills. This capacity has generally been assumed to be fixed. However, recent studies have suggested that WM can be improved by intensive, computerized training [Klingberg T, Fernell E, Olesen P, Johnson M, Gustafsson P, Dahlström K, et al. Computerized training of working memory in children with ADHD — a randomized, controlled trial. J Am Acad Child Adolesc Psych 2005;44:177–86]. A recent study by Olesen, Westerberg and Klingberg [Olesen P, Westerberg H, Klingberg T. Increased prefrontal and parietal brain activity after training of working memory. Nat Neurosci 2004;7:75–9] showed that group analysis of brain activity data show increases in prefrontal and parietal cortices after WM training. In the present study we performed single-subject analysis of the changes in brain activity after five weeks of training.

Three young, healthy adults participated in the study. On two separate days before practice and during one day after practice, brain activity was measured with functional magnetic resonance imaging (fMRI) during performance of a WM and a baseline task. Practice on the WM tasks gradually improved performance and this effect lasted several months. The effect of practice also generalized to improve performance on a non-trained WM task and a reasoning task. After training, WM-related brain activity was significantly increased in the middle and inferior frontal gyrus. The changes in activity were not due to activations of any additional area that was not activated before training. Instead, the changes could best be described by small increases in the extent of the area of activated cortex. The effect of training of WM is thus in several respects similar to the changes in the functional map observed in primate studies of skill learning, although the physiological effect in WM training is located in the prefrontal association cortex.

Keywords: Working memory; Plasticity; Training; Prefrontal cortex; Parietal cortex

1. Introduction

Working memory (WM) is the ability to retain information during short periods of time. The maximum amount of information that a person can retain – the WM capacity – is an important factor for many cognitive skills, including problem solving and reasoning ability [1–3]. WM capacity increases with age during childhood [1,4,5], and decreases during old age [6]. The increase in capacity is thought to depend on maturation of the brain, and the decrease at older ages could be due to neuronal degeneration. These processes are paralleled by increased cortical activity in the prefrontal and parietal cortex during childhood [7] and decreased dorsolateral prefrontal activity with aging [8].

It is largely unknown to what extent practice can affect WM capacity. This question in turn depends on whether practice can induce plasticity of the neural systems underlying WM. One previous study with macaque monkeys indicates that the WM systems are plastic [9]. In that study, the animals practiced delayed-response tasks for several weeks while difficulty was gradually increased by degrading the visual stimuli. Practice was found to change the receptive characteristics of neurons in the principal sulcus in the prefrontal cortex, such that they became more resistant to the effect of stimulus degradation.

In psychological studies, there are examples of successful training of attention [10], but previous attempts to improve WM by training have only achieved moderate success.

Repeated execution of WM trials, when difficulty level is not adapted, typically leads to faster reaction times, but not an increase in WM capacity [11,12]. Improved performance has been achieved after teaching rehearsal strategies to children

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with learning disabilities [13–15]. A general problem that these authors noted was the lack of generalization from trained tasks to non-trained tasks, and the lack of long-lasting effects. A case study describes a subject who could retain a large number of digits by associating to series of numbers stored in long-term memory [16]. The subject could remember more than 80 digits, but this ability did not increase his WM capacity for verbal material.

In the present study, we used a novel training paradigm in which subjects practice WM tasks for five weeks. Key features of this training include repetitive training with continuous adaptations of the difficulty level, with training lasting for weeks. We have recently been able to show that this training could improve WM in children with Attention Deficit Hyperactivity Disorder (ADHD), and that this also ameliorated the ADHD symptoms [17,18]. In the present study we investigated the effect of this training paradigm on healthy adults, without any WM deficits. Before and after practice, the subjects performed neuropsychological tests related to control of attention, WM and reasoning which were not part of the daily training, to see whether the training effect generalized to non-trained tasks. Training-induced changes in neuronal activity were estimated by measuring brain activity with fMRI before and after training.

Previous neuroimaging studies have observed practice-related decreases in activity in the prefrontal and cingulate cortex. Raichle et al. [19] showed that when subjects were asked to generate a verb from a noun, repeated presentation of the same noun resulted in less prefrontal and cingulate activity than initially observed. Reduced prefrontal activity has also been observed in several tasks involving declarative [20] and implicit encoding into long-term memory [21], as well as during repeated presentation of WM trials [22]. However, these were all studies of within-session effects of repeated task performance, but did not reflect the acquisition of skill. In studies of acquisition of motor and perceptual skills, practice has been shown to increase task-related activity [23,24] which is consistent with the literature from skill acquisition in primates [25,26]. Another study of skill acquisition found that several days of practice on reading mirror-reversed text significantly improved performance and also increased task-related brain activity in the inferior temporal cortex, cerebellum, striatum and left premotor/inferior prefrontal region [27]. Our hypothesis was that improvement after practice on WM tasks for several weeks would be akin to skill acquisition, and thus induce increased task-related activity in the prefrontal cortex.

Neuroimaging data can either be analysed by combining the results from several subjects, a so called group analysis, or by looking at activations in single subject. The former provide results that can be generalized to a larger population. The single-subject analysis, however, can sometimes give greater anatomical detail about the changes in brain activity.

We have previously reported the results from group analyses in experiments evaluating the effect of training of WM [28]. In the present study we will report the single-subject analysis from a subgroup of the subjects included in the study by Olesen et al.

2. Methods and materials

2.1. Subjects

Three healthy, male, right-handed volunteers (AP, DH, IK), aged 23, 20 and 22 years, participated in the training. A control group consisting of eleven healthy adult subjects, five men and six women, mean age 25.8 SEM 1.5 years, undertook repeated testing of the neuopsychological test battery with a five week test–retest period to provide a baseline for comparing the test–retest improvements from the other subjects. The study was approved by the local ethics committee at the Karolinska Hospital.

2.2. Procedure

On Day 1, subjects were tested on four cognitive tasks (see below), and then undertook the first scanning session. On Day 2 the subjects undertook the second scanning session and after this the WM training began. Subjects practiced four to six days a week for five weeks (20, 24 and 30 number of days for the three subjects AP, DH and IK respectively) on the three WM tasks. Scanning session three took place five weeks after scanning session two. On this day the subjects again completed the cognitive tasks and then undertook scanning. The neuropsychological tasks included: 1. Trained version of the visuo-spatial WM task: Circles were presented one at a time in a four-by-four grid. After a delay the subjects indicated the positions of the circles. The number of circles in the sequence started with two and was successively increased until the subject missed two trials in a row on the same level. The maximum level was 9. 2. Span-board task [29]: Ten blocks were arranged in an irregular pattern in front of the subject. The testing psychologist pointed to a sequence of blocks and the subject then pointed to the same blocks in the same order. 3. Stroop task [29]: Words describing colors were printed with ink in a color that was incongruent with the word, i.e., “green” printed in yellow ink. The subjects were asked to name the color of the ink for each word. 4. Raven’s Advanced Progressive Matrices: A series of non-verbal reasoning tasks [30]. Eighteen problems (odd numbered problems) were given before testing, and a new set of eighteen problems (even numbered problems) were given afterwards. These two sets of problems are considered of equal difficulty.

The statistical significance of the training effect was evaluated by forming a confidence interval of test–retest improvement on the cognitive task results in the control subjects, and then comparing each trained subject to this using one-sided confidence limits and the non-parametric Wilcoxon Signed-rank test. Statistical analysis of behavioral data was made using JMP software (SAS Institute, Cary, NC).

The WM task performed during scanning is illustrated in Fig. 1 and described in the figure legend. In the WM task, red circles were used as cues. In the baseline task, five green, filled circles were presented sequentially, and in the same order at every trial, on a white four-by-four grid on a black background. Thus, the color of the circles indicated to the subject that this was a control task. Presentation times for the cues were identical to

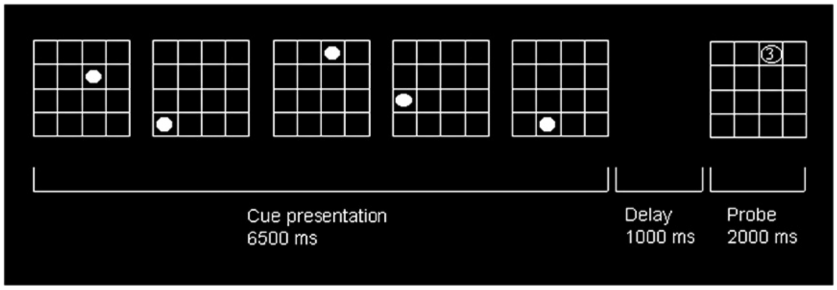

Fig. 1. Schematic drawing of the WM task performed during scanning. Each cue (filled circle) was presented for 900 ms, with 500 ms between cues. The subjects were asked to remember the location, as well as the order in which the cues were presented. After presentation of the last cue a 1000 ms delay ensued, followed by the presentation of the probe for 2000 ms and a 1000 ms inter-trial interval. The probe was a unfilled circle with a number (1–5) in the middle of it. The subjects should judge whether the probe was in the same location as any of the five cues, and if so, whether the number within the probe corresponded to the serial position of that cue. Only if both location and order matched the subject pressed their index finger to indicate "yes", otherwise they pressed the middle finger to indicate "no".

that in the WM task. After a 1500 ms delay a green, unfilled circle appeared in the middle of the grid with the number "6" within the circle. The subjects were instructed to look at each of the cues as they appeared and always press the button when the probe appeared. Four scanning session were completed each day of scanning.

2.3. Practiced WM tasks

Three sub-tests were presented during each training session: 1. A visuo-spatial WM task where the circles to be remembered were presented one at a time in a four-by-four grid. 2. Backwards digit-span. A keyboard with numbers was shown and digits read aloud. The subject remembered the digits, then marked the digits, but in the reverse order. 3. Letter-span task. Letters were read aloud one at a time. The subject should remember the identity and order of the letters. For all WM tasks, difficulty was automatically adjusted by changing the number of stimuli to be remembered so that it matched the capacity of the subject. Subjects completed 30 trials on each WM task every day. All training was recorded so that it was possible to verify the amount of training that the subjects undertook. Daily training time was approximately 40 minutes.

2.4. Data acquisition

Images were acquired using a 1.5 T GE Sigma scanner. T2*-weighted, gradient echo, spiral echo-planar images were acquired with TR = 2500 ms, TE = 70, flip angle = 85, 22 axial slices, 5.0 mm slice thickness, 220 × 220 mm FOV, 64 × 64 grid, resulting in voxels that were 3.4 × 3.4 × 5.0 mm. For each scanning session, 480 volumes were acquired during four 5 min sessions. T1-weighted spin echo images, FOV = 220 × 220 mm, 256 × 256 grid, were acquired in the same position as the functional images and used for anatomical normalization of the functional images.

2.5. Data analysis

The data were analyzed with SPM99 (Welcome Department of Cognitive Neurology, London, UK) [31]. Motion during scanning was estimated by six parameters (three translations, three rotations) which were used to realign the functional images to the first image in the series, and later used as confounds in the statistical analysis (because including these parameters reduces the degrees of freedom, they were only included in the group analysis, not in the single-subject analyses). The T1-weighted

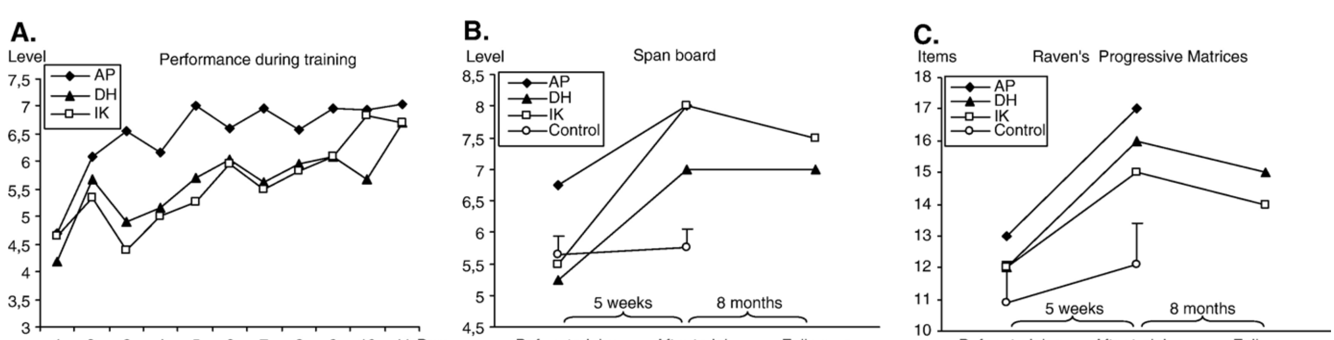

Fig. 2. A. Performance during the first eleven days of training on the visuo-spatial WM task for the three subjects. Level refers to the number of correctly remembered stimuli in a trial. Mean level from 30 trials is shown for each day. B. Performance before and after training and eight months after training (two subjects only) on the span-board task, which is a visuo-spatial WM task that was performed before and after training, but not practiced during training. Improvement was significant for all three trained subjects compared to test–retest changes in the control group ($P < 0.001$). C. Performance on Raven's Advanced Progressive Matrices, a non-practiced reasoning task. Improvement was significant for all three trained subjects compared to test–retest changes in the control group ($P < 0.001$).

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Table 1
Increases in WM-related brain activity after training — group analysis

	x	*y*	*z*	Size (cm^3)	*T*-value
Middle frontal gyrus (R)	36	21	18	0.8	3.9
Sup. and intra-parietal cortex (R)	18	−69	48	0.7	6.6
Sup. and intra-parietal cortex (L)	−15	−69	60	1.0	5.6
Inf. parietal cortex (R)	42	−57	45	0.8	4.1

R = right; L = left; sup = superior; inf = inferior.

images were normalized to Talairach space using the MNI template. The parameters from this normalization were then used to normalize the functional images, which were sampled to a voxel size of 3 × 3 × 3 mm and then smoothed with an isotropic Gaussian kernel of 6.0 mm. A Z-threshold of 2.33 was used in all statistical analyses, and only clusters with sizes yielding a $P < 0.05$ after correction for multiple comparisons, were considered statistically significant.

3. Results

3.1. Behavioral data from pre-and post-training tests

Subjects AP, DH and IK practiced 20, 24 and 30 days. Performance during training was continuously recorded, and showed a gradual and statistically significant improvement on the trained WM tasks (Fig. 2A). Test–retest improvement of the subjects on the neuropsychological tasks was compared to test–retest improvement in the control group. Training significantly improved performance on a computerized visuo-spatial WM task (each subject $P < 0.001$, all three were at ceiling), Span-board (Fig. 2B, each subject $P < 0.001$), RPM (Fig 2C, each subject $P < 0.01$) and the Stroop task (each subject $P < 0.05$). Two of the three subjects were also tested eight months after completion of the training (the third subject was unavailable for retesting). At this point the performance had deteriorated somewhat, but the difference compared to before training was significantly larger on the span-board task for both subjects ($P < 0.01$).

3.2. Behavior during scanning

All three subjects were scanned on two separate days (one session/day) before training. Post-training activity was compared to pre-training activity. Possible non-specific effects of being scanned repeatedly on separate days was thus incorporated into the statistical analysis. Behavioural data from the scanning showed that accuracy was high for all subjects both before and after training (Before: 91.5, 90.5 and 89.5 %, after: 91, 94 and 90% for AP, DH and IK respectively). Mean reaction time before training was 838, 1308, and 1077 ms, and after

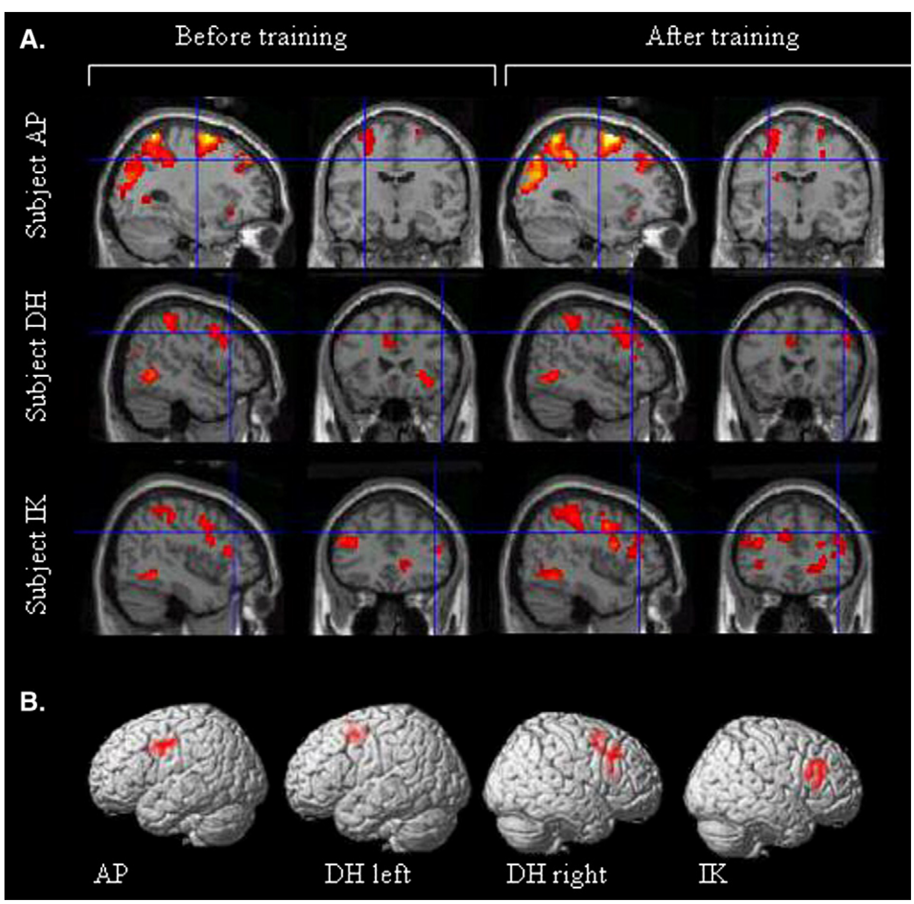

Fig. 3. Single-subject analysis. A. Working memory related activity before and after training. The blue cross is centered on the location of significant training-related increase in prefrontal activity. B. Training-related increases in prefrontal activity in the three subjects.

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training 796, 1231 and 864 ms for AP, DH and IK respectively. When reaction times were pooled from all subjects, there was a tendency towards slightly shorter reaction times after training ($P=0.14$) compared to before. There were no significant differences in reaction times between the first and second half of the first scanning session ($P=0.83$), nor between the first and the second scanning session ($P=0.62$) before training. No significant differences in accuracy were seen. The subjects thus improved on the WM tasks practiced during training (Fig. 2A) as well as the non-practiced tasks administrated outside the scanner (Fig. 2B,C), but not on the WM tasks used during scanning. This discrepancy was due to the fact that the scanning tasks were easier, and thus gave ceiling effects. This was intentional, in order to avoid large differences in error rates and time-on-task between scanning sessions.

3.3. Imaging results

fMRI data was analysed using the two factors Time (before vs. after training) and Task (baseline vs. WM task). The critical contrast was the positive interaction between these factors. When data from all three subjects were included in the analysis, significant positive interaction between Time and Task was found only in the right inferior and middle frontal gyrus, and in the intra-and inferior parietal cortex bilaterally (Table 1). Negative Time-by-Task interaction (=lower task-related activity after training) was only found in the anterior cingulate motor area (pre-SMA) ($X=-3$, $Y=6$, $Z=45$).

To identify the location of prefrontal and parietal activations in single individuals' data from each subject was analysed separately (Fig. 3). The pattern of activity was similar before and after training. From single-subject data we could identify significant positive Time-by-Task interactions in the middle or inferior frontal gyrus in all three subjects, and in the parietal cortex in two out of three subjects (Table 2, Fig. 3). In one subject the prefrontal activation was only significant in the left hemisphere, in one subject bilaterally and in one subject only in the right hemisphere (Fig. 3). As in the group analysis, all three subjects showed a significant negative time-by-task effect in the cingulate cortex.

Table 2
Increases in WM-related brain activity in the prefrontal and parietal cortex after training — single-subject analysis

	x	y	z	Size(cm^3)	T-value
AP					
Middle frontal gyrus (L)	−30	−12	42	0.8	4.0
DH					
Middle frontal gyrus (R)	48	24	39	1.6	4.7
Middle frontal gyrus (L)	−30	3	48	0.9	9.2
Parietal cortex (sup, intra, inf) (R)	15	−57	69	2.6	13.2
	18	−69	48	1.4	11.2
	45	−66	21	l.m.	4.5
Parietal cortex (sup, intra, inf) (L)	−18	−69	48	3.0	7.9
	−42	−45	60	l.m.	7.0
IK					
Middle frontal gyrus (R)	45	33	33	1.0	5.0
Parietal cortex (sup, intra, inf) (R)	15	−69	45	9.7	15.5
	51	0	42	l.m.	13.9
	21	−84	27	l.m.	11.7
Parietal cortex (sup, intra, inf) (L)	−18	−72	60	5.4	27.1
	−36	−48	66	l.m.	11.4
	−18	−60	54	l.m.	10.8

R = right; L = left; sup = superior; inf = inferior. l.m. = local maximum.

4. Discussion

The present results show that practice of WM tasks over several weeks induces a gradual improvement in performance (Fig. 2A). This improvement also generalized to a non-practiced visuo-spatial WM task and a non-practiced reasoning task (Fig 2B and C); effects which persisted for months. In agreement with the hypothesis, the training-induced significant increases in WM-related activity in the prefrontal cortex (Table 1 and 2; Fig. 3) in all three subjects. This finding is also in agreement with the previously reported group analysis of changes in activity after training of WM tasks [28].

A positive relationship between capacity and prefrontal activity, as seen in the present study, was also found in a study of development of WM capacity during childhood [7], as well as a study of the decrease in WM capacity during old age [8]. The increase in task-related activity is also consistent with imaging studies of skill acquisition, which show increased cortical activity after training [23,24,27]. The only consistent decrease in task-related activity we could observe in all subjects was in the cingulate motor area (pre-supplementary motor areas (SMA)). Activity in the pre-SMA during WM trials has been proposed to be related to motor planning [32]. Decreased activity could be similar to the practice effect described previously using other tasks [19].

Maintaining information in WM is based on sustained prefrontal activity during the delay, as shown in both electrophysiological studies in non-human primates [33,34] and human studies [35]. In computational modelling, performance is related to the stability of recurrent networks during performance of WM tasks [36,37]. The effect of enhanced task-related activity, or increased number of neurons with task-related activity, could possibly be to create networks that are more accurate and less susceptible to interference.

There are two mechanisms that might underlie practice-induced changes in cortical activity. On the neuronal level, it has been demonstrated that the response characteristics of single neurons can change as a result of training [25] and that practice of delayed-response tasks makes neurons in area 46 more stable to degradations of stimuli [9]. On the higher level of cortical organisation, it has been observed that the cortical map can change with practice, such that the area where task-related activity is seen increases in size [25,26].

Presumably, long-lasting plasticity of synapses, dendrites or other cellular properties underlies both these phenomena [38]. Both enhanced neuronal responsiveness and increased number of neurons with task-relevant activity would lead to an increase in regional fMRI signal, and could underlie the signal changes we observed after training of WM tasks. In all three subjects the significant changes corresponded to changes in the area of activation (Fig. 3A). This pattern is similar to previous

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findings [25] of a larger area of cortex that exhibits task-specific activity.

One interpretation of the training-induced changes in cortical activity is thus that they were due to training-induced, long-lasting structural changes of cortex, i.e., cortical plasticity. Differences in performance is always a possible confound in attempting to characterize training-induced effects [39]. In the present study we therefore used a relatively easy task to achieve ceiling effects, and could thereby avoid differences in the number of errors during scanning, before and after training. A decrease in reaction time was observed, but this would presumably be associated with a *shorter* time-on-task during the response phase, but could not explain the *higher* activity seen after training. In addition, the procedure of including repeated scanning, on different days, in the baseline before training was made in order to take into account possible non-specific effects of repeated scanning into the statistical model.

An alternative explanation to the training-induced increases in activity could be that the subjects employed a different strategy, i.e., solved the task in a different way, without there being any long-lasting structural changes. Strategies are very difficult to measure, and this possibility can never be entirely ruled out. However, if there was a change in strategy one would also expect a change in the pattern of activity. But from the single-subject analysis it can be seen that task-related activity before and after training was very similar (Fig. 3A). Training-induced increases in the intensity and size of activations, rather resulting in new activations. Furthermore, changes in strategy typically results in relatively fast changes in behaviour during the initial test-session [40]. In contrast, the observed improvement in WM performance was slowly acquired (Fig. 2A), and lasted for several months, a pattern typically seen in skill acquisition and suggested to be associated with cortical plasticity [38,40]. Changes in strategy during training were also excluded by a behavioral analysis in a previous report [28].

5. Concluding remarks

In summary, the slow training-induced changes in performance were associated with increased prefrontal activity in all three subjects. This change appeared to comprise a change in the area of activated cortex, similar to the changes in functional maps previously observed after training of motor and sensory tasks. The effect of training of WM is thus in several respects similar to the plastic effect of skill learning, although the physiological effect of WM training is located in the prefrontal association cortex.

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