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## **The changing brain : neurocognitive development and training of working memory**

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# Chapter 6

## The effects of working memory training on resting-state functional connectivity in adults and children

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## Abstract

Networks of functional connectivity are highly consistent across participants, suggesting that functional connectivity is for a large part predetermined. However, several studies have shown that functional connectivity may change depending on instructions or prior experience. In the present study, we investigated whether 6 weeks of practice with a working memory task changes functional connectivity during a resting period preceding the task. We focused on two task-relevant networks, the frontoparietal network and the default network, using seed regions in the right middle frontal gyrus and the medial prefrontal cortex, respectively. After practice, young adults showed increased functional connectivity between the right middle frontal gyrus and other regions of the frontoparietal network, including bilateral superior frontal gyrus, paracingulate gyrus, and anterior cingulate cortex. In addition, they showed reduced functional connectivity between the medial prefrontal cortex and right posterior middle temporal gyrus. Moreover, a regression with performance changes revealed a positive relation between performance increases and changes of frontoparietal connectivity, and a negative relation between performance increases and changes of default network connectivity. Next, to study whether experience-dependent effects would be different during development, we also examined practice effects in a pilot sample of 12-year-old children. No practice effects were found in this group, suggesting that practice-related changes of functional connectivity are age-dependent. Nevertheless, future studies with larger samples are necessary to confirm this hypothesis.

## 6.1 Introduction

It is well known that brain function depends on large-scale network interactions of brain regions (Mesulam, 1998). Such interactions can be studied with functional MRI (fMRI) by analyzing temporal correlations of (spontaneous) blood oxygen level dependent (BOLD) signal fluctuations between brain regions (Fox and Raichle, 2007). It has been demonstrated that brain regions with a similar functionality show a strong temporal correlation, or *functional connectivity*, even in a task-free setting (Biswal et al., 2010; Smith et al., 2009). For example, strong functional connectivity has been found within visual, auditory, and sensorimotor systems, the so-called *default network*, and between brain regions associated with higher cognitive functions (Damoiseaux et al., 2006; Smith et al., 2009). These networks of functional connectivity are highly consistent across participants (Damoiseaux et al., 2006), suggesting that functional connectivity is for a large part predetermined.

Other studies, however, have argued that functional connectivity patterns differ between different contexts, depending on the instructions that are given (e.g., Benjamin et al., 2010). Moreover, it has been demonstrated that functional connectivity at rest may predict individual differences in behavior (Hampson et al., 2010; Hampson et al., 2006; Kelly et al., 2008; Seeley et al., 2007), and that it can be modified as a result of extensive perceptual or motor training (Lewis et al., 2009; Voss et al., 2010). The goal of the present study was to examine whether experience-dependent changes of functional connectivity could also be observed after training of working memory.

Working memory, or the ability to temporarily store or manipulate information, is crucial for complex cognitive tasks such as reasoning, problem solving, or learning (Baddeley, 1992; Baddeley, 2003), and it has often been described as a driving force behind the development of cognitive control (Case, 1992; Hitch, 2002; Pascual-Leone, 1995). Several studies have shown that practice with a working memory task improves performance and modifies activation in the underlying frontoparietal network (Dahlin et al., 2008a; Jolles et al., 2010; Olesen et al., 2004; Sayala et al., 2006). Different explanations for the observed practice effects have been suggested (e.g., Kelly and Garavan, 2005), including strategy changes taking place on a trial-by-trial basis, a general change of approach (e.g., changes of attention or task preparation processes), and/or plastic changes in the underlying neural network.

Working memory training might also affect the functional connectivity between the regions that are involved in the task. First, a strategy change might not only lead to differential contributions of particular regions, but also to a change in their interactions. Second, task preparation processes could change the coordination of information flow through the brain, which may influence functional connectivity already before start of the task (Buzsaki and Draguhn, 2004; Fox and Raichle, 2007; Salinas and Sejnowski, 2001). Third, it has been suggested that repeated co-

activation of regions could lead to the Hebbian strengthening of the functional connections between them (e.g., Fair et al., 2007; Fox and Raichle, 2007; Kelly et al., 2009), suggesting that extensive practice with a working memory task could lead to the strengthening of frontoparietal connectivity on a more permanent basis. Here, we were specifically interested in those changes of functional connectivity that extended beyond the context of the task (i.e., the second and third possibility). Thus, the main question of the current study was whether practice with a working memory task affects functional connectivity during resting-state.

A secondary goal of the current study was to examine whether experience-dependent effects of functional connectivity would also be observed in (a pilot sample of) 12-year-old children and whether there would be differences between children and adults. Working memory functions, and related neural activity, improve until late adolescence (Crone et al., 2006; Klingberg et al., 2002a; Kwon et al., 2002; Olesen et al., 2007; Scherf et al., 2006). This is potentially related to the late maturation of the frontal and parietal regions that are involved in working memory (e.g., Diamond, 2002). However, in a recent study, we showed that children at the age of 12 were able to show a more adult-like frontoparietal activation pattern after extensive training (Jolles et al., submitted). Here, we examined whether children also show changes in resting-state functional connectivity after training and we compared these changes with the changes observed in adults. On the one hand, we expected that practice effects would be stronger in adults since they might require advanced cognitive and/or structural brain development. On the other hand, it could be that activity-dependent plasticity is actually stronger during development, when functional networks are not yet fully specialized (e.g., Dosenbach et al., 2010; Fair et al., 2009; Jolles et al., 2011b; Kelly et al., 2009; Littow et al., 2010; Supekar et al., 2009).

To test these hypotheses, we conducted two experiments. In the first experiment, we examined the effects of working memory training on resting-state functional connectivity in young adults. Using a seed-based correlation approach, we focused on two networks involved in the task: the frontoparietal network, which showed activation during the working memory task (e.g., Jolles et al., 2010), and the default network (Buckner et al., 2008; Raichle et al., 2001), which showed deactivation during the task (e.g., Jolles et al., 2010). The second experiment involved a pilot study that examined the effects of practice in children and compared practice effects between children and adults.

## 6.2 Method

### Participants

Fifteen adults ( $M = 22.04$  years,  $SD = 1.85$ , 8 female) and nine children ( $M = 12.24$  years,  $SD = .61$ , 5 female) were included in the analyses. Data from two other children were excluded due to scanner artifacts and because one child got engaged in an accident in between the scanning sessions. A chi-square analysis confirmed that the sex distribution did not differ between age groups ( $\chi^2(1, n = 24) = 0.11, p = .92$ ). All participants gave written informed consent for participation in the study. Parents of children that participated in the study gave written informed consent as well.

Prior to enrollment, participants were screened for psychiatric or neurological conditions, history of head trauma, and history of attention or learning disorders. No deviances were reported. Parents of the children filled out the Child Behavior Checklist (CBCL) (Achenbach, 1991) to screen for psychiatric symptoms. All children scored below clinical levels on all subscales of the CBCL. Participants completed two subscales (similarities and block design) of either the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1997) or the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1991) to obtain an estimate of their IQ. The estimated IQ scores did not differ between age groups (children: 107.8 ( $SD = 11.4$ ); adults: 113.0 ( $SD = 9.0$ );  $F(1,22) = 1.56, p = .23$ ). Adults received financial compensation for participation. Children received a gift and their parents received a monetary compensation for travel costs. The experiment was approved by the Central Committee on Research involving Human Subjects in the Netherlands.

### Procedure

All participants practiced with a working memory task for 6 weeks, and they were scanned before and after practice using event-related functional MRI (fMRI) while performing the task. Before the task fMRI scans, a resting-state fMRI scan was acquired. During this scan, participants were required to lie still with their eyes closed and not to fall asleep. In the present study, we describe practice-related changes of functional connectivity during the resting-state scan; practice effects during the task scans are described elsewhere (Jolles et al., 2010; Jolles et al., submitted).

The task that was practiced involved a modified version of the verbal working memory task that was previously used by Crone et al. (2006). In this task, participants were required to memorize a sequence of objects forward order (maintenance condition) or backward order (manipulation condition) during a delay of 6 seconds. After the delay period, one object was presented and participants had to indicate the position of the object in the forward or backward sequence. The task is referred to as *verbal working memory* because participants were explicitly instructed

to use a verbal strategy. All objects were easily associated with one- or two-syllable words. Each practice session consisted of three blocks of 30 trials each, in which 15 forward and 15 backward items were intermixed; one block with sequences of three objects, one block with sequences of four objects and one block with sequences of five objects. On average, the children practiced 15 times ( $SD = 2.76$ ) during the 6-week period and the adults practiced 16 times ( $SD = 1.73$ ). The number of practice sessions did not differ significantly between groups ( $F(1,22) = 3.00, p = .10$ ). The working memory task that was used during scanning sessions was the same as the task that was used for practice, except that different pictures were used and that there were jittered periods of fixation between the trials. Before the first scan, there was an extensive instruction of the task and participants performed a practice block of 32 trials to make sure that they understood task instructions. A mock scanner was used to acclimate the participants to the scanner environment.

### FMRI data acquisition

Scanning was performed with a standard whole-head coil on a 3-Tesla Philips Achieva MRI system. For the resting-state scan, a total of 160 T2\*-weighted whole brain echo planar images (EPIs) were acquired, including 2 dummy scans preceding the scan to allow for equilibration of T1 saturation effects (time repetition (TR) = 2.2 s; time echo (TE) = 30 ms, flip angle = 80°, 38 transverse slices,  $2.75 \times 2.75 \times 2.72$  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 scans, a high-resolution EPI scan and a T1-weighted anatomical scan were obtained for registration purposes (EPI scan: TR = 2.2 ms; TE = 30 ms, flip angle = 80°, 84 transverse slices,  $1.964 \times 1.964 \times 2$  mm; 3D T1-weighted scan: TR = 9.717 ms; TE = 4.59 ms, flip angle = 8°, 140 slices,  $.875 \times .875 \times 1.2$  mm, FOV =  $224.000 \times 168.000 \times 177.333$ ). All anatomical scans were reviewed and cleared by a radiologist. No anomalous findings were reported.

### FMRI data analyses

We used a seed-correlation approach (e.g., Fox et al., 2005) to examine functional connectivity within and between two networks that were involved in the working memory task, i.e., the frontoparietal network and the default network. For each network, we selected a region of interest (i.e., a *seed region*) and defined the correspondence between the BOLD time course of this region and the time courses of all other voxels in the brain.

#### *Preprocessing*

FMRI 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](http://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 dataset by a single multiplicative factor; 100s high-pass temporal filtering (corresponding to 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).

#### *Selection of seed regions*

The frontoparietal seed was placed in the right middle frontal gyrus (MFG). We selected this region because of its importance in working memory manipulation processes (Curtis and D'Esposito, 2003; D'Esposito et al., 1999; Sakai and Passingham, 2003; Smith and Jonides, 1999; Wagner et al., 2001) and because of the reported changes in this region after working memory practice (Jolles et al., 2010; Jolles et al., submitted). The seed was functionally defined in an independent sample of seven adults and seven children, and comprised all voxels within the right MFG that showed delay period activation during the working memory task described above (determined by  $z > 2.3$  and a cluster corrected significance threshold of  $p < 0.05$ ).

The default network seed was placed in the medial prefrontal cortex (PFC) and comprised voxels that showed deactivation during the delay period of the task. We selected this region based on prior developmental studies (Fair et al., 2008; Kelly et al., 2009) and because negative correlations of this region are more similar to the frontoparietal network (or *task-positive network*) than negative correlations of other default network regions (Uddin et al., 2009). Because of the large spatial extent of deactivation in the medial PFC, we created a 12 mm diameter sphere centered at the most ventral peak voxel (8, 48, 10 in MNI space), which was closest to the seed regions in prior studies (Fair et al., 2008; Kelly et al., 2009).

#### *Whole brain functional connectivity analyses*

In native space, for each seed, we first created a reference time course with Featquery (FMRIB.ox.ac.uk/fsl/feat5/featquery.html). Then we calculated how strongly that time course fitted the data at each voxel using a general linear model (GLM) with local autocorrelation correction (Woolrich et al., 2001). Along with the time course of the seed and its temporal derivative, other sources of variance were included in the model: (a) the whole brain signal averaged over an individual whole brain mask and its temporal derivative, (b) the signal from a ventricular seed and its temporal derivative, (c) the signal from a white matter seed and its temporal derivative, (d) six motion parameters (e.g., see also Fox et al., 2005).

The individual maps of parameter estimates related to the time courses of the two seed regions of interest (as well as the corresponding variance maps)



were submitted to second-level mixed-effects group analyses. For each seed region, we first examined the group means of functional connectivity for the sessions before and after practice. Next, we performed repeated-measures analyses to examine functional connectivity changes between the two sessions.

Furthermore, we investigated whether individual differences in functional connectivity changes were related to individual differences in performance changes. To this end, demeaned performance scores were added to the repeated-measures analyses (accuracy and response times separately) and orthogonalized to the main effect of training. The results of these analyses were masked (prethreshold) with the group means of functional connectivity, thereby focusing on regions that showed positive functional connectivity with the seed region before and/or after practice.

Finally, we examined practice effects in the pilot sample of children and we tested for an interaction between practice and age group, using a time (before and after practice)  $\times$  group (adults and children) GLM. All statistical parametric images were thresholded using clusters determined by  $z > 2.3$  and a cluster corrected significance threshold of  $p < 0.05$  (Worsley, 2001).

## 6.3 Results

The goal of the present fMRI study was to examine whether extensive practice with a working memory task changes functional connectivity during a resting period preceding the task (Experiment 1). A secondary goal was to investigate whether practice effects were different in children compared with young adults (Experiment 2). We focused on two functional networks: the frontoparietal network and the default network, which were studied using seed regions in right MFG and medial PFC respectively.

### Experiment 1: Practice effects in adults

#### *Behavioral results*

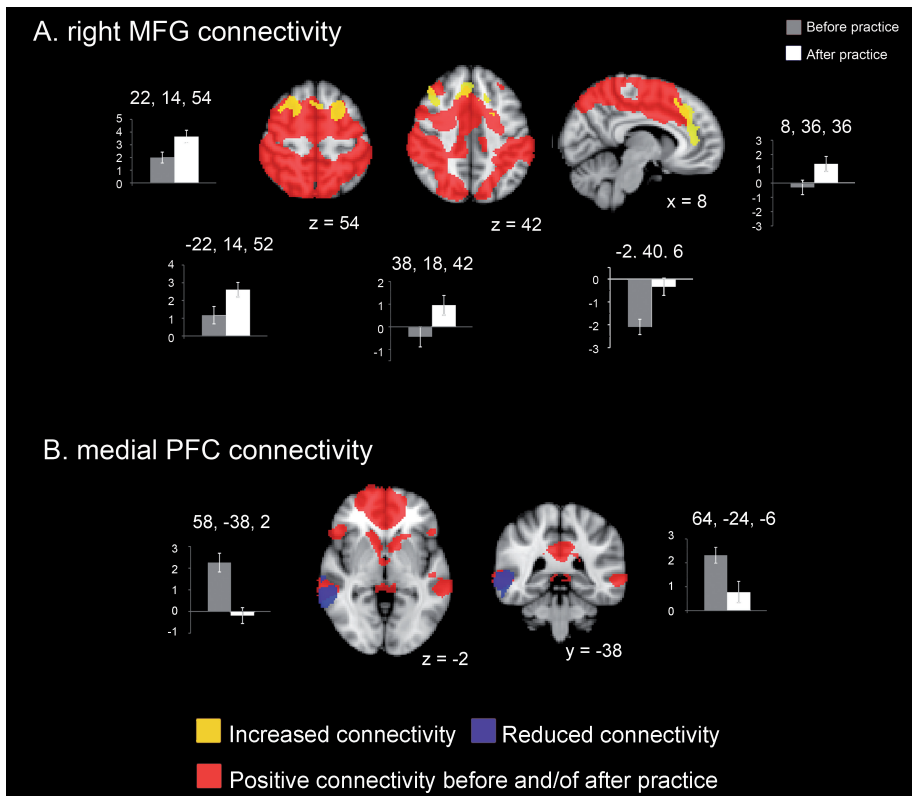
For a detailed description of the behavioral effects of the training procedure, we refer to our prior work (Jolles et al., 2010). In brief, participants performed more accurately and faster after training. That is, accuracy increased from 78.52 % ( $SD$  10.32) to 90.15 % ( $SD$  9.80) after training ( $F(1,14) = 18.39, p < .005$ ), while response times decreased from 1418.08 ms ( $SD$  191.37) to 1207.32 ms ( $SD$  202.78) after training ( $F(1,14) = 30.97, p < .001$ ).

#### *Functional connectivity results*

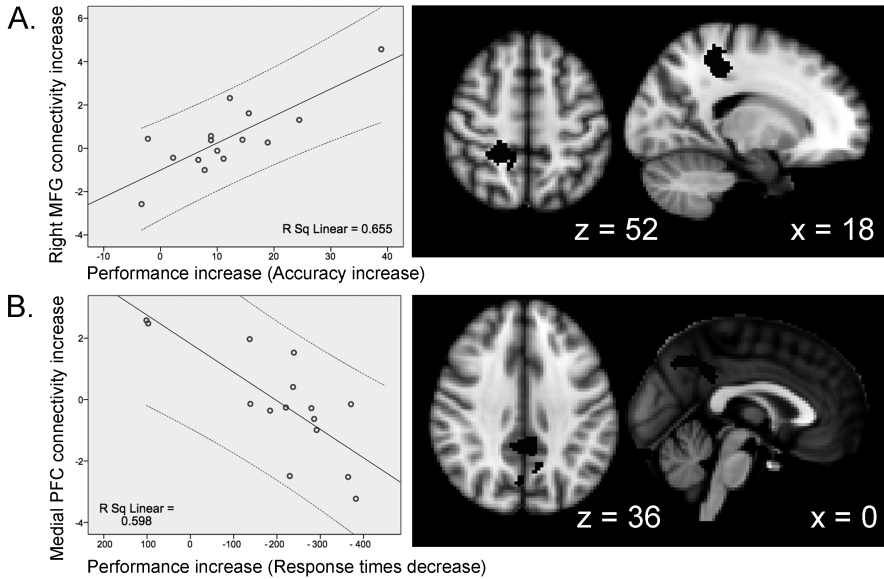
Before practice, the right MFG seed was positively correlated with a bilateral frontoparietal network, including lateral prefrontal cortex, dorsal anterior cingulate cortex, supplementary motor cortex, superior parietal cortex, and supramarginal gyrus

and it was negatively correlated with default network regions such as medial PFC, posterior cingulate cortex, precuneus and lateral parietal cortex (Supplementary figure S6.1A). The connectivity pattern shown by the medial PFC was the opposite of that in the right MFG. That is, medial PFC was positively correlated with default network regions, including posterior cingulate cortex (PCC), precuneus and lateral parietal cortex (extending into the middle temporal gyrus) and it was negatively correlated with frontoparietal regions such as lateral prefrontal cortex, dorsal anterior cingulate cortex, supplementary motor cortex, superior parietal cortex, and supramarginal gyrus (Supplementary figure S6.1B).

After practice, participants showed increased functional connectivity be-



**Figure 6.1** Effects of practice on functional connectivity with the right MFG and medial PFC in adults. A) Right MFG showed increased connectivity after practice (yellow), which is overlaid on the regions that showed positive functional connectivity with right MFG before and/or after practice. B) Medial PFC showed reduced connectivity after practice (blue), which is overlaid on the regions that showed positive functional connectivity with medial PFC before and/or after practice. Images are overlaid on a standard anatomical image. The left of the image is the right of the brain. Graphs represent mean z-values before and after practice in 8 mm diameter spheres centered around the peak coordinates that showed changes of functional connectivity.



**Figure 6.2** Changes of functional connectivity related to performance changes in adults. A) Increased functional connectivity between right MFG and superior parietal cortex was related to accuracy increases; B) Reduced functional connectivity between the medial PFC and the precuneus/posterior cingulate cortex was related to decreased response times. Images are overlaid on a standard anatomical image. The left of the image is the right of the brain. Scatter plots denote within-subject performance difference scores against connectivity differences scores (z-values after training minus z-values before training). The centre line indicates the group mean effect; the outer lines indicate 95% confidence intervals. The correlation between performance changes and changes of z-values in the ROIs was still significant when outliers were removed from the analyses.

tween the right MFG and other regions of the frontoparietal network, including bilateral superior and middle frontal gyri, paracingulate gyrus, and anterior cingulate gyrus (Figure 6.1A; Supplementary table S6.1). In addition, they showed reduced functional connectivity between medial PFC and right posterior middle temporal gyrus (Figure 6.1B; Supplementary table S6.1). It should be noted that at the cluster corrected threshold, the reduced medial PFC connectivity was specific to the right hemisphere. Yet, when we lowered the threshold to  $p < .001$  (uncorrected for multiple comparisons) we also found reduced functional connectivity between medial PFC and left posterior middle temporal gyrus.

Finally, performance scores were added to the model to examine whether functional connectivity changes were related to individual differences in performance changes. For the right MFG seed, there was an association between accuracy changes and changes of functional connectivity with a region in the superior

parietal cortex (including postcentral gyrus, precuneus, and superior parietal lobe), such that participants who improved most on the working memory task also showed the largest increases of functional connectivity between the right MFG and the superior parietal cortex (Figure 6.2A). In addition, for the medial PFC seed, we found a relation between changes in response times and changes of functional connectivity with the precuneus/posterior cingulate cortex, such that participants who showed the largest decreases in response times also demonstrated the largest reductions of functional connectivity between the medial PFC and the precuneus/posterior cingulate cortex (Figure 6.2B).

## Experiment 2: Practice effects in a pilot sample of children

### *Behavioral results*

Just like the adults, children showed increased performance after training. That is, their accuracy increased from 61.85% ( $SD$  14.11) to 80.86% ( $SD$  11.27) after training ( $F(1,8) = 18.26, p < .005$ ), and their response times decreased from 1558.52 ms ( $SD$  128.37) to 1310.64 ms ( $SD$  190.11) after training ( $F(1,8) = 20.08, p < .005$ ). Before training, adults performed more accurately than children, but there were no significant differences in response times (accuracy:  $F(1,22) = 11.15, p < .005$ ; response times:  $F(1,22) = 3.79, p = .07$ ). After training, children performed at the same level as adults before training (accuracy:  $F(1,22) = 0.27, p = .61$ ; response times:  $F(1,22) = 1.78, p = .20$ ).

### *Functional connectivity results*

Before investigating practice effects in children and time  $\times$  group effects, we first examined whether there were any group differences before the start of the training. Functional connectivity in children was similar to that of adults. That is, right MFG showed positive connectivity with frontoparietal regions (including lateral PFC, dorsal anterior cingulate cortex, supplementary motor cortex, superior parietal cortex, and supramarginal gyrus), and negative connectivity with default network regions (including medial PFC and PCC) (Supplementary figure S6.2A). In contrast, medial PFC showed positive connectivity with default network regions and negative relations with parts of the frontoparietal network (Supplementary figure S6.2B).

Direct age group comparisons did not reveal any differences within the core regions of the frontoparietal network. Yet, there were group differences in functional connectivity between right MFG and bilateral insula/temporal regions (Supplementary table S6.2). Within these regions, a large part of voxels showed negative connectivity in children, but no significant connectivity in adults. For the medial PFC, group comparisons revealed differences between children and adults within the anterior part of the default network. That is, the seed region in the ventral medial PFC showed increased functional connectivity with the frontal pole/dorso-medial PFC in adults relative to children (Supplementary table S6.2).

After practice, group differences in medial PFC were still significant. Age differences in bilateral insula and temporal regions were no longer significant, but it is possible that this was a thresholding effect, since we did not find a significant effect of practice in these regions for either group. In fact, when we statistically compared children's connectivity patterns before and after practice, we did not find any significant effects of practice for either seed region. The time  $\times$  group analyses, however, did not reach significance.

It should be noted that the sample of children was small, and it is possible that the study was underpowered to find time effects in children at the whole brain level. Therefore, we performed a region of interest analysis that focused specifically on the regions that showed practice effects in adults. We extracted mean  $z$ -values from five regions that showed increased functional connectivity with right MFG in adults and from two regions that showed reduced functional connectivity with the medial PFC (i.e., by creating 8 mm diameter spheres centered around the peak coordinates in the adult data; Supplementary table S6.1). None of these seven ROIs showed a significant effect of practice in children (all  $ps > .118$ ; Supplementary figure S6.3). Finally, to study the possible effect of different sample sizes, we re-analyzed the adult data using a (randomly selected) subset of the participants ( $n = 9$ ). This analysis still revealed increased functional connectivity between the right MFG and other frontoparietal regions at the cluster corrected threshold. However, the reduced functional connectivity between medial PFC and posterior middle temporal gyrus was not significant in this subset of participants. Together, these findings indicate that sample size may have played a role, but it was probably not the only reason for the absence of practice effects in children.

To summarize, after practice, adults showed increased functional connectivity within the frontoparietal network and reduced functional connectivity between medial PFC and posterior middle temporal gyrus. In addition, there was a positive relation between performance increases (i.e., increases of accuracy) and functional connectivity between the right MFG and the superior parietal cortex, and a negative relation between performance increases (i.e., decreases of response times) and functional connectivity between the medial PFC and the precuneus/posterior cingulate cortex.

Second, children's functional connectivity patterns were similar to those observed in adults, although a direct comparison showed reduced functional connectivity between the ventral medial PFC seed and a region in the dorsomedial PFC. We did not observe any effects of working memory training in children.

## 6.4 Discussion

In the present study, we examined changes of resting-state functional connectivity after working memory training. The data showed that repeated task performance changed functional connectivity for two task-relevant functional networks: the frontoparietal network and the default network. Practice-related changes were only found in young adults; we did not observe practice-effects in a pilot sample of 12-year-old children.

### *Experiment 1: Practice effects in young adults*

To examine functional connectivity within and between the frontoparietal network and the default network, we independently assessed functional connectivity of two seed regions that were associated with these networks: right MFG and medial PFC. As expected, the right MFG seed was positively correlated with regions in the frontoparietal network, and it was negatively correlated with regions in the default network. The medial PFC seed showed the opposite correlation pattern: it was positively correlated with default regions and negatively correlated with frontoparietal regions. These findings are in agreement with prior studies examining functional connectivity within and between the frontoparietal network (also called the task positive network) and the default network (e.g., Fox et al., 2005; Greicius et al., 2003; Uddin et al., 2009). Moreover, there was a strong similarity with the networks that showed increased and decreased activation during the working memory task (Crone et al., 2006; Jolles et al., 2010).

Consistent with our hypotheses, functional connectivity within the frontoparietal network increased after practice. That is, right MFG showed increased functional connectivity with bilateral superior and middle frontal gyri, paracingulate gyrus, and anterior cingulate gyrus. Moreover, a regression with performance changes revealed a positive relation between performance increases (i.e., accuracy increases) and changes of frontoparietal connectivity (i.e., between the right MFG and the superior parietal cortex). In contrast, functional connectivity between medial PFC and posterior middle temporal gyrus was reduced after practice and we found a negative relation between performance increases (i.e., decreases of response times) and changes of default network connectivity (i.e., between the medial PFC and the precuneus/posterior cingulate cortex). The exact role of spontaneous BOLD activity and its modulation after experience is still not clear. Fox and Raichle (2007) have proposed three possibilities (ranging from a general memory of coactivation in the past, to the direct organization and coordination of neuronal activity), which may help to explain the observed functional connectivity changes after working memory training. It is important to note that these three possibilities are not mutually exclusive, and that training effects likely reflect a combination of factors.

The first possibility suggests that functional connectivity represents a re-

cord of previous use, showing increased correlations between regions that have frequently been activated together. This indicates that the increased functional connectivity in the frontoparietal network might simply be explained by the fact that these regions have repeatedly been coactivated during the practice period (e.g., see also Fair et al., 2009; Lewis et al., 2009). Second, functional connectivity could also reflect a prediction about which regions are likely to be used together in the future (Raichle, 2006; Raichle, 2010). This is in line with the proposal that the brain is not a purely reflexive system, but that it constantly anticipates future demands (Bar, 2007; Kording and Wolpert, 2006; Raichle, 2010). According to this hypothesis, the connectivity changes in the present study may not only reflect coactivation in the past, but also the expectation about coactivation in the future (which might be triggered for instance by the context of the experiment). Third, it has been argued that correlated activity may have a *direct* role in the modulation and coordination of information processing, for example by biasing input selection or binding cell assemblies (Buzsaki and Draguhn, 2004; Engel et al., 2001; Fox and Raichle, 2007; Salinas and Sejnowski, 2001). Although these examples apply specifically to neuronal oscillations, similar coordinative processes may occur at the systems-level. These processes might, for example, explain why functional connectivity is modulated during task performance (Fransson, 2006; Hampson et al., 2002; Kelly et al., 2008; Lowe et al., 2000), and possibly also during task preparation. Thus, the practice effects that were found in the present study might also relate to changes in task preparation processes.

It remains to be determined to which extent the functional connectivity changes reflect context-specific processes or long-lasting experience-dependent processes, and this should be examined in future studies by collecting resting-state scans in isolation from task scans. Finally, one might argue that changes in functional connectivity after practice could be related to reduced scanner-related anxiety during the second scan. Although we cannot rule out this possibility, we have tried to minimize scanner-related anxiety by giving extensive instructions and using a mock scanner. Moreover, a prior study showed that scanner-related anxiety was associated with functional connectivity in the so-called *saliency network*, rather than the frontoparietal network (Seeley et al., 2007).

#### *Experiment 2: Practice effects in a pilot sample of children*

Before we studied the effects of practice in children, we first examined the functional connectivity patterns in children and compared these with the functional connectivity patterns that were found in adults. Consistent with prior studies, 12-year-old children showed similar functional connectivity patterns as adults. That is, within the frontoparietal network, they showed functional connectivity between the right MFG and lateral PFC, dorsal anterior cingulate cortex, supplementary motor cortex, superior parietal cortex, and supramarginal gyrus. Within the default network, children showed functional connectivity between medial PFC and PCC, precu-

neus, and lateral parietal cortex.

The core dorsal frontal and parietal regions of the frontoparietal network were not significantly different between children and adults (e.g., in agreement with Jolles et al., 2011b; Littow et al., 2010). There were, however, some age differences within the core default network. That is, children showed reduced functional connectivity between the ventral medial PFC seed and a region in the dorsomedial PFC. The group differences in the present study are in line with prior studies that also found reduced functional connectivity for children in (dorso) medial PFC (Fair et al., 2008; Supekar et al., 2010). However, there is some inconsistency between studies, as there have also been studies that reported increased connectivity in these areas for children (Kelly et al., 2009; Littow et al., 2010). Another point of inconsistency involves the correlations between anterior and posterior nodes within the default network. Whereas some studies have found reduced functional connectivity between anterior and posterior default network regions in children (Fair et al., 2008; Kelly et al., 2009; Supekar et al., 2010), other studies, including the study presented here, did not report any differences (Jolles et al., 2011b; Littow et al., 2010). One possible explanation for these contradicting findings is the age of the participants. Children in the studies that reported age differences along the anterior-posterior axis were generally younger than the participants in the studies that did not find age differences. Other factors that may have contributed to the differences in findings include the instructions that were given, the presence of a task before or after the resting-state scan, and the methodological approach that was used to analyze the data (e.g., the seeds that were selected, the use of global mean regression, or the use of independent component analysis) (Benjamin et al., 2010; Cole et al., 2010; Ma et al., 2007; Power et al., 2010). It remains to be determined how different findings across studies can be integrated.

After practice, functional connectivity differences in medial PFC were still present, suggesting that working memory training did not influence age differences in default network connectivity. Moreover, there was no direct evidence of practice effects in children. These findings argue against the interactive specialization hypothesis (Johnson, 2011), which predicts more plasticity in a less specialized brain. One explanation for the absence of practice effects in children suggests that there were maturational constraints related to the immature brain structure of children. However, this explanation is not likely because children already showed functional connectivity between the core regions of the functional networks before practice. An alternative explanation suggests that working memory training may have less impact on functional connectivity in children because they already experience much practice with working memory in school. This explanation relates to the time displacement hypothesis, which states that training should always be valued in relation to the activities it displaces (e.g., Bavelier et al., 2010). A third explanation argues that the absence of practice effects in children may be related to immature planning or preparation processes concerning the upcoming task. Prior studies have shown



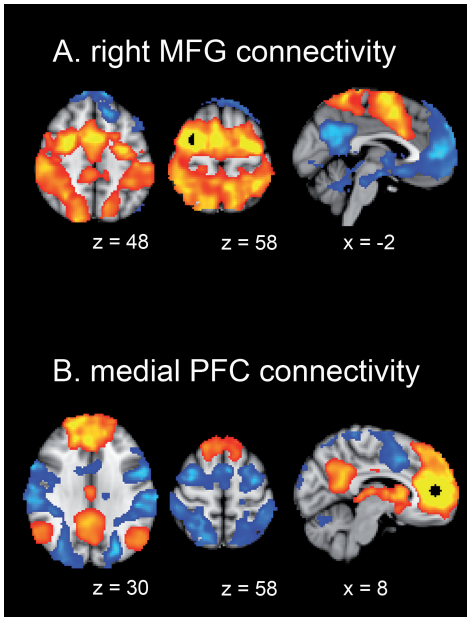
that during planning tasks, children fail to invest enough time in the preparation of a response, resulting in reduced performance (Asato et al., 2006; Huizinga et al., 2006). In addition, it has been demonstrated that the ability to maintain a task set is still immature in children. In stead, children adopt a more reactive strategy that operates on a trial-by-trial basis (Brahmbhatt et al., 2010; Velanova et al., 2009).

Finally, it is important to note that the pilot study involved only nine children, and it is possible that the power was too low to find practice effects at the whole brain level. Although we have demonstrated that practice effects in the adult frontoparietal network were still present when we examined a subset of nine adults, children often demonstrate a more motion (e.g., Yuan et al., 2009), as well as larger interindividual variability in anatomy (e.g., Sowell et al., 2002a) and cognitive strategies (e.g., Bunge et al., 2002; Williams et al., 2005), which may have further reduced the sensitivity of the fMRI data in children (cf. Thirion et al., 2007). Therefore, it is important to validate the present results in a larger number of participants.

#### *Conclusion and future directions*

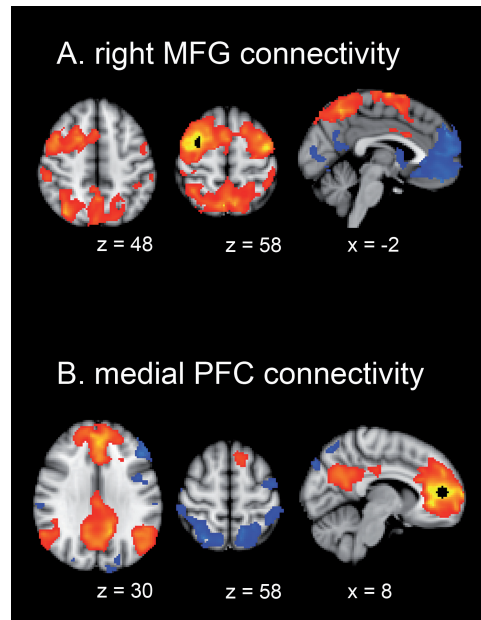
In the present study, we demonstrated that repeated performance of a working memory task changes functional connectivity during a resting-state period preceding the task. These changes, which might have been related to repeated coactivation and/or anticipation for the upcoming task, emphasize the dynamic nature of functional connectivity and underscore the importance of the context in which the experiment is conducted. We argue that resting-state connectivity might not only be influenced by a preceding task (e.g., Albert et al., 2009; Barnes et al., 2009), but that it can also be modified by (implicit or explicit) preparatory processes in anticipation of a task. Practice effects were absent in a pilot sample of 12-year-old children, which suggests experience-related changes depend on the age of the individual. However, because of the small number of children in the pilot study, these results should be validated in future studies using a larger group of children. In addition, future studies should investigate the temporal stability of practice effects, and differentiate between task preparation processes and long-lasting experience-dependent processes.

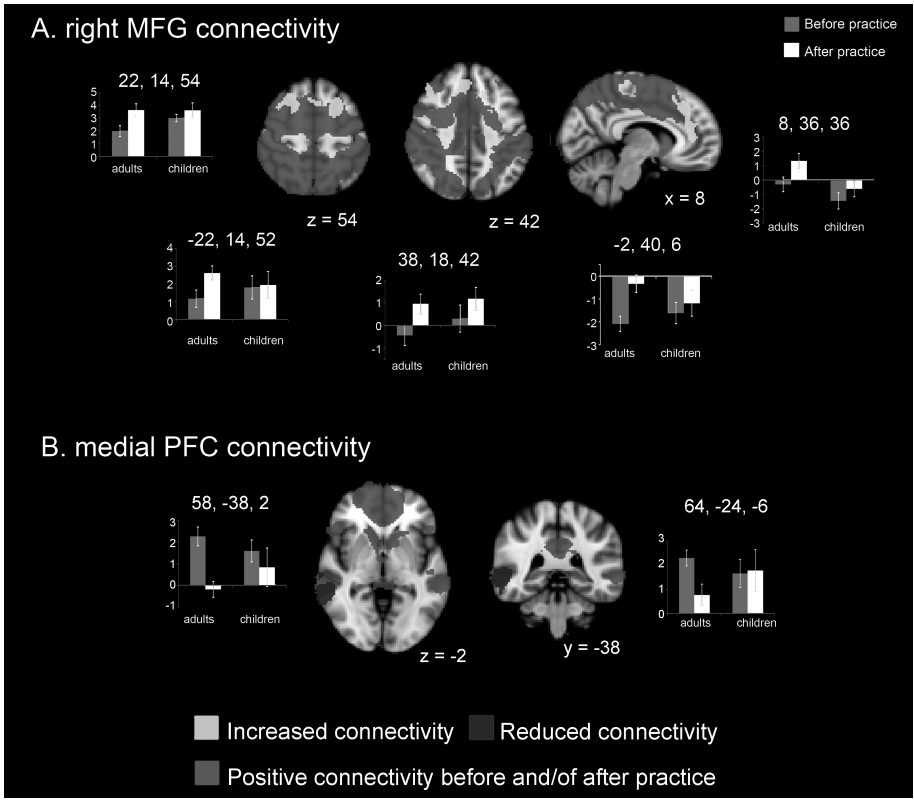
## 6.5 Supplementary material



**Figure S6.1** Functional connectivity in young adults ( $n = 15$ ) for the right MFG (A) and medial PFC (B) before practice. Seed regions are shown in black. Red-Yellow is positive functional connectivity; Blue-Light Blue is negative functional connectivity. Images are overlaid on axial and sagittal slices of a standard anatomical image. The left of the image is the right of the brain.

**Figure S6.2** Functional connectivity in children ( $n = 9$ ) for the right MFG (A) and medial PFC (B) before practice. Seed regions are shown in black. Red-Yellow is positive functional connectivity; Blue-Light Blue is negative functional connectivity. Images are overlaid on axial and sagittal slices of a standard anatomical image. The left of the image is the right of the brain.





**Figure S6.3** Black and white copy of Figure 6.1, but now including children’s graphs. The graphs represent mean z-values before and after practice in peaks obtained from the whole brain contrast in adults.

**Table S6.1** Functional connectivity changes in adults

# voxels	z-value	peak voxels		
		x	y	z
<b>Increased connectivity with right MFG</b>				
2115				
4.02	-22	14	52	Superior Frontal Gyrus, Middle Frontal Gyrus*
4.01	-24	14	56	Superior Frontal Gyrus, Middle Frontal Gyrus
3.89	22	14	54	Superior Frontal Gyrus*
3.81	8	36	36	Paracingulate Gyrus*
3.62	38	18	42	Middle Frontal Gyrus*
3.11	-2	40	6	Cingulate Gyrus, anterior division*
<b>Reduced connectivity with medial PFC</b>				
1026				
4.43	58	-38	2	Middle Temporal Gyrus, temporooccipital part, Middle Temporal Gyrus, posterior division, Supramarginal Gyrus, posterior division*
3.45	70	-48	2	Middle Temporal Gyrus, temporooccipital part
3.33	64	-24	-6	Middle Temporal Gyrus, posterior division, Superior Temporal Gyrus, posterior division*
2.77	66	-16	-10	Middle Temporal Gyrus, posterior division, Superior Temporal Gyrus, posterior division

Coordinates are in MNI space; \* peak voxels that were selected for the ROI analyses; † 3 peak voxels were omitted from the analyses because they were too close to other peak voxels

Table S6.2 Age group differences in functional connectivity

# voxels	z-value	peak voxels			Region
		x	y	z	
<b>Right MFG connectivity before practice: adults &gt; children</b>					
1983					
	3.22	-54	2	-4	Planum Polare
	3.12	-48	6	-8	Temporal Pole, Planum Polare
	3.11	-44	-44	20	Planum Temporale
	3.06	-50	-20	4	Heschl's Gyrus, Planum Temporale
	3.01	-58	-26	10	Planum Temporale, Parietal Operculum Cortex
	2.91	-58	-36	14	Planum Temporale, Superior Temporal Gyrus, posterior division
1676					
	3.62	62	-10	20	Postcentral Gyrus
	3.37	46	-2	0	Insular Cortex, Central Opercular Cortex, Planum Polare
	3.27	54	6	-2	Planum Polare, Central Opercular Cortex, Temporal Pole
	3.03	56	-10	4	Heschl's Gyrus, Planum Temporale, Central Opercular Cortex
	3.02	54	-10	0	Heschl's Gyrus
	3.01	52	16	-2	Inferior Frontal Gyrus, pars opercularis, Frontal Operculum Cortex
<b>Right MFG connectivity after practice</b>					
ns					
<b>Medial PFC connectivity before practice: adults &gt; children</b>					
1240					
	3.6	22	36	52	Frontal Pole, Superior Frontal Gyrus
	3.49	22	32	50	Superior Frontal Gyrus
	3.42	20	50	42	Frontal Pole
	3.3	26	50	40	Frontal Pole
	3.28	22	34	56	Superior Frontal Gyrus, Frontal Pole
	3.16	18	56	32	Frontal Pole

**Table S6.2.** continued

**Medial PFC connectivity after practice: adults > children**  
914

3.55	4	48	Superior Frontal Gyrus, Frontal Pole
3.24	28	44	38 Frontal Pole
3.2	12	40	54 Frontal Pole, Superior Frontal Gyrus
3.18	16	38	54 Frontal Pole, Superior Frontal Gyrus
3.16	28	56	18 Frontal Pole
3.11	24	58	24 Frontal Pole

Coordinates are in MNI space

