

Processing of Intentional and Automatic Number Magnitudes in Children Born Prematurely: Evidence From fMRI

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This study examined the neural correlates of intentional and automatic number processing (indexed by number comparison and physical Stroop task, respectively) in 6- and 7-year-old children born prematurely. Behavioral results revealed significant numerical distance and size congruity effects. Imaging results disclosed (1) largely overlapping fronto-parietal activation for intentional and automatic number processing, (2) a frontal to parietal shift of activation upon considering the risk factors gestational age and birth weight, and (3) a task-specific link between math proficiency and functional magnetic resonance imaging (fMRI) signal within distinct regions of the parietal lobes—indicating commonalities but also specificities of intentional and automatic number processing.

The aim of the present study was to investigate the neural correlates of intentional and automatic magnitude processing in 6- and 7-year-old children born prematurely. Even in the absence of neurological complications prematurity puts affected children at high risk of developing learning disabilities with severe mathematical learning difficulties affecting up to 50% of children born prematurely (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Aylward, 2005; Colvin, McGuire, & Fowlie, 2004; Saigal et al., 2003). Furthermore, beyond exerting negative effects on brain development in general (Aylward, 2005; Peterson, 2003), premature birth was found to be associated with structural brain abnormalities predominantly manifesting as reduced volumes of grey matter in parietal and sensorimotor areas (Hüppi et al., 1998; Inder, Warfield, Wang, Hüppi, & Volpe, 2005; Peterson, 2003). As regards the neural basis of calculation difficulties associated with preterm birth Isaacs, Edmonds, Lucas, and Gadian (2001) observed reduced grey matter density in parietal brain regions on the left hemisphere associated with number processing.

Upon considering the high incidence rates of mathematics learning difficulties in children born prematurely and our limited understanding of the neurofunctional underpinnings of academic difficulties in this population, it is somewhat surprising that there are so few studies systematically investigating the neural correlates of number processing in children born prematurely. The present study aimed to fill this gap by identifying the neural underpinnings of both, the processing of numerical and physical magnitudes (tapping intentional and automatic number processing, respectively) in a carefully selected group of neurologically unimpaired 6- and 7-year-old children born prematurely with influences of gestational age, birth weight, estimated intelligence (general cognitive abilities), and math proficiency considered.

In the following, we will first give a brief overview on the neural correlates of number processing in the developing brain before describing the rationale for the tasks used in the current study and specifying our hypotheses.

NEUROFUNCTIONAL CORRELATES OF NUMBER MAGNITUDE PROCESSING IN THE DEVELOPING BRAIN

Converging evidence from studies with *adult* participants associates the processing of numerical information with the parietal cortices (Dehaene, Piazza, Pinel, & Cohen, 2003, for a review). In particular, the bilateral (horizontal segment of the) intraparietal sulcus (IPS) is assumed to subservise the processing of number magnitude information, while posterior and superior parts of the parietal lobe bilaterally (PSPL) are associated with attentional shifts along the mental number line. Additionally, the left angular gyrus (AG) is thought to be critically involved in verbally

mediated aspects of number processing such as counting but also overlearned arithmetical (multiplication) fact retrieval.

With respect to *developmental* studies, the link between the IPS and number magnitude processing was observed repeatedly employing functional (e.g., Ansari & Dhital, 2006; Cantlon, Brannon, Carter, & Pelphey, 2006; Cantlon et al., 2009; Kaufmann et al., 2006; Kaufmann, Vogel, et al., 2009; Kucian, von Aster, Loenneker, Dietrich, & Martin, 2008; Kucian et al., 2006) and structural brain imaging (e.g., Isaacs et al., 2001; Rotzer et al., 2008; Rykhlevskaia, Uddin, Kondos, & Menon, 2009). Notably, the findings of a recent meta-analysis of developmental functional magnetic resonance imaging (fMRI) studies by Kaufmann, Wood, Rubinsten, and Henik (2011) disclosed that activation patterns are reliably influenced by age and math proficiency. With respect to math proficiency, significant activation differences were found in both directions: On the one side, compared with less proficient children more proficient ones exhibited stronger activations in left parietal regions including the precuneus and the IPS as well as in frontal regions bilaterally (left paracentral frontal lobe (BA 6), left superior frontal gyrus (BA 10), and right middle frontal gyrus (BA 9)). On the other hand, children with dyscalculia were found to recruit the left postcentral gyrus as well as the bilateral supramarginal gyrus (BA 40) more strongly (in the right hemisphere closely neighboring the anterior IPS, in the left adjacent to the lateral IPS).

As regards age, the findings of Kaufmann et al. (2011) revealed a fronto-parietal activation shift, both on the whole brain level but also within number-related (intra)parietal regions. In particular, results of the latter meta-analysis disclosed that with increasing age there is a shift of activation from frontal number-unspecific cortex sites to (intra)parietal regions specifically associated with the processing of numerical information (see also Rivera, Reiss, Eckert, & Menon, 2005). The authors suggest that with increasing age number processing becomes more specific, meaning that activation patterns elicited by numerical tasks get more and more focused on (intra)parietal areas whereas activations in primary frontal areas associated with domain-general processes such as working memory or executive functions decrease (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon et al., 2006, 2009; Kaufmann et al., 2006; Kucian et al., 2008). Moreover, the meta-analysis revealed that even within (intra)parietal areas activations observed in adults were located more posterior than those of children reflecting increasing functional specialization of the parietal cortex for number processing. Finally, recent findings further extended these results on grey matter activation locations by indicating considerable age- and competence-dependent modulations of neural white matter connectivity (e.g., Rosenberg-Lee, Barth, & Menon, 2011).

NUMBER COMPARISON TASKS AS AN INDEX FOR SEMANTIC NUMBER KNOWLEDGE

So far, the majority of developmental fMRI studies investigating number processing employed magnitude comparison tasks requiring participants to make smaller/larger decisions based on the magnitude of presented numbers (cf. Kaufmann et al., 2011). Interestingly, there are two versions of the magnitude comparison task allowing to either investigate the *intentional processing of number magnitude* or the *automatic processing of number magnitudes*.

In the first variant, numbers have to be compared with respect to their numerical magnitude (e.g., whether 7 is smaller or larger than 5). In such number comparison tasks the so-called

numerical distance effect (NDE, reflecting a negative correlation between response time and numerical distance of the to-be-compared numbers, e.g., Moyer & Landauer, 1967) indicates the intentional recruitment of number magnitude information because it is task relevant. The NDE was replicated frequently in children and adults alike (e.g., Holloway & Ansari, 2008). Importantly, these number comparison tasks have been frequently employed in brain imaging studies because the NDE reliably modulates number-relevant (intra)parietal activation (e.g., Pineda, Dehaene, Rivière, & LeBihan, 2001; see Kaufmann et al., 2011 for a meta-analysis of developmental fMRI studies).

In the second variant, the so-called physical Stroop task, participants have to compare the physical magnitudes of the presented numbers (i.e., their font-size). Importantly, number magnitude information is irrelevant in this task. However, as indicated by the size congruity effect (SCE, Henik & Tzelgov, 1982) reaction times are slower and error rates higher whenever physical (i.e., font-size) and numerical magnitude information lead to opposing response biases (e.g., 5 < 3). The presence of a SCE is thought to index automatic processing of number magnitudes because numerical magnitude is task-irrelevant. Please note that in typically developing children the SCE seems to emerge during the course of the first school year when number magnitude representations become established and easily accessible (Rubinsten, Henik, Berger, & Shahar-Shalev, 2002). Importantly, fMRI studies investigating the activation patterns elicited by the SCE report (intra)parietal activations in regions overlapping with those observed for number magnitude comparison and the NDE (children and adults: Wood, Ischebeck, Koppelstaetter, Gotwald, & Kaufmann, 2009; adults: Cohen Kadosh et al., 2007; Cohen Kadosh, Bien & Sack, 2012; Kaufmann et al., 2005; but see Kaufmann et al., 2006). Furthermore, it is important to note that recent behavioral findings in children suggest that intentional and automatic number magnitude processing may be dissociable from each other (children without developmental dyscalculia [DD]: Bugden & Ansari, 2011; children with DD: Landerl & Kölle, 2009).

STUDY RATIONALE AND WORKING HYPOTHESES

As (mathematics) learning difficulties are frequently associated with premature birth, school-age children born prematurely are an interesting population to evaluate functional activity in brain regions assumed to subservise the processing of (number) magnitude information. In particular, upon entering school children present with highly variable skill levels that are likely to persist when untreated (term-born children: Dowker, 2008; children born prematurely: Kiechl-Kohlendorfer, Ralser, Pupp Peglow, Pehboeck-Walser, & Fussenegger, 2013). Hence, the age group of 6- to 7-year-olds seemed to be an ideal study population for our research questions because our study was conceptualized as a within group design and targeted—among others—at evaluating interindividual differences in an at-risk population for developing mathematics difficulties (for a recent review on math difficulties in prematurely born children, see Simms, Cragg, Gilmore, Marlow, & Johnson, 2013). Therefore, the present study involved 6- and 7-year-old children born prematurely who had to solve two experimental tasks in the scanner assessing intentional (i.e., number magnitude comparison with NDE) and automatic processing of number magnitude information (i.e., physical Stroop task with SCE).

Additionally a control task was used to control for activation associated with visual-perceptual, decision-making, and response execution processes. Moreover, math proficiency as

well as gestational age, birth weight, and general cognitive abilities (estimated intelligence) were considered in the analyses to evaluate their respective influences on the neural correlates of intentional and automatic processing of number magnitudes. Birth weight and gestational age were entered as covariates because a recent meta-analysis disclosed significant positive associations between these and math achievement, among others (Aarnoudse-Moens et al., 2009).

In particular, our hypotheses were as follows.

Regarding behavioral performance we expected

- i. our group of prematurely born children to exhibit reliable effects of NDE and SCE. In addition, in both experimental tasks, math proficiency should correlate positively with accuracy and negatively with response latencies. Moreover, in line with Holloway and Ansari (2008, for the case of typically developing children) we expected a negative correlation between math proficiency and the NDE (as derived from the *number comparison task*). However, because number processing is task-irrelevant in the *physical Stroop task*, we did not expect the correlation between math proficiency and SCE to be significant.

With respect to the *fMRI data* we hypothesized that

- i. on a general level the neural correlates of intentional (number magnitude comparison) and automatic processing of number magnitude (physical Stroop task) should overlap considerably in the fronto-parietal network of number processing (Cohen Kadosh et al., 2007); if there is nevertheless any differentiation between intentional and automatic processing of number magnitudes it should be observed in cortex areas associated with math proficiency;
- ii. when evaluating the influence of estimated intelligence and math proficiency the two experimental tasks should be more demanding for children with lower estimated intelligence and poorer math proficiency resulting in increased activation of the entire fronto-parietal network of number processing;
- iii. finally, by specifically examining the influences of gestational age and birth weight we should observe an activation shift from frontal brain areas (associated with rather domain general processes) to parietal areas (more specifically associated with number processing) with increasing gestational age and higher birth weight— reflecting increasing developmental status.

METHODS

Study Group

Participants were 6- to 7-year-old right-handed formerly preterm children with a gestational age of <32 weeks. Children with neuropathological findings in the neonatal period (e.g., intracerebral hemorrhages, periventricular leucomalacia) and those with severe neurological and/or neuropsychiatric diseases requiring pharmacological treatment were not considered. Two children had a late (but none an early) onset sepsis, one child suffered from a necrotizing enterocolitis and five children required surfactant treatment for respiratory distress syndrome (however, none had a chronic lung disease). All participating children were from average to high socioeconomic status. As regards maternal data, five out of 15 mothers had an educational level <12 years,

three smoked during pregnancy, four had a premature rupture of membranes and all mothers received antenatal steroids. Moreover, none of the children included in the study were diagnosed with either reading disorder (RD), attention deficit hyperactivity disorder (ADHD), or any other developmental disorder. Out of 18 children initially tested, one had to be excluded because response accuracy in the physical Stroop task was just slightly above chance level, another one was not able to comply with the scanning procedure, and a third child had to be excluded because of an unexpected structural cerebral abnormality. Thus, the final sample comprised 15 children (11 females/4 males, including three pairs of identical twins) with 27.3 to 31.6 completed weeks of pregnancy, a mean age of 7.2 years (range 6.3 to 7.9 years) and a mean birth weight of 1,347 g (ranging from 830 to 1,880 g). While most children attended either first or second grade (first grade: $n = 7$, second grade: $n = 4$), four children were placed in preschool.¹ All participating children had average estimated intellectual abilities at time of testing. Written informed consent was obtained from parents and caretakers of participating children. The present study was approved by the local ethical committee.

Background Variables

General cognitive ability was estimated by utilizing four subtests (i.e., vocabulary, similarities, block design, picture completion) of the German-language version of the Wechsler Intelligence Scale for Children–4th Revision (HAWIK–IV; Petermann & Petermann, 2008).² The mean of the subtest standard scores ($M = 10$, $SD = 3$) across the four subtests served as dependent variable with the observed mean in our sample being 10.4 ($SD = 1.34$).

Number processing and calculation skills were assessed using the German version of the number processing and calculation test TEDI-MATH that provides normative data from kindergarten to third grade (Kaufmann, Nuerk, et al., 2009). In the present study, the total score of the TEDI-MATH was used for further analyses. As expected due to the premature birth of our sample, math proficiency scores varied considerably with total scores of the standardized calculation test TEDI-MATH (Kaufmann, Nuerk, et al., 2009) distributed evenly across the proficiency spectrum (exact percentile values being: 15, 22, 24, 27, 30, 30, 41, 41, 44, 45, 50, 62, 67, 67, 76, 96; $M = 46/SD = 22$).

Experimental tasks in the scanner. In the *physical Stroop paradigm* (modified after Kaufmann et al., 2005; see also Rubinsten et al., 2002) participants were shown two one-digit Arabic numerals that differed in numerical magnitude and font size. The numerical distance between the two to-be-compared numerals was either small (with a distance of 1, number pairs: 2–3, 3–4, 4–5, 6–7, 7–8) or large (with a distance of 4, number pairs: 2–6, 3–7, 4–8). Additionally, the font-size of the two to-be-compared digits was systematically manipulated (i.e., 55, 64 and 73 pixels) to create number pairs with either small (i.e., 9 pixels) or large (i.e., 18 pixels) font-size difference. Numerical and physical magnitudes were combined in a congruent and an incongruent condition.

¹The different grade placements are explained by the Austrian school system that (although in general stipulating school entrance by 6 years of age) allows delayed school starts for medical reasons, among others. As slight developmental delays regarding physical and/or socioemotional factors are frequently associated to prematurity, parents in Austria tend to allow their children an extra year in kindergarten (thus children may be already 7 years old when entering school).

²The WISC subtests vocabulary, similarities, picture completion and block design were used for intelligence estimation as these subtests have previously been reported to highly correlate with overall IQ (Sattler & Ryan, 2009).

In the congruent condition both the numerical and the physical comparison trigger the same decision (e.g., 2 > 6) whereas in the incongruent condition the numerical and the physical comparison yield opposing decision biases (i.e., 2 < 6). Children were asked to decide by button press whether the left or the right digit was physically larger irrespective of its numerical magnitude.

In the *number comparison task* children were again presented with two one-digit Arabic numerals (of the same physical size) and had to indicate by button-press which one of the two numbers was the numerically larger numeral. The number comparison task used the same stimuli as the physical Stroop task, except that this time the font size was held constant (i.e., 64 pixels). Thus, numerical distance between the two numerals was either small (i.e., 1) or large (i.e., 4).

Finally, a *visual identification task* served as control condition for influences of perceptual and response selection related activation. Children were presented with the non-meaningful and nonverbal symbol “ Φ ”. Afterward they had to indicate in a visual identification task (e.g., “ μ ” vs. “ Φ ”) on which side the symbol Φ appeared by pressing a corresponding button.

Experimental Setup

To ensure high signal power, tasks were presented in a box-car-design. Stimulus duration was 3,000 msec. A fixation cross was presented prior to each trial for 1,000 msec and between blocks (17,000 msec rest condition) to ensure recovery of the hemodynamic response. The physical Stroop task was always presented before the number comparison task to minimize potential transfer effects from number comparison which requires an explicit focus on number magnitudes. Each experimental task consisted of eight blocks with six trials each ($n = 48$ for both, the physical Stroop task and the number comparison task, making a total of $n = 96$ trials). The control task consisted of only four blocks with eight trials each (summing up to $n = 24$ trials). Within each block, the same task condition was presented (i.e., physical Stroop task: incongruent or congruent stimuli; number comparison task: small or large numerical distance). Within blocks stimuli were presented in randomized order. Right- and left-hand responses occurred equally often. Stimuli were projected on a screen outside the scanner. Participants could see the screen through a mirror fixed on the headcoil. The presentation software E-Prime (Schneider, Eschman, & Zuccolotto, 2002) was used for stimulus presentation and response collection. Before the actual fMRI session started, children were shown a short video clip to explain the scanning procedure and to familiarize children with the MRI device. To ensure task comprehension, children were asked to solve practice trials outside the scanner on a laptop. In both tasks, practice was terminated when children reached a response criterion of at least 80% correct trials. Instructions emphasized both response accuracy and speed.

fMRI Acquisition

Images were acquired with a 1.5 Tesla whole-body system (Siemens Magnetom Avanto). For the functional measurements a gradient-echo echo-planar (GE-EPI) sequence was used (TR = 2,300 msec, TE = 50 msec, flip angle = 90°, FOV = 220, 64 x 64 matrix, 24 axial slices, voxel size = 3.4 x 3.4 x 4 mm³). Each session comprised the acquisition of 370 functional images. For co-registration, a high resolution T1-weighted, 3-dimensional iso-voxel volume (voxel size = 1 x 1 x 1 mm³, TR = 1,800 msec, TE = 2.92 msec, 265 x 265 matrix) was acquired.

Data Analyses

Behavioral results comprised both response times (RT) and error rates (ER). Analyses of RT were based on trials followed by a correct response only. A subsequent trimming procedure eliminated all trials for which RT fell outside the interval $\pm 2 SD$ around a participant's mean RT. One participant was excluded from further analyses because of an ER exceeding 35% in at least one task condition. Because RT variability was considerable in our participant group, we chose to compute relative RT differences whenever calculating specific RT effects such as the SCE for the physical magnitude comparison task and the NDE for the number comparison task. These were calculated as follows: For each child, the mean RT difference between the two respective task conditions (physical Stroop task: incongruent minus congruent trials; number comparison task: small numerical distance minus large numerical distance) was divided by the individual's overall mean RT for the respective task.

Brain imaging data were analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). The anatomical scans were normalized to the population template generated from the T1 images of all children by using the implementation of a Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra (DARTEL) algorithm in SPM8. The fMRI time series was motion corrected and realigned to each participant's first image. fMRI data was then co-registered to the DARTEL population template and normalized into standard stereotaxic Montreal Neurological Institute (MNI) space. Images were resampled every 3.5 mm using 4th degree spline interpolation and smoothed with a 7 mm FWHM Gaussian kernel to accommodate inter-subject variation in brain anatomy and to increase signal to-noise ratio in the images. The data were high-pass filtered (128 s) to remove low-frequency signal drifts and corrected for autocorrelation assuming an AR(1) process. Brain activity was convolved over all experimental trials with the canonical hemodynamic response function (HRF) and its derivative.

On the second level, the main effects for physical and numerical magnitudes were evaluated in an ANCOVA with the within-participant factor condition (physical vs. numerical magnitude) and the covariates gestational age, birth weight, general cognitive ability (i.e., estimated intelligence), and math proficiency (i.e., TEDI-Math score). For anatomical localization of effects, the SPM Anatomy Toolbox (Eickhoff et al., 2005), available for all published cytoarchitectonic maps from http://www.fz-juelich.de/ime/spm_anatomy_toolbox, was used where applicable. In areas not yet implemented, the anatomical automatic labelling tool (AAL) in SPM8 (http://www.cyceron.fr/web/aal_anatomical_automatic_labeling.html) was used.

Activations were calculated at an uncorrected p -value of $<.001$ and a cluster size of $k = 10$ voxels at the voxel level and were reported when they remained significant following family-wise error correction (FWE) on cluster-level at $p_{\text{cluster-corr}} <.05$. Finally, beta weights were extracted at intraparietal brain regions.

RESULTS

Behavioral Results

Generally, children were significantly faster at making physical (1,063 msec) than numerical magnitude judgments [1,385 msec; $t(15) = 6.69, p <.001$]. Regarding overall mean accuracy participants performed near ceiling in both experimental tasks (physical Stroop: 9.1% errors, number

magnitude comparison: 10.8% errors) with the between-task difference not being significant [$t(15) = 0.82$, $p = .425$].

A more fine-grained analysis aimed at examining SCE and NDE. In the physical Stroop task, children were significantly slower and less accurate for incongruent (1,093 msec, 9.1% errors) compared with congruent trials (1,039 msec, 5.7% errors) indicating the presence of a SCE [RT: $t(15) = 2.14$, $p = .049$; ER: $t(15) = -3.57$, $p = .003$].

For the number comparison task, results revealed a highly significant NDE regarding both RT [$t(15) = -4.79$, $p < .001$] and errors [$t(15) = 4.86$, $p < .001$] indicating that children were significantly slower and less accurate for number pairs with a small distance (1,443 msec, 15.4% errors) as compared to pairs with a large distance (1,295 msec, 6.3% errors).

Additionally, a significant negative correlation was observed between SCE and NDE for RT [$r(14) = -.552$, $p = .033$] reflecting that participants with a higher SCE also exhibited a smaller NDE and vice versa.

Link Between Intentional and Automatic Number Processing and Math Proficiency

With respect to the *physical Stroop task*, neither the correlation between math proficiency and overall mean ER [$r(14) = -.24$, $p = .390$] nor the one with overall mean RT [$r(14) = -.17$, $p = .554$] was significant.

A somewhat different picture emerged regarding the *number comparison task*. While the correlation between math proficiency and overall mean ER was not significant [$r(14) = .34$, $p = .210$], a significant negative correlation emerged between math proficiency and overall mean RT [$r(14) = -.67$, $p = .007$]. In line with our expectation children with poor math performance were significantly slower upon making numerical classifications than were their more proficient peers.

Finally, math proficiency was neither correlated significantly with the SCE [RT: $r(14) = .32$, $p = .249$; ER: $r(14) = -.25$, $p = .372$] nor with the NDE [RT: $r(14) = -.08$, $p = .789$; ER: $r(14) = -.16$, $p = .579$].

fMRI Results

In the following we will first report the brain activation patterns associated with the experimental tasks (i.e., physical and numerical magnitude comparison) before describing the results of the analyses appraising the influence of the covariates reflecting either clinical (i.e., risk factors gestational age and birth weight) or cognitive background variables (i.e., general cognitive ability and math proficiency).

Brain Activation Patterns for Physical and Numerical Magnitude Comparison

The ANCOVA comprising the within-participant factors physical magnitude vs. fixation and numerical magnitude vs. fixation as well as the covariates gestational age, birth weight, estimated intelligence, and math proficiency (i.e., TEDI-MATH score) revealed a largely identical pattern of fronto-parietal activation for both main effects (see [Figure 1A](#) and [1B](#), [Table 1](#)). In particular, the IPS (Brodmann Area [BA] 7) was activated bilaterally. Further clusters of voxels jointly activated in both tasks versus fixation were found in the left supplementary motor area (BA 6) and in the bilateral middle frontal gyrus (BA 8, 9 and 10). In the physical Stroop task ([Figure 1A](#)), right precentral (BA 44) and right inferior frontal gyrus (BA 45) were activated additionally, while

in the number comparison task (Figure 1B) the left inferior frontal gyrus (BA 44) and the right insular cortex were found active. However, when comparing both conditions directly, no significant activation difference was observed. A conjunction across both experimental tasks confirmed that between-task similarities were considerably larger than were their differences (Figure 1C). The conjunction revealed bilateral activation of the IPS (BA 7) and the middle frontal gyrus (BA 9, 10, and 44), and activation in the left supplementary motor area (BA 6) and the right precentral gyrus (BA 44).

Effects of Prematurity Risk Factors on Brain Activation Patterns

Gestational age. Lower gestational age at birth was associated with activation of the left inferior frontal gyrus (BA 44) as well as the right inferior frontal gyrus (BA 45, both depicted in

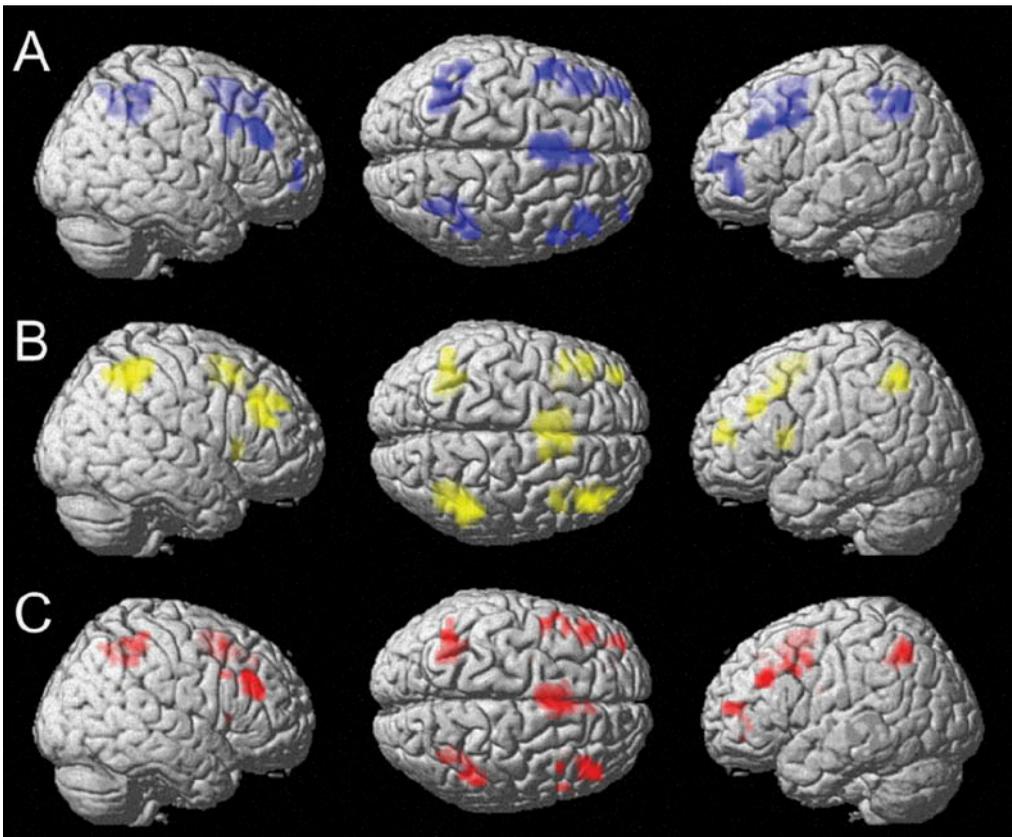


FIGURE 1 Panel A (blue) shows activation in the physical Stroop task, while Panel B (yellow) depicts cortical areas associated with the processing of the number processing task. As can be seen, the fronto-parietal areas observed were nearly identical. Only in the number comparison task, additional activation in the inferior frontal gyrus is observed. Panel C depicts the conjunction over the two experimental tasks (given in red).

TABLE 1
Cortical Regions More Strongly Activated in the Physical/Numerical Magnitude Tasks Than in the Fixation Control Task as Well as the Conjunction of Both Contrasts

<i>Contrast</i>	<i>Brain region (BA)</i>	<i>MNI (x, y, z)</i>			<i>Cluster size</i>	<i>z score</i>
Physical stroop vs. fixation	LH intraparietal sulcus (BA 7, hIP3)	-29	-56	41	88	4.59
	RH intraparietal sulcus (BA 7, hIP2)	38	-46	41	67	3.92
	LH supplementary motor area (BA 6)	-5	14	52	129	5.03
	LH precentral gyrus (BA 44)	-54	14	38	43	4.67
	LH middle frontal gyrus (BA 9)	-43	32	31	40	4.51
	LH middle frontal gyrus (BA 10)	-36	53	13	50	4.47
	RH middle frontal gyrus (BA 10)	34	56	-5	10	3.83
	RH inferior frontal gyrus (BA 45)	45	35	24	72	4.67
Number comparison vs. fixation	RH intraparietal sulcus (BA 7, hIP2)	41	-53	52	137	4.79
	LH intraparietal sulcus (BA 7, hIP3)	-33	-53	45	81	4.30
	LH supplementary motor area (BA 6)	-5	14	52	158	4.69
	LH middle frontal gyrus (BA 10)	-36	53	13	24	4.79
	LH middle frontal gyrus (BA 9)	-43	32	34	44	4.56
	LH middle frontal gyrus (BA 8)	48	18	48	12	3.64
	RH middle frontal gyrus (BA 9)	41	32	34	84	4.47
	LH inferior frontal gyrus (BA 44)	-43	11	10	34	4.36
	RH insula	34	18	6	14	4.21
Conjunction PS and NC	LH intraparietal sulcus (BA 7, hIP3)	-33	-56	45	60	4.08
	RH intraparietal sulcus (BA 7, hIP2)	45	-42	45	39	3.73
	LH supplementary motor area (BA 6)	-5	14	52	85	4.69
	LH middle frontal gyrus (BA 10)	-36	53	13	14	4.47
	LH middle frontal gyrus (BA 9)	-43	32	31	27	4.35
	LH middle frontal gyrus (BA 44)	-50	18	41	10	3.39
	RH middle frontal gyrus (BA 9)	41	28	31	42	4.22
	LH precentral gyrus (BA 44)	-54	14	38	10	3.75

Note. FWE cluster-threshold corrected $p < .05$ ($k = 10$ voxels); BA = Brodmann Area; LH = left hemisphere; MNI = Montreal Neurological Institute coordinates; RH = right hemisphere.

green in Figure 2A and Table 2). In contrast, higher gestational age was associated with activation in bilateral parietal regions (shown in red, Figure 2A). In particular, left angular (BA 39) and supramarginal gyrus (BA 40) as well as bilateral precuneus (BA 31 and 7) activation was observed to be associated with higher gestational age. Further clusters of activated voxels were found in bilateral superior temporal gyri (BA 42), the left parahippocampal gyrus (BA 34) and the right cuneus (BA 19).

Birth weight. Lower birth weight was primarily associated with parietal activation comprising the left IPS (BA 7), bilateral angular gyrus (BA 39), bilateral precuneus (BA 7 and 19), bilateral postcentral gyrus (BA 3 and 1), as well as the left supplementary motor area (BA 6) and the left superior temporal gyrus (BA 22). Note that larger birth weight did not expose any suprathreshold clusters of activation.

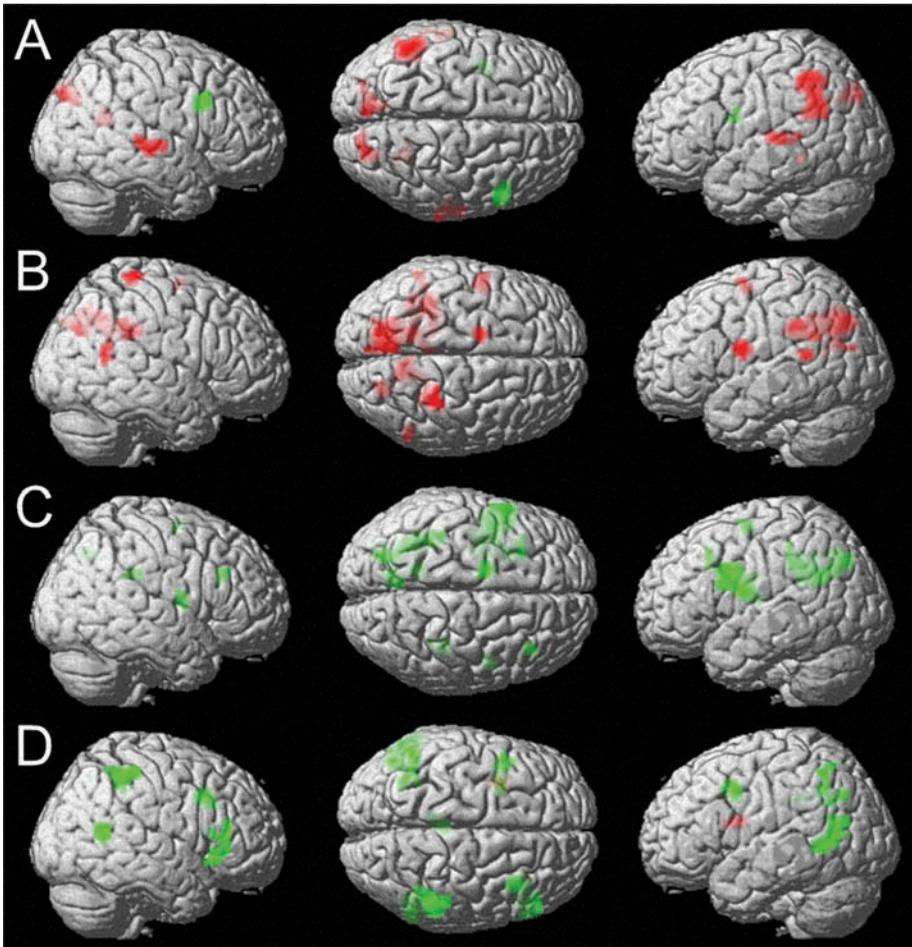


FIGURE 2 Panel A depicts activation associated with the covariate gestational age. While a lower gestational age was associated with bilateral inferior frontal activation (green), a larger gestational age was associated with predominant activation in bilateral parietal regions (red) as well as bilateral superior temporal areas. Panel B shows primarily extended parietal activation associated with a larger birth weight comprising left intraparietal sulcus (IPS), bilateral angular gyrus, precuneus, postcentral gyrus. Panel C depicts activation associated with lower general cognitive ability (as indexed by estimated intelligence). The picture is dominated by frontal activation in the supplementary motor area, bilateral inferior frontal and left middle frontal gyrus but also extends into parietal regions such as the IPS. Panel D depicts activation associated with math proficiency (as indexed by TEDI-MATH scores). While higher math proficiency was associated with left inferior frontal activation (red), lower math proficiency was found to activate the fronto-parietal network (green), including bilateral parietal regions, bilateral superior temporal areas, right inferior frontal and bilateral middle frontal cortices.

TABLE 2
Cortical Regions Associated With Either Smaller or Larger Values of the Covariates Gestational Age, Birth Weight, General Cognitive Abilities, and TEDI-MATH Scores

<i>Covariates</i>	<i>Brain region (BA)</i>	<i>MNI (x, y, z)</i>			<i>Cluster size</i>	<i>z score</i>
Gestational age: smaller	RH inferior frontal gyrus (BA 45)	48	14	27	30	3.61
	LH inferior frontal gyrus (BA 44)	-40	0	24	12	3.14
Gestational age: larger	LH angular gyrus (BA 39, PGa)	-47	-53	31	100	3.68
	LH supramarginal gyrus (BA 40, PF)	-54	-46	48	30	3.39
	RH precuneus (BA 31)	24	-53	24	19	3.48
	LH precuneus (BA 7)	-8	-81	38	35	3.12
	LH superior temporal gyrus (BA 42)	-64	-25	10	19	3.10
	RH superior temporal gyrus (BA 42)	62	-21	-1	35	3.94
	LH parahippocampal gyrus (BA 34)	-26	-42	-5	10	3.05
	RH cuneus (BA 19)	20	-84	38	22	3.20
Birth weight: larger	LH intraparietal sulcus (BA 7, hIP1)	-33	-39	34	40	3.61
	LH angular gyrus (BA 39, PGa)	-40	-53	31	11	2.89
	RH angular gyrus (BA 39, PGa)	55	-53	20	11	2.89
	LH precuneus (BA 7)	-8	-67	45	117	3.62
	RH precuneus (BA 19)	24	-74	31	11	3.27
	RH precuneus (BA 7)	6	-60	38	43	3.08
	LH postcentral gyrus (BA 3)	-50	-4	17	24	3.65
	RH postcentral gyrus (BA 1)	34	-35	69	14	3.46
	LH supplementary motor area (BA 6)	-15	-4	66	11	3.10
	LH superior temporal gyrus (BA 22)	-57	-49	13	10	3.10
GCA: smaller	LH intraparietal sulcus (BA 7, hIP1)	-36	-42	34	100	4.11
	LH precuneus (BA 7)	-8	-67	45	16	3.24
	LH supplementary motor area (BA 6)	-15	-4	66	17	3.82
	LH inferior frontal gyrus (BA 44)	-57	14	32	146	3.79
	LH middle frontal gyrus (BA 9)	-29	21	41	12	3.03
	RH rolandic operculum	52	0	10	11	3.13
	RH inferior frontal gyrus (BA 45)	38	25	27	10	3.11
TM scores: better	LH inferior frontal gyrus (BA 44)	-41	5	11	18	3.33
TM scores: worse	RH intraparietal sulcus (BA 7)	52	-35	55	42	3.32
	LH posterior superior lobule (BA 7)	-33	-63	59	11	3.02
	LH intraparietal sulcus (BA 7)	-36	-53	52	12	2.91
	LH supramarginal gyrus (BA 40, PFM)	-47	-53	52	14	3.01
	LH angular gyrus (BA 39, PGa)	-54	-56	41	12	2.97
	LH angular gyrus (BA 39, PGa)	-43	-67	38	12	2.98
	RH middle frontal gyrus (BA 9)	38	14	38	17	3.22
	LH middle frontal gyrus (BA 9)	-47	7	41	28	3.17
	RH inferior frontal gyrus (BA 45)	52	25	-5	39	3.07
	RH hippocampus	17	-14	-12	10	3.17
	RH middle temporal gyrus (BA 21)	52	-56	17	23	3.18
	LH middle temporal gyrus (BA 21)	-61	-56	3	71	4.14
	LH middle cingulate cortex (BA 31)	-5	-39	34	13	3.04

Note. FWE cluster-threshold corrected $p < .05$ ($k = 10$ voxels); BA = Brodmann Area; GCA = general cognitive abilities; LH = left hemisphere; MNI = Montreal Neurological Institute coordinates; RH = right hemisphere; TM = TEDI-MATH.

Association of Cognitive Background Variables With Brain Activation Patterns

General cognitive ability. Lower estimated intelligence was associated with frontal activation in the supplementary motor area (BA 6) and the bilateral inferior frontal (BA 44 and 45) and left middle frontal gyrus (BA 9 and 44). However, further clusters of activated voxels also extended into the left IPS (BA 7) and left precuneus (BA 7). On the other hand, higher estimated intelligence did not elicit suprathreshold activation.

TEDI-MATH scores. In order to evaluate the impact of math proficiency on neural response patterns, TEDI-MATH scores were entered as the last covariate. While a higher score (indicating higher math proficiency) was associated with left inferior frontal activation (BA 44, depicted in green in [Figure 2D](#)), a lower score activated nearly the entire fronto-parietal network (shown in red). In particular, the IPS (BA 7) was modulated bilaterally, while the left posterior superior parietal lobule (PSPL, BA 7) was also found active. Further activated clusters were found in the left supramarginal (BA 40) and angular gyrus (BA 39), the bilateral middle frontal gyrus (BA 9), right inferior frontal gyrus (BA 45), and hippocampus as well as the bilateral middle temporal gyrus (BA 21) and the left middle cingulate cortex (BA 31). Interestingly, when extracting corresponding beta weights from left PSPL ([Figure 3A](#)) and bilateral IPS ([Figure 3B](#)), a differential pattern of activation was observed for physical and number magnitude processing. In particular, while in left PSPL the physical Stroop task was associated with larger activation, the number comparison task led to a stronger activation in bilateral IPS (see also the bar charts below the activation figures for the case of the left IPS).

DISCUSSION

The present study aimed at investigating the neural correlates of intentional and automatic number processing in 6- and 7-year-old children born prematurely. Behavioral and imaging results revealed significant effects for both intentional and automatic number processing. Intentional and automatic number processing were associated with largely overlapping activation in the fronto-parietal network of number processing with no reliable differences in direct comparison. Interestingly, as regards activation changes due to the risk factors gestational age and birth weight we observed a shift from frontal to parietal activation with increasing gestational age and birth weight replicating recent findings that with development number processing related activation is more and more focused on parietal cortex areas (e.g., Kaufmann et al., 2011; Kucian et al., 2008; Rivera et al., 2005). For children with lower general cognitive abilities and/or lower math proficiency more distributed activation within the fronto-parietal network of number processing was found corroborating the assumption that the respective tasks were more cognitively demanding for these children. However, while behaviorally neither the NDE nor the SCE were significantly associated with math proficiency, a task-specific association between math proficiency and activation within distinct regions of the parietal cortex was observed. In the following we will discuss these findings in turn.

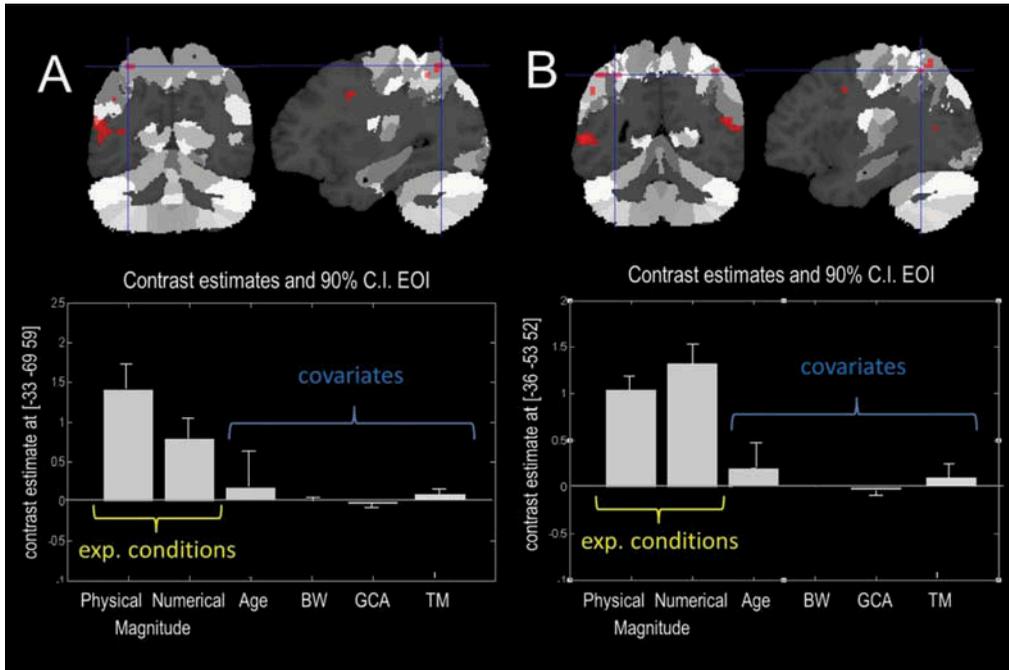


FIGURE 3 Panel A depicts the activation in the left superior parietal lobule on the cytoarchitectonic brain maps, while Panel B shows the activation center in the left intraparietal sulcus (IPS). The bar charts below the activation figures depict the corresponding beta estimates for the respective brain region. Note that differential effects can be found in these regions for physical and numerical magnitude processing: while the physical Stroop task elicited larger activation in the left superior parietal lobule, the number comparison task led to stronger activations of the IPS. *Note.* BW = birth weight; GCA = general cognitive abilities; TM = TEDI-MATH; EOI = effects of interest.

Size Congruity and Numerical Distance Effect

Our data revealed that 6- to 7-year-old children born prematurely expose well-established representations on number magnitude that can be accessed both intentionally (as indexed by the NDE) as well as automatically (as indicated by the SCE). Most notably, the significant SCE suggests that even young children being at high risk to develop math difficulties seem to activate number magnitude representations automatically. Moreover, the observed negative correlation between NDE and SCE regarding response latencies suggests that in our study group automatic activation of number magnitudes is associated with effortless intentional processing of number magnitudes (cf. Holloway & Ansari, 2008).

With the observation of a reliable SCE our findings add to the so far inconsistent results regarding the presence of a SCE in first graders. While Girelli, Lucangeli, and Butterworth (2000) as well as Landerl and Kölle (2009) failed to observe a SCE in first graders, Bugden and Ansari

(2011) found a reliable SCE for the same age group (see also Rubinsten et al., 2002, for a reliable SCE at the end of grade one). Methodological differences between studies may provide an explanation of these discrepancies. While in our study the majority of participants were first- and second-grade students born prematurely, previous studies were targeted at typically developing children or children with DD (Landerl & Kölle, 2009) employing grade-wise data analyses. Moreover, compared with previous studies failing to find a SCE in first graders, we used smaller differences in physical size of the to-be-compared stimuli thus reducing the saliency of physical size (differences). This might have facilitated an automatic activation of number magnitudes as suggested by modelling of the SCE (Schwarz & Ischebeck, 2003).

Importantly, these behavioral findings suggesting intentional as well as automatic processing of number magnitude information in children born prematurely and known to have a high risk to develop math difficulties are further corroborated by our neuroimaging data. For both, intentional (in the number magnitude comparison task) and automatic processing of number magnitude (in the physical Stroop task) we observed activation of the fronto-parietal network of number processing (e.g., Arsalidou & Taylor, 2011; Dehaene et al., 2003). This strongly supports the assumption that the automatic activation of number magnitude information whenever one encounters a number is already established in 6- to 7-year-old former preterm children. Yet, the large overlap in fronto-parietal brain regions with the lack of significant activation differences between both tasks points to the fact that a difference between intentional and automatic number processing may not be apparent at this stage of development. Interestingly, activation of a fronto-parietal network of overlapping and neighbouring cortex regions for processing numerical (in the magnitude comparison task) and physical magnitudes (in the size congruity task) is very well in line with the literature suggesting a shared representation of numbers and space (e.g., Walsh, 2003; see also Hubbard, Piazza, Pinel, & Dehaene, 2005).

Results of the conjunction analysis disclosed overlapping areas in circumscribed parietal regions in the bilateral intraparietal cortex as well as frontal regions in the bilateral frontal dorso-lateral prefrontal cortex (DLPFC) and the supplementary motor area (SMA). Within the frontal cortex, DLPFC and SMA have repeatedly been suggested to play a supporting role for processes of numerical cognition including the retrieval of arithmetic facts of performing carry and borrowing procedures in mental arithmetic (e.g., Ansari, 2008; Kong et al., 2005). In particular, the DLPFC has been associated with working memory (Ashcraft & Kirk, 2001; Kazui, Kitigaki, & Mori, 2000; Menon et al., 2000), the resolution of interference and processes of response selection (e.g., Liu, Banich, Jacobson, & Tanabe, 2004), strategic organization (Rickard et al., 2000), and processes of cognitive control (e.g., Miller, 2000), representing and maintaining the attentional demands of the task at hand (for respective reviews, see Cabeza & Nyberg, 2000; MacDonald, Cohen, Stenger, & Carter, 2000).

The bilateral IPS has frequently been reported to be a key area for number magnitude processing in both adults (Arsalidou & Taylor, 2011; Dehaene et al., 2003) and children (Houdé, Rossi, Lubin, & Joliot, 2010; Kaufmann et al., 2011). Yet, beyond the processing of number magnitude the IPS also subserves the processing of non-numerical magnitudes and has also been suggested to be involved in other cognitive functions such as attention and visual-spatial skills, among others (attention and episodic memory: Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; spatial processing: Cohen Kadosh, Lammertyn, & Izard, 2008; Hubbard et al., 2005). Hence, our results revealing joint activations in response to numerical and physical magnitude processing in bilateral IPS extend previous respective findings in adults by showing that also in 6- to

7-year-old children born prematurely, magnitude processing is subserved by (intra)parietal brain regions. Altogether, results of the conjunction analysis are consistent with previous findings in adults by indicating a shared network of fronto-parietal brain regions being engaged in numerical and physical magnitude processing alike (e.g., Cohen Kadosh et al., 2012).

In the remainder of this article we will first discuss the association of cognitive background variables (i.e., general cognitive ability and math proficiency) with brain activation patterns in children born prematurely before evaluating the influence of prematurity (i.e., risk factors gestational age and birth weight) on brain activation pattern.

Neural Correlates of Higher Cognitive Functions in Children Born Prematurely

The evaluation of the influence of general cognitive abilities and math proficiency revealed a similar pattern for both variables: the lower general cognitive abilities or math proficiency, the more pronounced and distributed activation of the fronto-parietal network of number processing we observed. This is in line with our hypothesis that the two experimental tasks should be more demanding for children with lower estimated intelligence and poorer math proficiency, which then results in the stronger activation observed. In particular, bilateral IPS, PSPL, SMA, DLPFC, and temporal areas were activated more strongly if cognitive ability and/or math proficiency were low. Interestingly, with poorer math proficiency we also observed stronger activation in the left angular gyrus and the right hippocampus. This combination of brain areas additionally indicates higher efforts in trying to retrieve (arithmetic) facts from long-term memory (e.g., Klein, Moeller, Glauche, Weiller, & Willmes, 2013; see Montaldi & Mayes, 2010; Rugg & Yonelinas, 2003 for reviews).

Association of Math Proficiency With Intentional and Automatic Number Magnitude Processing

In contrast to our hypothesis that access to mental number representations (even if these are task-irrelevant as in the physical Stroop task) may be modulated by math proficiency, the correlation between math proficiency and RT and/or ER *physical Stroop task* was not significant. This finding suggests that upon solving the physical Stroop task, math proficiency may be less important because number magnitude processing is not relevant to the task at hand. This is in line with the results of a recent study by Heine et al. (2010, see also Bugden & Ansari, 2011) who also observed no influence of math proficiency on the SCE as well as overall RT and ER for children of comparable math proficiency as our group. Nevertheless, for children with DD differences to normally achieving children were observed with regard to both RT as well as the SCE in the physical Stroop task (Heine et al., 2010; Landerl & Kölle, 2009).

A somewhat different picture emerged for the *number comparison task*. In line with our expectation (and Heine et al., 2010) children with poorer math performance were significantly slower upon making numerical classifications than were their more proficient peers. On the contrary, the correlation between math proficiency and ER as well as NDE was not significant. This finding of a significant association between math proficiency and RT (but not the NDE) is only partially consistent with previous studies. At least in typically developing children the NDE is associated with actual math proficiency (e.g., Holloway & Ansari, 2009; Bugden & Ansari, 2011; Landerl &

Kölle, 2009; Mundy & Gilmore, 2009). Additionally, it may even be a reliable predictor of later math proficiency (DeSmedt, Verschaffel, & Ghesquière, 2009). A plausible explanation for the non-significant correlation between the NDE and math proficiency may be that previous studies were targeted at typically developing children, while our participants were born prematurely and as such an at-risk-group to develop math difficulties (even though none of them actually fulfilled the required criteria). Additionally, our participants aged 6 and 7 were slightly younger than children examined previously with four out of 15 participating children still attending preschool at the time of testing and thus, did not receive formal math education yet.

Most importantly, when evaluating the impact of math proficiency at the neural level we found an activation of the typical fronto-parietal network of number processing comprising bilateral activation of the IPS. Closer inspection of the left IPS, a core region in numerical and non-numerical magnitude processing (e.g., Cohen Kadosh et al., 2005; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003, for review see Cohen Kadosh et al., 2008) indicates a differential pattern of activation within different parts of the left IPS for numerical and physical magnitude was identified. In particular, low math proficiency was associated with reliably more pronounced activation in the bilateral horizontal IPS when processing numerical magnitude. In contrast, activation in the left superior parietal lobule was stronger in physical than in numerical magnitude processing. Thus, the present results extend the behavioral findings reported by Bugden and Ansari (2011) who found that intentional—but not automatic—number processing was modulated by children's math proficiency. Thereby, these neuroimaging data further corroborate the differential development of intentional and automatic number processing. Further studies that will examine other age groups would allow to examine whether such dissociation between different types of magnitudes at earlier developmental stage are an indicator of non-efficient magnitude systems, in line with current developmental models (Kucian & Kaufmann, 2009).

Influences of Prematurity on Brain Activation Patterns

Interestingly, parametric evaluation of the influence of the risk factors indicated that lower gestational age was associated with increased frontal activation, whereas higher gestational age as well as birth weight were associated with increased parietal activation. Generally, this is well in line with the shift from frontal to more focused parietal activation observed with numerical development. It was proposed that this frontal to parietal shift reflects the establishment and focusing of processes of mental number processing within the dedicated parietal brain areas meaning that activation of frontal areas associated with more domain-general processes such as working memory (see Kaufmann et al., 2011; also see Houdè et al., 2010). This fits nicely with the finding that lower gestational age was associated with larger activation in the inferior frontal gyrus, bilaterally, probably indicating higher demands on working memory (Weiller, Bormann, Saur, Musso, & Rijntjes, 2011) and/or the use of additional verbal strategies involving Broca's area (Dehaene, 1992). On the other hand, higher gestational age was associated with activation in temporal and parietal regions such as the left angular gyrus and supramarginal gyrus, bilateral precuneus, and bilateral superior temporal gyrus. Activation of both the angular as well as the supramarginal gyrus have been suggested to be associated with arithmetic fact retrieval (e.g., Dehaene et al., 2003; Delazer et al., 2003; Grabner et al., 2009). The additional activation in the left hippocampus—in particular, when synced with the activation of the angular gyrus—indicates

the recruitment of a network subserving (arithmetic) fact retrieval from long-term memory (Klein et al., 2013; see Montaldi & Mayes, 2010; Rugg & Yonelinas, 2003 for reviews the involvement of the hippocampus in memory).

Importantly, from a methodological point of view the present findings also indicate that a within-group approach with careful consideration and evaluation of the influences of specific variables of interest (e.g., risk factors but also math proficiency) is capable to replicate and extend findings, which have so far been typically investigated by comparing different participant groups or would be expected in longitudinal approaches. In numerical cognition research most studies investigating the neural correlates of numerical development focused on differences between developing and mature brain systems (e.g., Ansari et al., 2005; Ansari & Dhital, 2006; Cantlon et al., 2009; Kaufmann et al., 2006, 2008; Kucian et al., 2008; Rivera et al., 2005). Only recently, there have been attempts to take a closer look at developmental changes on the neural level for smaller time intervals. For instance, Rosenberg-Lee et al. (2011) found that there are considerable age-dependent activation differences in number-relevant brain regions between 2nd and 3rd graders. A valid comparison of arithmetic skills between our study group and a random non-preterm population is given in so far as the arithmetic test was standardized and gives a percentile score that reflects performance compared to normal developing children. Therefore, we are confident that it is sensible to examine interindividual variability in a carefully selected at-risk population (without neurological, neuropsychiatric and/or neuropathological findings).

Taken together, our data not only replicated previous findings regarding a frontal to parietal shift of activation with numerical development using a within-participant design but also suggested that for children born prematurely the factors gestational age and birth weight might be important predictors for later patterns of specific brain activation and associated impairments in both intentional and automatic processing of number magnitude.

CONCLUSIONS

The results of the present study suggest reliable associations of higher cognitive functions with brain activation in children born prematurely. The lower general cognitive ability and math proficiency the more widespread are number-relevant fronto-parietal activations associated with intentional and automatic number magnitude processing. Additionally, decreasing math proficiency was associated with increased activation in the left inferior frontal cortex. Most importantly, however, we were able to pinpoint influences of prematurity on children's brain activation patterns to intentional and automatic number magnitude processing. In particular, our results disclosed reliable associations of the two clinical factors gestational age and birth weight with brain activation patterns: While increasing gestational age and birth weight were associated with more (intra)parietal activation, decreasing gestational age was related to more activation in frontal cortex areas. Overall, our findings are plausibly explained by an age-related general shift from frontal to parietal activation patterns on processing number magnitudes indicating more elaborate processing in typically developing children (Houdé et al., 2010; Kaufmann et al., 2011). On the other hand, our results are novel as we showed a similar association with gestational age and—to a lesser degree—with birth weight in prematurely born children known to be at risk to develop learning disabilities.

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