



## Visuospatial working memory in very preterm and term born children—Impact of age and performance



I. Mürner-Lavanchy<sup>a,c,e</sup>, B.C. Ritter<sup>a,e</sup>, M.M. Spencer-Smith<sup>a,b</sup>, W.J. Perrig<sup>d,e</sup>,  
G. Schroth<sup>c</sup>, M. Steinlin<sup>a,e</sup>, R. Everts<sup>a,c,e,\*</sup>

<sup>a</sup> Division of Neuropediatrics, Development and Rehabilitation, Children's University Hospital, Inselspital, Bern, Switzerland

<sup>b</sup> Critical Care and Neurosciences, Murdoch Childrens Research Institute, Melbourne, Australia

<sup>c</sup> Institute of Diagnostic and Interventional Neuroradiology, University Hospital, Inselspital, Bern, Switzerland

<sup>d</sup> Institute of Psychology, University of Bern, Bern, Switzerland

<sup>e</sup> Centre for Cognition, Learning and Memory, University of Bern, Bern, Switzerland

### ARTICLE INFO

#### Article history:

Received 27 August 2013

Received in revised form 6 February 2014

Accepted 11 February 2014

#### Keywords:

fMRI

Children

Premature birth

Visuospatial

Short-term memory

Working memory

### ABSTRACT

Working memory is crucial for meeting the challenges of daily life and performing academic tasks, such as reading or arithmetic. Very preterm born children are at risk of low working memory capacity. The aim of this study was to examine the visuospatial working memory network of school-aged preterm children and to determine the effect of age and performance on the neural working memory network. Working memory was assessed in 41 very preterm born children and 36 term born controls (aged 7–12 years) using functional magnetic resonance imaging (fMRI) and neuropsychological assessment. While preterm children and controls showed equal working memory performance, preterm children showed less involvement of the right middle frontal gyrus, but higher fMRI activation in superior frontal regions than controls. The younger and low-performing preterm children presented an atypical working memory network whereas the older high-performing preterm children recruited a working memory network similar to the controls. Results suggest that younger and low-performing preterm children show signs of less neural efficiency in frontal brain areas. With increasing age and performance, compensational mechanisms seem to occur, so that in preterm children, the typical visuospatial working memory network is established by the age of 12 years.

© 2014 The Authors. Published by Elsevier Ltd. Open access under [CC BY-NC-ND license](https://creativecommons.org/licenses/by-nc-nd/4.0/).

### 1. Introduction

Working memory refers to the ability to encode and actively process task relevant information in mind over a short period of time (Baddeley, 1986; Klingberg, 2006). Working memory is crucial for meeting the challenges of

daily life and the performance of academic tasks, such as reading or arithmetic. Hence, working memory capacity is essential for the cognitive development throughout childhood.

In healthy term born children and adolescents, functional magnetic resonance imaging (fMRI) studies have detected a fronto-parietal working memory network (Klingberg, 2006; Klingberg et al., 2002; Thomason et al., 2009) involving the superior and middle frontal gyri and sulci, anterior cingulate cortex and large parts of the superior and inferior parietal lobes. The visuospatial working memory network is suggested to vary as a function of

\* Corresponding author at: Division of Neuropediatrics, Development and Rehabilitation, Children's University Hospital, Inselspital, 3010 Bern, Switzerland. Tel.: +41 31 632 41 30.

E-mail address: [regula.everts@insel.ch](mailto:regula.everts@insel.ch) (R. Everts).

age, sex and working memory performance in childhood (Spencer-Smith et al., 2013).

The investigation of the impact of early brain development on later outcomes is particularly interesting in children who were born very prematurely (<32 gestational weeks) and/or with very low birth weight (<1500 g). Very preterm born children are at risk of reduced working memory capacity in the pre-school period (Woodward et al., 2005) and during school years (Anderson and Doyle, 2003). Even in very preterm born children without major neurological deficits and with normal cognitive abilities, working memory performance has found to be reduced (Vicari et al., 2004).

Very preterm born children demonstrate alterations in structural brain development with prolonged maturation of the frontal lobes, smaller cortical and cerebellar volumes, decreased corpus callosum size, larger lateral ventricles and reduced white matter volume (Nosarti et al., 2008; Parker et al., 2008). Particularly in the frontal regions, the structural maturation of white matter coincides with the formation and improvement of working memory performance (Klingberg, 2006). As structural maturation in fronto-parietal areas is associated with changes in brain activity in the working memory network (Olesen et al., 2003), it is likely that very preterm born children show differences in their working memory network when compared to term born controls.

The visuospatial working memory network has been rarely examined in very preterm born children. To the authors' knowledge, only Taylor et al. (2011) investigated neural processing during a visuospatial working memory fMRI task in very preterm born children ( $n = 10$ , 7–9 years) and term born controls ( $n = 28$ , 6–12 years). fMRI task performance did not differ between the groups, but while controls showed typical frontal activations, very preterm born children presented no frontal involvement and lower activation in the right parahippocampal gyrus and the left precuneus. Since the precuneus is linked to the monitoring of cognitive functions, the authors suggested that low precuneus activation was related to a reduction of organizational activity in very preterm born children, resulting in different cognitive strategies applied to solve the visuospatial working memory fMRI task (Taylor et al., 2011).

As the visuospatial working memory network in very preterm born children has not been investigated intensely yet, the developmental trajectories of the neural representation of working memory in these children are not fully known. On the one hand, it is possible that very preterm born children show persistent immature neural networks, resulting in lower working memory performance. On the other hand, potential alterations in structural and functional development might only exist initially (at younger age) and could be compensated through the recruitment of additional brain regions or enhanced neural effort, resulting in increased working memory performance (Jolles et al., 2012). To gain more knowledge on the development of the visuospatial working memory network, it is therefore important to investigate age and performance effects in very preterm and term born children.

The aim of the present study was to investigate the visuospatial working memory network in a relatively large

sample of very preterm born and term born children comparable for age, gender and handedness, using an established fMRI task in children, with normative data available in the literature (Klingberg et al., 2002; Olesen et al., 2007; Spencer-Smith et al., 2013). We hypothesized that very preterm born children show alterations in visuospatial working memory activation when compared to term born controls. Specifically, based on the limited literature (Taylor et al., 2011), less involvement of frontal areas was expected in the working memory network of very preterm born children compared to term born controls. To shed light on developmental aspects of the working memory network we aimed to examine associations of brain activity during the fMRI task with age and fMRI task accuracy.

## 2. Methods

The present study reports on a subset of data from the NEMO (NEuropsychology and MeMOry) research program, a clinical trial examining cognitive development of very preterm born children and healthy term born controls. The study was approved by the ethics committee of the Children's University Hospital in Bern and the local ethics committee of Bern in Switzerland. All children and caregivers provided informed written consent prior to participation, consistent with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

### 2.1. Participants

#### 2.1.1. Preterm born children

The medical reports of all very preterm (<32 weeks of gestation) and/or low birth weight (<1500 g) children born in the 1998–2003 cohort at the Children's University Hospital in Bern, Switzerland, were reviewed for study inclusion criteria. We included native German speakers aged between 7 and 12 years, who had normal or minimally abnormal neonatal ultrasound (no or mild periventricular leukomalacia, grade I and II; no or mild neonatal cerebral lesions, hemorrhage grade I) no chronic illness (e.g. no birth deformities, congenital heart defect, cerebral palsy, epilepsy), no medical problems influencing development (e.g. no history of meningitis, encephalopathy, traumatic brain injury, shaken baby syndrome, tumors, cancer), no reported neurodevelopmental disorders at the time of recruitment (e.g. autism, attention deficit hyperactivity disorder (ADHD)), and General IQ > 85. Fifty-five very preterm born children completed neuropsychological assessment and a working memory fMRI task. Four children were excluded because of technical problems and seven children were excluded due to low accuracy in the fMRI task (<50% correct responses). Three children were excluded due to AD(H)D (diagnosed during the neuropsychological assessment). A total group of 41 very preterm born children was included in the study (22 girls, 19 boys).

#### 2.1.2. Term born control children

Term born controls (aged 7–12 years) were recruited using announcements on notice boards in the hospital and local schools. Forty-two healthy controls completed the neuropsychological assessment and the fMRI task, however

two children were excluded because of technical problems and four children were excluded due to low accuracy (<50% correct responses) in the fMRI task. Overall, 36 healthy term born controls were included in the study (17 girls, 19 boys). All children (very preterm born children and controls) had normal or corrected-to-normal vision and hearing. Handedness was determined based on a telephone interview with the parents prior to the assessment. Socio-economic status (SES) was estimated by the mother's and father's highest level of education at the time of the neuropsychological assessment (no high school graduation = 1, high school graduation = 2, college graduation = 3, university degree = 4).

## 2.2. Study procedure

In a first appointment, very preterm born children and controls visited the Children's University Hospital of Bern to complete a neuropsychological test battery. On a second appointment, children underwent an fMRI examination at the Department of Diagnostic and Interventional Neuro-radiology in the University Hospital of Bern, which took approximately 1 h including preparation and instructions preceding the actual examination (mean time between neuropsychological assessment and MRI was 11.5 days, ranging from 1 to 33 days). Children were rewarded with a movie voucher.

## 2.3. Neuropsychological measures

General IQ was assessed using the short form of the German version of the 'Wechsler Intelligence Scale for Children, Fourth Edition' (WISC-IV short form: Crawford et al., 2010). Index scores were calculated from scores on seven subtests of the original WISC-IV. Working memory performance outside the scanner was assessed using a visuospatial shape location task from the Learning and Memory Test (BASIC-MLT; Lepach and Petermann, 2007). Different shapes (circle, triangle, square) were presented to the child on a grid and immediately following presentation the child was asked to place the shapes on the grid in the same locations. The number of shapes presented increased across trials. The variable of interest was the number of correct trials, with high scores reflecting better functioning.

## 2.4. fMRI task

All children completed a dot location task (Fig. 1) previously used in child and adolescent studies to detect the visuospatial working memory network (Klingberg et al., 2002; Olesen et al., 2007; Spencer-Smith et al., 2013). The fMRI task was presented in a block-design using E-prime (Psychology Software Tools, PST, Pittsburgh) with five baseline blocks and four activation blocks. Each block lasted 33 s. The active condition required the child to view red dots presented sequentially (each dot presented for 1500 ms) in a 4 × 4 grid and remember the location of the dots. After the presentation of red dots, an unfilled red circle appeared for 2500 ms on the grid. The child was asked to decide if the unfilled circle was in the same location as one of the filled dots that appeared before.

Response buttons allowed for a "yes" (left hand) or "no" (right hand) answer. The first and second trials presented a series of three red dots and the third and fourth trials presented a series of four red dots. The correct answer was either one, two or three dots before the last presented dot. The blank delay which appeared before the unfilled circle varied in length (first and second trial: 1500 ms, third and fourth trial: 2500 ms). In the baseline condition, the child viewed four green dots presented sequentially in the four corners of the grid. Each green dot was presented for 1500 ms. After a 1500 ms delay, a green unfilled circle appeared for 2500 ms and the child was asked to press both response buttons. The inter-stimulus interval lasted for 1500 ms before the next sequence of four filled green dots started. The location of dots and unfilled circles was pseudo randomized, and overall odds were 50:50.

Children were introduced to the scanner surrounding and prepared for the fMRI task. All children demonstrated understanding of the task before commencing the task inside the scanner. Following the MRI scan, children completed a short questionnaire designed to assess their feelings and the difficulty level of tasks during the scan, e.g., "how distressing was the fMRI task for you?" and "how difficult was the fMRI task?". Responses were provided on a 5-point scale ranging from 0 to 4, with a low score reflecting less distress or difficulty.

## 2.5. fMRI data acquisition

Data were acquired on a Verio 3 Tesla whole body scanner (Siemens Erlangen, Germany) equipped with a 40 mT/m (200 mT/m-ms) gradient system and a CP standard head coil (12 channels). The scanner was equipped with the Syngo MR 2002B (VA17) software release. Anatomical imaging was obtained using a T1-weighted, sagittally oriented 3D-MPRAGE sequence (TR 2300 ms, TE 2.98 ms, 40 slices, 0 mm gap, matrix 64, FoV 256) with a 1 mm isovoxel resolution, providing 160 contiguous sagittal slices. Functional images were acquired by using a multi-slice single-shot T2-weighted echo planar imaging sequence, with 40 interleaved axial oblique slices, positioned in-line with the bicommissural axis (TR 3000 ms, no delay, TA 5 min 35 s, TE 30 ms, 3 mm resolution, 108 measurements). The sequences were driven in a 3D PACE mode (Siemens Erlangen) to enable prospective motion correction. The Lumina LP-400 response pads for fMRI (Cedrus) were used to record performance in the fMRI task.

## 2.6. Data analysis

### 2.6.1. Statistical analysis of the behavioral data

Analyses were performed using IBM SPSS Statistics 21.0. Non-parametric statistical test methods were applied because the majority of the variables were not normally distributed within the groups. Two-sided Pearson's chi-square tests were conducted for categorical variables (sex, handedness) and two-sided Mann-Whitney *U*-tests were computed for continuous and ordinal variables (age, IQ, SES of mother and father, fMRI task accuracy, visuospatial working memory performance outside the scanner, head

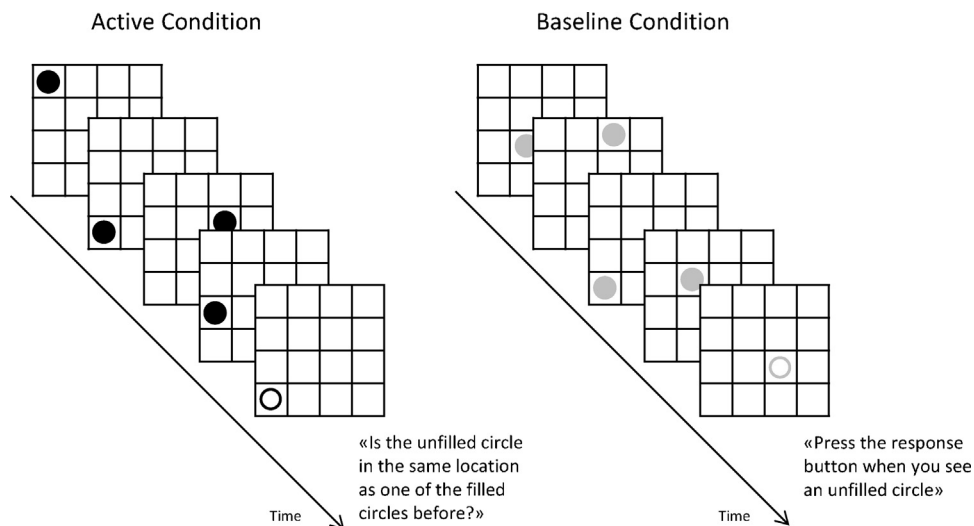


Fig. 1. Active and baseline conditions of the visuospatial working memory fMRI task.

movement in scanner, percent signal change). Correlations were performed using two-sided Spearman correlations.

### 2.6.2. fMRI data analysis

Data were analyzed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK) running in Matlab 7.1 (Mathworks, Natick, MA, USA). The first 12 scans of the functional series (first block of the baseline condition) were deleted to allow for stabilization of longitudinal magnetization. After slice timing, functional images were spatially realigned and unwarped using the individually acquired B0 fieldmap, correcting for both EPI and motion \*B0 distortions (Andersson et al., 2001). Children moving more than 1 voxel size (3 mm) in any direction were excluded from further processing. To allow for inter-participant comparison, data were normalized using custom-generated pediatric reference data (TOM toolbox, Wilke et al., 2008). Functional images were smoothed by a 9 mm Full Width at Half Maximum Gaussian kernel. First level analyses were conducted using the General Linear Model contrasting the active and baseline conditions and the resulting contrast images were entered into random-effect second level analyses. To examine whole-brain working memory activation, one-sample *t*-tests were performed on a voxel-by-voxel basis. FWE correction for multiple comparisons was employed with  $p < .05$  and an extent threshold of  $k > 20$  voxels in group analyses. Multiple regression analyses were performed to examine specific effects of age and fMRI task accuracy on brain activity during the fMRI task. A full factorial design was computed to analyze the interaction between performance (high and low) and group (preterm born children and controls). In these analyses, significance was assumed at  $p < .005$  (cluster-wise) and an extent threshold of  $k > 20$  voxels without multiple comparison correction. Results were overlaid on a custom-made gray matter template, generated using the TOM toolbox (Wilke et al., 2008).

### 2.6.3. Percent signal change

Percent signal change (PSC) is a measure that quantifies the blood oxygen-level dependent effect, computing the signal change in relation to a whole brain activation of 100. To calculate PSC, regions of interest (ROIs) were defined using the intersection of activation clusters found in term born and very preterm born children. The ROIs were rendered symmetrical by combining left and right ROIs with their respective mirror-images to allow for a direct comparison of hemispheres. The ROIs were: left parietal, right parietal, left superior frontal, right superior frontal, left middle frontal and right middle frontal. PSC was computed using a custom-made script. Based on first level statistics modeling only the active condition, PSC was calculated as  $PSC = \beta_{\text{active task}} \times 100 / \beta_{\text{constant term}}$ , scaled by the maximum of the contrast vector. To reduce the possibility that any given effects resulted from general activation differences between groups in the regions outside the working memory network (e.g. due to better data quality in one group), we defined the brain outside the defined ROIs as control ROI (whole brain – ROIs).

## 3. Results

The characteristics of the very preterm born and control group are presented in Table 1. Groups were comparable with regard to age, sex and handedness. SES of the mother and father as well as general IQ of the children differed significantly between groups, with parents of the controls holding higher educational degrees than parents of the very preterm born children and controls showing a higher general IQ than very preterm born children.

### 3.1. fMRI task accuracy

Very preterm born children and term born controls did not differ in fMRI task accuracy (Table 1). fMRI task accuracy correlated significantly with age in both groups: the older

**Table 1**

Demographic and neuropsychological data of control children and very preterm born children.

n	Group		U(z)  $\chi^2$	p
	Very preterm born 41	Controls 36		
Age (years), mean (SD)	9.83 (1.61)	9.65 (1.59)	687 (–0.52)	.603
Sex female/male	22/19	17/19	0.32	.573
Handedness R/L/A	32/4/5	30/3/3	0.38	.825
SES mother 1/2/3/4	0/30/7/3	0/12/9/15	SES mother U 381, z (–3.92)	.001
SES father 1/2/3/4	0/28/3/9	1/12/4/18	SES father: U 475, z (–2.67)	.008
Gestational age in weeks (SD)	30.21 (2.05)	–	–	–
Birth weight in gram (SD)	1286.92 (356.54)	–	–	–
General IQ (SD) <sup>a</sup>	101.51 (9.20)	109.64 (7.82)	363 (–3.84)	.001
WM task accuracy in % (SD)	84.13 (12.74)	86.58 (10.37)	664 (–0.77)	.442
WM outside the scanner (SD) <sup>b</sup>	44.46 (9.39)	45.33 (14.21)	659 (–0.81)	.416

Note. SD = standard deviation; R = right; L = left; A = ambidexter; SES = socio-economic status: mother's and father's education ranging from 1 (none) to 4 (university); WM = working memory; U = Mann–Whitney's U; z = z-value;  $\chi^2$  = chi square; p = significance. Mann–Whitney test was computed for continuous variables and chi-square test was computed for categorical variables.

<sup>a</sup> Wechsler Intelligence Scale for Children, IQ score (mean 100, SD 15).

<sup>b</sup> T-score (mean 50, SD 10).

the children were, the better they performed the fMRI task ( $r(77) = .288, p = .005$ ).

The fMRI task was rated as not very difficult to complete (rating of 0 or 1) by 79.2% and as slightly difficult to complete (rating of 2) by 19.5% of all children. One child (1.3%) found the fMRI task difficult to complete (rating of 3). The MRI scan was described as not distressing (rating of 0 or 1) by 71.4% and as slightly distressing by 27.3% of all children. One child (1.3%) found the fMRI task distressing. There was no difference in perceived fMRI task difficulty or distress between very preterm born children and controls.

### 3.2. Movement

The mean largest translational movement across the X, Y, and Z head directions for the controls was 0.61 mm (SD 0.43). The mean largest translational movement of the very preterm born children was 0.99 mm (SD 0.94). Movement parameters did not differ significantly between very preterm born children and controls ( $U = 612, z = -1.124, p = .261$ ). One participant had to be excluded because of excessive head movement.

### 3.3. Brain activation during fMRI task

Areas activated during the fMRI task in very preterm born children and controls are presented in Fig. 2. The very preterm born children showed activation clusters in bilateral superior parietal regions and bilateral superior frontal gyri (posterior part). The controls showed main activation clusters in bilateral superior and inferior parietal regions, bilateral superior frontal gyri (posterior part) and right middle frontal gyrus. There were no areas with significantly higher activation in the baseline compared to the active condition in very preterm born children and controls.

A two-samples *t*-test comparing working memory activation of the very preterm born and control groups directly revealed a cluster in the posterior part of the right middle frontal gyrus which showed significantly less activation in the very preterm than in the control group (Fig. 2).

#### 3.3.1. Age-related activation

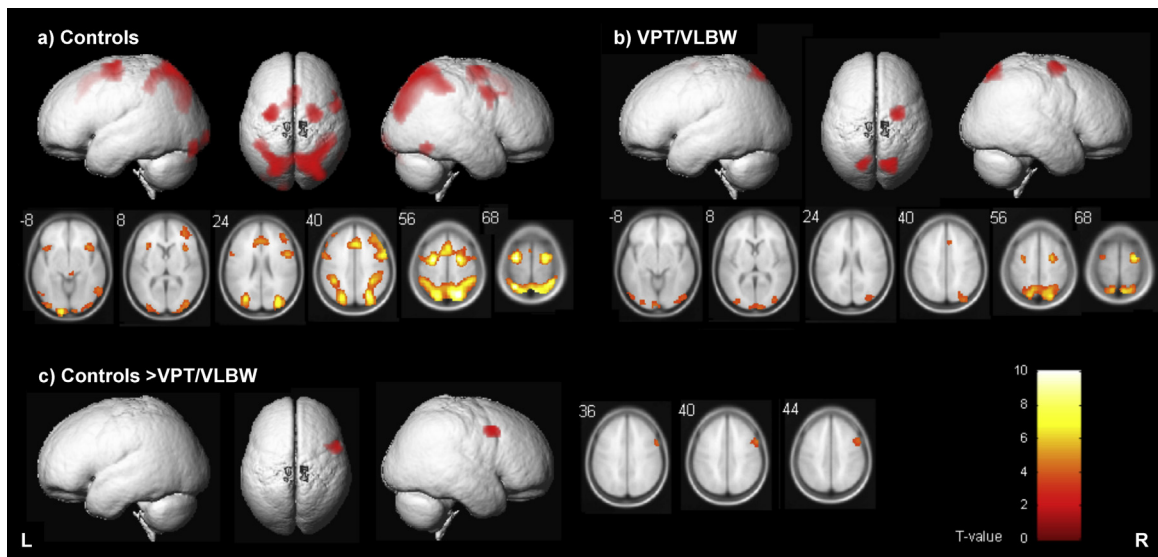
In the very preterm born group, age was not significantly associated with working memory activation during the fMRI task. In the control group, multiple regression analyses examining the relationship between age and visuospatial working memory activation, showed that age was positively associated with activation mainly in the right parietal lobe ( $p < .005$ , uncorrected; Fig. 3a), indicating that more activation in this region was associated with higher age.

#### 3.3.2. Activation related to fMRI task accuracy

In the very preterm born group, a multiple regression analysis revealed that fMRI task accuracy was positively associated with activation in left and right superior parietal regions (Fig. 3b). In the control group, a multiple regression analysis examining the relationship between fMRI task accuracy and working memory activation, revealed that fMRI task accuracy was positively associated with activation in the left frontal region and right precuneus (Fig. 3b), indicating that more activation in these regions was associated with higher fMRI task accuracy.

To analyze possible interactions between fMRI task performance and working memory activation we computed a factorial design with performance (low vs. high) and group (preterm children and controls) as factors. This analysis did not show any significant interaction. To further analyze the association between fMRI task accuracy and the working memory network, group analyses were conducted separately for low performers (lower tercile of the group,  $n = 13$ ) and high performers (upper tercile,  $n = 15$ ). In the control and very preterm born group, low performers showed smaller activation clusters than high performers (Fig. 4). Low performers of the very preterm born group showed an activation cluster in the posterior part of the medial frontal gyrus. High performers of the very preterm born group showed similar working memory network characteristics as the total control group. Post hoc analyses revealed that high-performing very preterm born children were significantly older than low-performing very preterm born children ( $U = 46.5, z = -2.35, p = .017$ ).





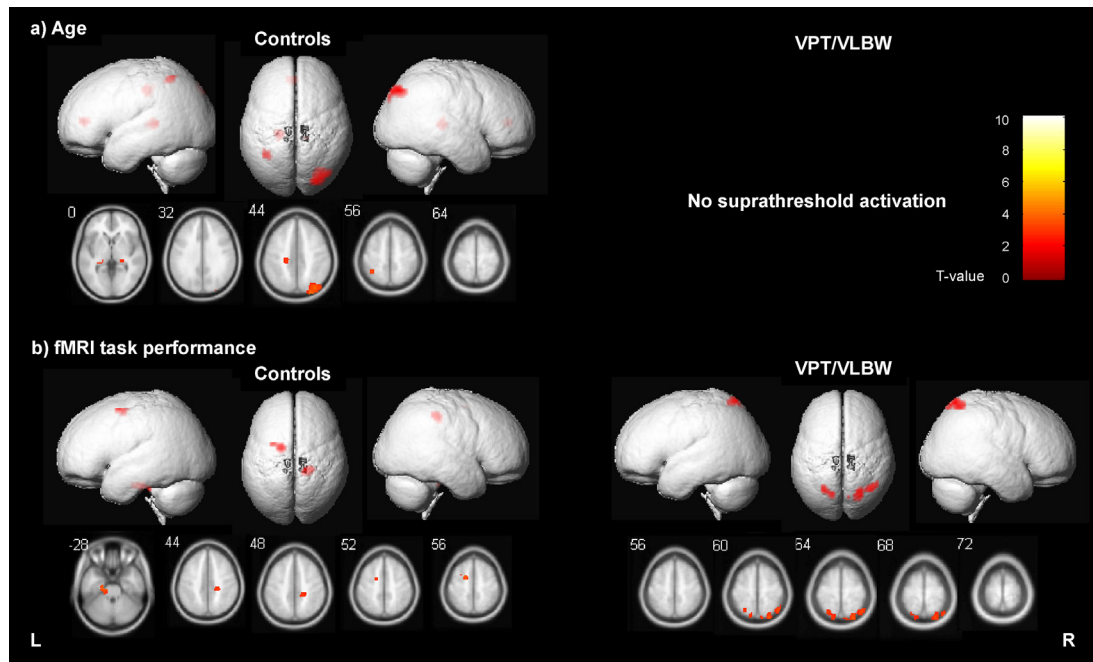
**Fig. 2.** Group analyses (activation > baseline) in (a) term born controls and (b) VPT/VLBW (very preterm and/or very low birth weight) children ( $p < .05$ , FWE corrected). (c) Two samples  $t$ -test contrasting controls and very preterm born children ( $p < .001$ ). Results are shown in render and slice view (slices with main activation clusters are shown). L = left, R = right. The reverse contrast (VPT/VLBW > controls) did not yield any significant suprathreshold clusters.

### 3.4. Percent signal change

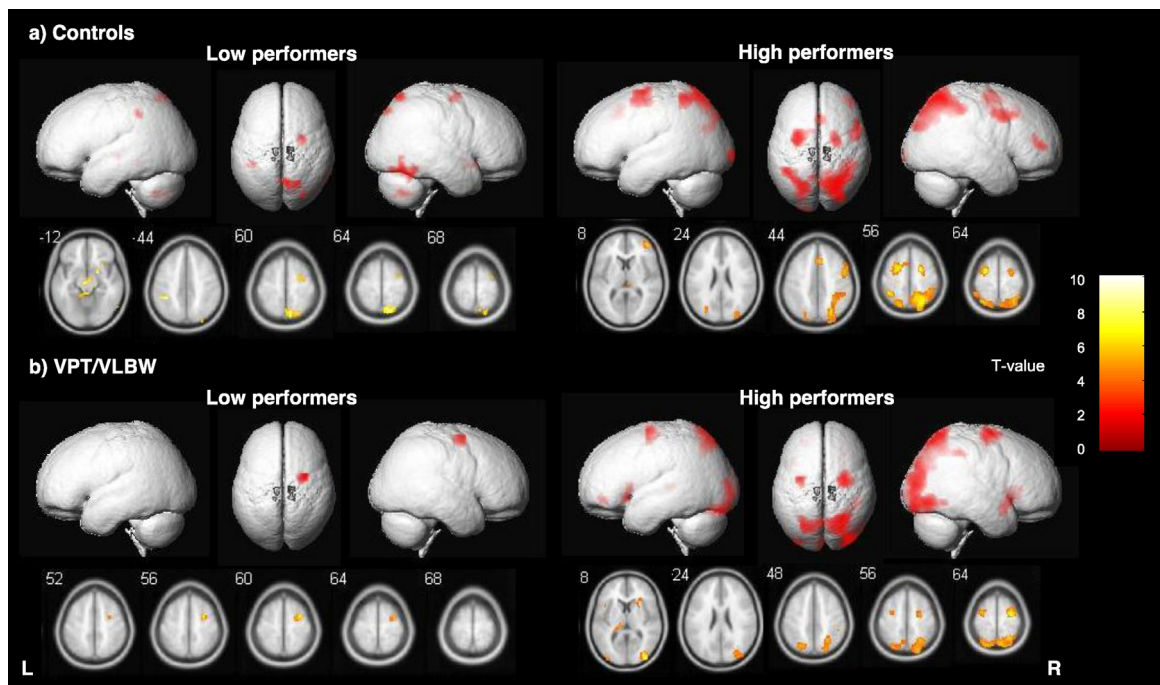
#### 3.4.1. Tests for normal distribution and equality of variances

Tests of normal distribution and equality of variances were computed for all ROIs in very preterm born children and controls. In very preterm born children, PSC was not normally distributed in all six ROIs. In

controls, PSC was normally distributed in all ROIs except the left middle frontal ROI. Variances in PSC differed between very preterm children and controls in left parietal ( $F(1, 75) = 4.811, p = .031$ ) and left and right middle frontal regions (left  $F(1, 75) = 4.382, p = .040$ ; right  $F(1, 75) = 4.887, p = .030$ ) with variances being larger in very preterm born children than in controls. Variances in PSC did not differ between very preterm children and



**Fig. 3.** Correlations of age and fMRI task performance with fMRI task activation. fMRI task activation clusters significantly associated with (a) age (positive regression) and (b) fMRI task accuracy (positive regression) in controls and VPT/VLBW (very preterm and/or very low birth weight) children ( $p < .005$ ). Results are shown in render and slice view (slices with main activation clusters are shown). L = left, R = right. WM = working memory.



**Fig. 4.** fMRI task activation of low (lower tercile) and high (upper tercile) performers of the fMRI task in controls and VPT/VLBW (very preterm and/or very low birth weight) children (one-sample *t*-tests;  $p < .005$ ). Results are shown in render and slice view (slices with main activation clusters are shown). L = left, R = right.

controls in right parietal and left and right superior frontal regions.

#### 3.4.2. Group differences in percent signal change

Very preterm born children and controls did not differ significantly regarding PSC in the whole brain control ROI ( $M_{\text{very preterm born}} = 0.126$ ,  $SD = 0.52$ ,  $M_{\text{controls}} = 0.012$ ,  $SD = 0.25$ ,  $U = 577$ ,  $z = -1.644$ ,  $p = .100$ ). PSC was significantly higher in very preterm born children than in controls in left and right superior frontal regions (left  $U = 434$ ,  $z = -3.099$ ,  $p = .002$ ; right  $U = 504$ ,  $z = -2.389$ ,  $p = .017$ ; Fig. 5). No significant difference between groups was found in the other ROIs. In very preterm born children, no correlations were found between age, fMRI task accuracy, performance outside the scanner (shape location task) and PSC. In controls, age was significantly correlated with PSC in the left superior frontal ROI ( $r(36) = .349$ ,  $p = .037$ ). No other correlations were found between age, fMRI task accuracy, performance outside the scanner (shape location task) and PSC in controls.

## 4. Discussion

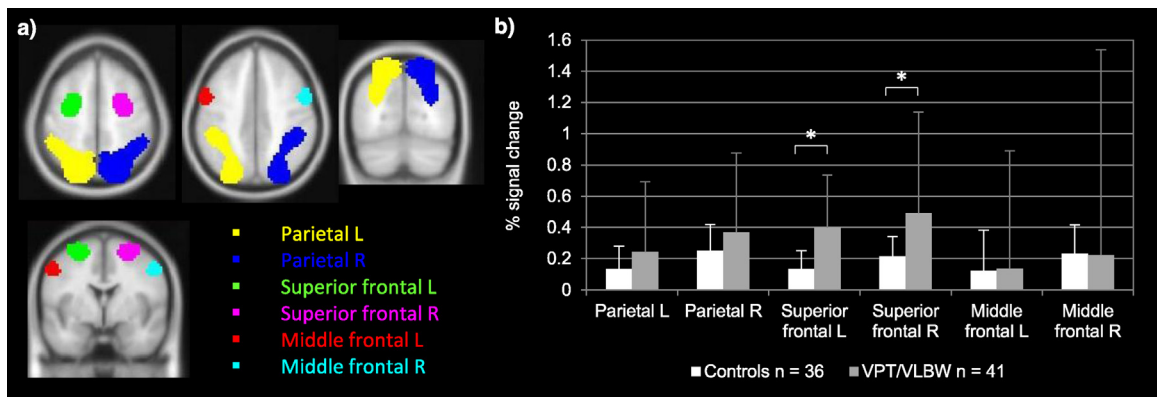
The present study examines the visuospatial working memory network in very preterm born and term born children. We hypothesized that very preterm born children show alterations in visuospatial working memory activation when compared to term born controls. We further examined the associations between age, performance and brain activity during the fMRI task. Up to date, no study has investigated the working memory network in the restricted age range of 7–12 year-old very preterm born children.

This study aims to contribute to the understanding of how higher order cognitive functions such as visuospatial working memory are represented in the brain of children born very preterm and how age and performance affect the visuospatial working memory network.

We identified the fronto-parietal working memory network in very preterm born children. Despite similar fMRI task performance, the working memory network differed between very preterm children and term born controls in regard to the recruitment of frontal areas. In preterm born children, the low-performing, younger children showed an atypical working memory network, whereas the high-performing, older children showed the typical visuospatial working memory network seen in term born children.

#### 4.1. The visuospatial working memory network in very preterm born children

In preterm born children, core visuospatial working memory areas in bilateral fronto-parietal brain areas were activated which is in agreement with previous studies including healthy children and adults (Klingberg, 2006; Klingberg et al., 2002; Thomason et al., 2009). However, in preterm born children clusters are smaller in the described areas than in controls. One possible explanation for these differences is a high intra-group variance in the very preterm born sample. If the variance in a group is large, few significant clusters may result for the whole group although the mean beta values might be high. We assume that large variance in the very preterm born group led to fewer and less extended clusters on a group level. Further, the working memory network in the very preterm born



**Fig. 5.** Regions of interest for percent signal change analyses. (a) Regions of interest of the visuospatial working memory network. MNI coordinates: transversal slices  $z=56$ ,  $z=44$ , coronal slices:  $y=-73$ ,  $y=0$ . (b) BOLD percent signal change in ROIs for control and VPT/VLBW (very preterm and/or very low birth weight) children. L=left, R=right. \*Mann–Whitney  $U$ -test,  $p<.05$ .

children did not include the anterior cingulate cortex such as suggested in previous studies (Klingberg et al., 2002; Thomason et al., 2009). Besides its crucial role within the visuospatial working memory network, this region has found to be particularly involved in executive control and error monitoring (Carter and van Veen, 2007). Despite similar fMRI task accuracy of very preterm born children and controls, very preterm born children might perform less error monitoring during the task, which could be reflected by less activation in the anterior cingulate cortex (Badgaiyan and Posner, 1998).

According to our knowledge, only one study has investigated the working memory network in ten very preterm born children so far: Taylor et al. (2011) found no frontal involvement in a visuospatial working memory task in very preterm born children aged 7 to 9 years. In line with these findings, our larger very preterm born group of 7–12 year-olds showed significantly less frontal activation than the term born controls (as indicated by the group difference map, Fig. 2c). However, unlike Taylor et al. (2011), we observed some involvement of frontal areas in very preterm born children on a group level. It is possible that these diverging findings reflect the wider age range being examined in the present study or differences in fMRI tasks used to examine the working memory network. For example, Taylor et al. (2011) used an fMRI task with lower working memory demands than the task used in the present study, with decreasing working memory demands usually requesting less frontal involvement.

#### 4.2. Group differences between very preterm born children and controls

The comparison between term born children and very preterm born children showed less activation in the posterior part of the right middle frontal gyrus in very preterm born children (as indicated by the group difference map, Fig. 2). This region has been shown to be involved in the processing and storage of spatial information (Leung et al., 2002) as well as the continuous updating processes needed during a working memory task (Wager and Smith, 2003). It

is possible that very preterm born children cannot recruit this area in the same way as term born controls. Given the known neurostructural alterations in very preterm born children (Nosarti et al., 2008; Parker et al., 2008), it is rather surprising, that only small activation differences are found in the direct comparison between very preterm born children and controls.

Although activation in the superior frontal gyrus was found in the working memory network of both, very preterm born and control children, the intensity of activation in this frontal region was higher in very preterm born children (as indicated by a significant PSC difference). The higher intensity of frontal activation in very preterm born children – despite equal task performance – might reflect the use of compensational mechanisms used to solve the working memory task. Another reason for the higher frontal activation intensity of very preterm born children might be the less widespread working memory network, probably requiring more involvement of the superior frontal region in order to perform comparably to their term born peers. In very preterm born children, higher intensity of activation as indicated by PSC was found in almost all ROIs, although significance was only reached in the left and right superior frontal ROIs. The consistently lower intensity of activation in controls might reflect a somewhat more efficient neural processing than seen in very preterm born children, with both groups showing similar working memory performance. Decreased brain activation is thought to reflect better selection and optimization of cognitive resources or enhanced neural efficiency with less neuronal substrate activated to solve the task and hence, better precision of the functional network (Kelly and Garavan, 2005; Schneiders et al., 2012). When interpreting our study results, whole brain task activations and PSC in chosen ROIs cannot be compared directly, because they represent different computational approaches.

Despite alterations in the recruitment of brain areas, very preterm born children perform equal to the term born controls in the fMRI task. Thus, the somewhat different recruitment of neural resources does not seem



to be disadvantageous for the performance outcome in very preterm born children. To the contrary, as the children did not have major neonatal complications, IQ within the normal range and moderate to high socioeconomic background, the sample represents a relatively healthy subgroup of preterm children. Hence, in our preterm sample, a compensation of the effects of prematurity can be more easily anticipated than in children with a more detrimental course of development.

#### 4.3. Influence of age and performance on the visuospatial working memory network

A further aim of the study was to investigate the influence of age and fMRI task accuracy on the working memory network in very preterm born and term born children. Consistent with previous studies investigating the visuospatial working memory network, higher age was associated with more activation mainly in the parietal region in term born children (Ciesielski et al., 2006; Crone et al., 2006; Klingberg et al., 2002; Kwon et al., 2002; Olesen et al., 2007; Scherf et al., 2006; Spencer-Smith et al., 2013). This finding suggests that older children rely more heavily on one of the core regions of the visuospatial working memory network, whereas younger children might use different neural mechanisms to solve the fMRI task. In very preterm born children, regression analyses revealed no relation between working memory activation and age. fMRI task accuracy was positively associated with working memory activation in bilateral parietal regions in very preterm born children. This relationship between fMRI task accuracy and working memory activation was also found in typically developing teenagers (Nagel et al., 2005) supporting the notion that higher activation in parietal lobes reflects increased storage capacity of visuospatial information (Edin et al., 2007, 2009; Macoveanu et al., 2006).

Analyzing separately the low and high fMRI task performers in the very preterm born group we found that low performers in the very preterm born group showed only a small frontal activation cluster while high performers showed activations which were similar to the working memory network of the total group of term born controls. However, closer inspection revealed that high performers were older than low performers in the very preterm born group. It is possible that the younger, low-performing very preterm born children cannot engage the same widespread network seen in controls, because they are still in the process of functional organization of working memory, leading to different network characteristics (Olesen et al., 2003). The delayed ongoing maturation of the frontal lobes as a consequence of premature birth could be one reason for alterations in neurofunctional development (Diamond, 2002; Giedd et al., 1999; Nosarti et al., 2008). However, the fact that our sample represents a relatively healthy subgroup of preterm children might contribute to a catch-up of functional development (such as suggested in Luu et al., 2011) rather than presenting persistent functional alterations.

Taken together, our results suggest a shift from an atypical neural organization toward the typical functional working memory network in very preterm born children

between the ages of 7 and 12 years. This is in line with behavioral data of executive functions previously published using the same study sample. These data indicate a catch-up rather than an ongoing deficit in three of the core executive functions (shifting, working memory and inhibition) in very preterm born children between the ages of 8 and 12 years (Ritter et al., 2013).

It can therefore be concluded that although the younger and lower performing very preterm born children show signs of less neural efficiency, this pattern does not seem to be persistent. To the contrary, with increasing age and performance, compensational mechanisms seem to occur, so that the typical organization of visuospatial working memory is reached by the age of 12 years in very preterm born children.

#### 4.4. Limitations

The choice of an fMRI control task (baseline condition), has important effects on the results and their interpretation. The aim of a baseline condition is to subtract functional activity common to both task conditions, in order to obtain only activity related to the condition of interest. Differences in group performance in the baseline condition can erroneously result in the assumption of group differences in the experimental conditions ("Task B" problem, see Church et al., 2010). Although accuracy rates and working memory activation in our study did not differ between groups in the baseline condition, there is still a certain probability that the baseline condition does not control for all factors of interest. Further, it has been shown that in resting-state fMRI, preterm born infants display greater variability in fMRI signal than their term born peers (Smyser et al., 2010). Consequently we cannot rule out the possibility that variance in the fMRI signal during the baseline task is higher in our very preterm group than in the control group. The inclusion of a low-level baseline task, in which participants are scanned during rest or a simple fixation task would be helpful in future studies to control for this confounding factor.

Where family wise error correction was not possible due to small group size, significance was assumed at a conservative threshold of  $p < .005$ . Still, particularly when dealing with brain data (over a million voxels per brain), a correction for multiple comparisons is inevitable. Future studies therefore require larger sample sizes to provide adequate power allowing for the correction for multiple comparisons. Another promising method to analyze brain data is permutation-based testing, which would be particularly interesting when non-normally distributed data are given (Nichols and Holmes, 2002).

As mentioned earlier, we included a relatively healthy preterm sample from moderate to high socioeconomic background. The compensation of possible functional deficits can therefore not be generalized to the total of very preterm born children with more severe neonatal complications, who have been shown to have more serious consequences on neural structural and functional outcome (Luu et al., 2011; Nosarti et al., 2008).

#### 4.5. Conclusion

The present study identified the visuospatial working memory network in very preterm born children as a fronto-parietal network with bilateral superior parietal and superior frontal core regions. While very preterm born children and term born controls showed equal working memory performance, group activation maps presented less involvement of the right middle frontal gyrus but higher fMRI activation in frontal regions (as indicated by PSC) in very preterm born children. In detail, our data show that in the preterm group, younger and low-performing preterm children presented an atypical working memory network whereas the older high-performers recruited a working memory network similar to the controls. These findings suggest that younger low-performing very preterm children demonstrate signs of less neural efficiency in frontal brain areas during a visuospatial working memory task. However, with increasing age and performance, compensational mechanisms seem to occur, so that in preterm born children, the typical visuospatial working memory network is established by the age of 12 years.

#### Conflict of interest statement

None of the authors have any conflicts of interest to declare.

#### Acknowledgements

The authors thank Marko Wilke for his assistance with the data analysis and the reviewers for their helpful comments. We gratefully acknowledge the contributions of all children and their parents. This work was funded by project grants and fellowships from the Swiss Science Foundation (PZ00P1\_126309, IZKOZ1\_137130/1 and PZ00P1\_143173).

#### References

- Anderson, P., Doyle, L.W., 2003. *Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990*. *JAMA* 289, 3264–3272.
- Andersson, J., Hutton, C., Ashburner, J., Turner, R., Friston, K., 2001. *Modeling geometric deformations in EPI time series*. *Neuroimage* 13, 903–919.
- Baddeley, A., 1986. *Working Memory*. Oxford University Press, Oxford.
- Badgaiyan, R.D., Posner, M.I., 1998. *Mapping the cingulate cortex in response selection and monitoring*. *Neuroimage* 7, 255–260.
- Carter, C.S., van Veen, V., 2007. *Cingulate cortex and conflict detection: an update of theory and data*. *Cogn. Affect. Behav. Neurosci.* 7, 367–379.
- Church, J.A., Petersen, S.E., Schlaggar, B.L., 2010. *The task B problem and other considerations in developmental functional neuroimaging*. *Hum. Brain Mapp.* 31, 852–862.
- Ciesielski, K., Lesnik, P., Savoy, R., Grant, E., Ahlfors, S., 2006. *Developmental neural networks in children performing a categorical N-back task*. *Neuroimage* 2, 980–990.
- Crawford, J.R., Anderson, V., Rankin, P.M., MacDonald, J., 2010. *An index-based short-form of the WISC-IV with accompanying analysis of the reliability and abnormality of differences*. *Br. J. Clin. Psychol.* 49, 235–258.
- Crone, E.A., Wendelken, C., Donohue, S., van Leijenhorst, L., Bunge, S.A., 2006. *Neurocognitive development of the ability to manipulate information in working memory*. *Proc. Natl. Acad. Sci. U.S.A.* 103, 9315–9320.
- Diamond, A., 2002. *Normal development of the prefrontal cortex from birth to young adulthood: cognitive functions, anatomy, and biochemistry*. In: Stuss, D.T., Knight, R.T. (Eds.), *Principles of Frontal Lobe Function*. Oxford University Press, New York, pp. 466–503.
- Edin, F., Klingberg, T., Johansson, P., McNab, F., Tegner, J., Compte, A., 2009. *Mechanism for top-down control of working memory capacity*. *Proc. Natl. Acad. Sci. U.S.A.* 106, 6802–6807.
- Edin, F., Klingberg, T., Stodberg, T., Tegner, J., 2007. *Fronto-parietal connection asymmetry regulates working memory distractibility*. *J. Integr. Neurosci.* 6, 567–597.
- Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. *Brain development during childhood and adolescence: a longitudinal MRI study*. *Nat. Neurosci.* 2, 861–863.
- Jolles, D.D., van Buchem, M.A., Rombouts, S.A.R.B., Crone, E.A., 2012. *Practice effects in the developing brain: a pilot study*. *Dev. Cogn. Neurosci.* 25, 180–191.
- Kelly, A.M., Garavan, H., 2005. *Human functional neuroimaging of brain changes associated with practice*. *Cereb. Cortex* 15, 1089–1102.
- Klingberg, T., 2006. *Development of a superior frontal-intraparietal network for visuo-spatial working memory*. *Neuropsychologia* 44, 2171–2177.
- Klingberg, T., Forssberg, H., Westerberg, H., 2002. *Increased brain activation in frontal and parietal cortex underlies the development of visuo-spatial working memory capacity during childhood*. *J. Cogn. Neurosci.* 14, 1–10.
- Kwon, H., Reiss, A., Menon, V., 2002. *Neural basis of protracted developmental changes in visuo-spatial working memory*. *Proc. Natl. Acad. Sci. U.S.A.* 99, 13336–13341.
- Lepach, A., Petermann, F., 2007. *Memory and Learning Test battery for Children (MLT-C)*. Huber, Bern.
- Leung, H.-C., Gore, J.C., Goldman-Rakic, P.S., 2002. *Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda*. *J. Cogn. Neurosci.* 14, 659–671.
- Luu, T.M., Vohr, B.R., Allan, W., Schneider, K.C., Ment, L.R., 2011. *Evidence for catch-up in cognition in and receptive vocabulary among adolescents born very preterm*. *Pediatrics* 128, 313–322.
- Macoveanu, J., Klingberg, T., Tegner, J., 2006. *A biophysical model of multiple-item working memory: a computational and neuroimaging study*. *Neuroscience* 141, 1611–1618.
- Nagel, B., Barlett, V., Schweinsburg, A., Tapert, S., 2005. *Neuropsychological predictors of BOLD response during a spatial working memory task in adolescents: what can performance tell us about fMRI response patterns*. *J. Clin. Exp. Neuropsychol.* 27, 823–839.
- Nichols, T.E., Holmes, A.P., 2002. *Non-parametric permutation tests for functional neuroimaging: a primer with examples*. *Hum. Brain Mapp.* 15, 1–25.
- Nosarti, C., Giouroukou, E., Healy, E., Rifkin, L., Walshe, M., Reichenberg, A., Chitnis, X., Williams, S.C.R., Murray, R.M., 2008. *Grey and white matter distribution in very preterm born adolescents mediates neurodevelopmental outcome*. *Brain* 131, 205–217.
- Olesen, P., Nagy, Z., Westerberg, H., Klingberg, T., 2003. *Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network*. *Brain Res. Cogn. Brain Res.* 18, 48–57.
- Olesen, P., Macoveanu, J., Tegner, J., Klingberg, T., 2007. *Brain activity related to working memory and distraction in children and adults*. *Cereb. Cortex* 17, 1047–1054.
- Parker, J., Mitchell, A., Kalpakidou, A., Walshe, M., Jung, H.-Y., Nosarti, C., Santosh, P., Rifkin, L., Wyatt, J., Murray, R.M., Allin, M., 2008. *Cerebellar growth and behavioural neuropsychological outcome in preterm adolescents*. *Brain* 131, 1344–1351.
- Ritter, B.C., Nelle, M., Perrig, W., Steinlin, M., Everts, R., 2013. *Executive functions of children born very preterm – deficit or delay?* *Eur. J. Pediatr.* 172, 473–483.
- Scherf, K.S., Sweeney, J.A., Luna, B., 2006. *Brain basis of developmental change in visuospatial working memory*. *J. Cogn. Neurosci.* 18, 1045–1058.
- Schneiders, J.A., Opitz, B., Tang, H., Deng, Y., Xie, C., Li, H., Mecklinger, A., 2012. *The impact of auditory working memory training on the fronto-parietal working memory network*. *Front. Hum. Neurosci.* 6, 173.
- Smyser, C.D., Inder, T.E., Shimony, J.S., Hill, J.E., Degnan, A.J., Snyder, A.Z., Neil, J.J., 2010. *Longitudinal analysis of neural network development in preterm infants*. *Cereb. Cortex* 20, 2852–2862.
- Spencer-Smith, M., Ritter, B.C., Mürner-Lavanchy, I., El-Koussy, M., Steinlin, M., Everts, R., 2013. *Age, sex and performance influence the visuospatial working memory network in childhood*. *Dev. Neuropsychol.* 38, 236–255.
- Taylor, M.J., Donner, E.J., Pang, E.W., 2011. *fMRI and MEG in the study of typical and atypical cognitive development*. *Neurophysiol. Clin.* 42, 19–25.

- Thomason, M., Race, E., Burrows, B., Whitfield-Gabrieli, S., Glover, G., Gabrieli, J., 2009. Development of spatial and verbal working memory capacity in the human brain. *J. Cogn. Neurosci.* 21, 316–332.
- Vicari, S., Caravale, B., Carlesimo, G.A., Casadei, A.M., Allemand, F., 2004. Spatial working memory deficits in children at ages 3–4 who were low birth weight, preterm infants. *J. Neuropsychol.* 18, 673–678.
- Wager, T., Smith, E., 2003. Neuroimaging studies of working memory: a meta-analysis. *Cogn. Affect. Behav. Neurosci.* 3, 255–274.
- Wilke, M., Holland, S., Altabe, M., Gasser, C., 2008. Template-O-Matic: a toolbox for creating customized pediatric templates. *Neuroimage* 41, 903–913.
- Woodward, L.J., Edgin, J.O., Thompson, D., Inder, T.E., 2005. Object working memory deficits predicted by early brain injury and development in the preterm infant. *Brain* 128, 2578–2587.