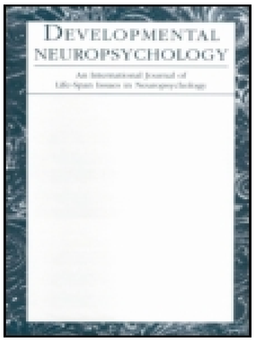

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Meta-Analyses of Developmental fMRI Studies Investigating Typical and Atypical Trajectories of Number Processing and Calculation

Liane Kaufmann

Institute of Applied Psychology, University for Health Sciences, Medical Informatics and Technology, Hall in Tyrol, Austria

Guilherme Wood

Department of Psychology, Karl-Franzens-University of Graz, Graz, Austria

Orly Rubinsten

Edmond J. Safra Brain Research Center for the Study of Learning Disabilities, Department of Learning Disabilities, University of Haifa, Haifa, Israel

Avishai Henik

Department of Psychology and Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer Sheva, Israel

The main aim of the present coordinate-based meta-analysis is to identify brain regions that are commonly activated in functional magnetic resonance imaging studies (fMRI) investigating number processing and calculation in children. Here, we include 19 developmental fMRI papers, five of which also examine children diagnosed with developmental dyscalculia and/or mathematical disability. Results reveal that children produce consistent fronto-parietal activation patterns in response to number processing and calculation. Importantly, activation patterns are clearly modulated by notation, task complexity, and competence level. Activation differences between children with and without dyscalculia are observable in number-relevant parietal regions as well as in (pre)frontal and occipital cortex.

Developmental functional magnetic resonance imaging (fMRI) studies in the numerical cognition field are scarce. At the time of data search for this article (April 15, 2010), few papers were published that report fMRI data on children's performance on number processing and calculation tasks (inclusion requirements are provided in the method's section). In contrast to this rather modest number of studies on the neural correlates of number processing and calculation in children, the neural correlates of adult numerical cognition are rather well described (for

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Correspondence should be addressed to Liane Kaufmann, University for Health Sciences, Medical Informatics and Technology, Institute of Applied Psychology, Eduard Wallnoefer Zentrum 1, A-6060 Hall in Tyrol, Austria. E-mail: liane.kaufmann@umit.at

respective overviews see e.g., Ansari, 2007; Dehaene, Molko, Cohen, & Wilson, 2004; Nieder, 2005). The large body of the literature by and large supports the adult-based anatomo-functional calculation model proposed by Dehaene, Piazza, Pinel, and Cohen (2003) postulating three distinct, but functionally interrelated neural networks supporting different components of number processing and calculation. First, mental representations of number magnitude (also referred to as "number sense") are thought to be subserved by intraparietal regions and more specifically, by the horizontal segment of the intraparietal sulcus (IPS; Dehaene et al., 2003). Nonetheless, it is important to note that the functional role of the IPS is not domain-specific. Rather, the IPS supports numerical and non-numerical information alike (attention and episodic memory: Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; spatial processing: Cohen Kadosh, Lammertyn, & Izard, 2008; Hubbard, Piazza, Pinel, & Dehaene, 2005; time and space: Walsh, 2003; processing of ordinal series: Fias, Lammertyn, Caessens, & Orban, 2007; Kaufmann, Vogel, Starke, Kremser, & Schocke, 2009a). A classical task tapping number magnitude knowledge is the number comparison task. Here, subjects have to classify the larger of two simultaneously presented one-digit numbers (e.g., 3 vs. 5). The numerical distance effect (NDE) denotes a negative correlation between numerical distance and reaction time and has been frequently employed to examine the integrity of the mental number line (for alternative views, see Verguts, Fias, & Stevens, 2005; Santens & Gevers, 2008). Importantly, according to Dehaene et al. (2003) the IPS processes numerical information in an abstract way. The latter notion is derived from findings revealing consistent and notation-independent IPS activation in response to number processing. Second, encoding and retrieval of arithmetic facts (e.g., $3 + 5$, 3×5) are supported by the left angular gyrus which is situated in the inferior parietal lobe and closely neighbors language-relevant regions. The anatomical vicinity to brain regions supporting language is not surprising upon acknowledging that in most Western cultures, arithmetic facts are acquired and retrieved phonologically. In skilled calculators, arithmetic fact knowledge is retrieved effortlessly and hence, does not require explicit calculation procedures. Recent evidence supports the notion that in skilled adults' overlearnt calculation is mediated by the left angular gyrus (Delazer et al., 2005; Ischebeck, Zamarian, Schocke, & Delazer, 2009; Grabner et al., 2007, 2009). Third, processing of written calculation depends on the integrity of occipital brain regions including the so-called visual word-form-area (VWFA; for a critical view on the functional specificity of the VWFA, see Price & Devlin, 2003). Research has shown that regions in and around the VWFA respond to Arabic digits and thus, it seems that the VWFA is not specific to written language (i.e., letter) processing, but may be sensitive to the processing of written symbols in general (McCandliss, Cohen, & Dehaene, 2003; but see for example Polk and colleagues (2002) who showed that this area, specifically near the left fusiform gyrus, is more involved in processing letters than digits).

Importantly, there is accumulating evidence from adult studies that (pre)frontal and subcortical brain regions also play important roles in number processing and calculation. For instance, Delazer and collaborators (2004) report a patient with basal ganglia calcification who demonstrated difficulties with number fact retrieval (that were not present prior to the onset of the neurological disease). Furthermore, frontal brain regions are known to be important for complex calculation (that draw on executive functions and working memory resources) but were also reported to be involved in simple number processing and calculation tasks (e.g., Dehaene et al., 2003; Piazza, Mechelli, Price, & Butterworth, 2006; for a respective overview see also Nieder, 2005).

STUDY RATIONALE

The aim of the present meta-analysis is to provide a systematic and statistically based overview of brain regions that are consistently activated in developmental fMRI studies investigating numerical cognition. Importantly, to date fMRI studies investigating number processing and calculation in children (with and without dyscalculia) are scarce and produce heterogeneous patterns of results. Moreover, many of these studies are not directly comparable because authors used different sets of stimuli, different instructions, tasks, and criteria for inclusion. Some used a non-symbolic number comparison task (Kaufmann et al., 2008; Kovas et al., 2009; Kucian et al., 2006; Price, Holloway, Räsänen, Vesterinen, & Ansari, 2007), while others asked participating children to compare Arabic numbers (Kaufmann et al., 2009b; Meintjes et al., 2010; Mussolin et al., 2010) or to process simple calculations (Davis et al., 2009a, 2009b; Kucian et al., 2006; Meintjes et al., 2010) or abacus calculations (Chen et al., 2006). Likewise, studies are not identical as regards definitional criteria for dyscalculia. While some studies employ the so-called discrepancy criterion for dyscalculia diagnosis (i.e., average intellectual abilities in the presence of subaverage arithmetic skills; American Psychiatric Association, 1994), others rely on arithmetic performance solely. Notably, quite different cutoff scores are currently used to define dyscalculia (sometimes also referred to as math learning disability; for a recent differentiation between dyscalculia and math learning disability, see Rubinsten & Henik, 2009), mainly depending on sensitivity and specificity issues. For instance, a generous cutoff of 30% means that children performing below the 30% quantile of the tested population will be tagged as math learning disabled, while upon using a more stringent cutoff criterion of 5% would exclude the majority of the very same children from the sample of math learning disability (thus being eligible to be included in the control group).

MAIN RESEARCH QUESTIONS AND WORKING HYPOTHESES

1. *Symbolic versus non-symbolic number magnitude processing in typically developing children*: According to Dehaene and co-workers (2003) numbers are represented in an abstract format and thus, the IPS ought to subserve number processing irrespective of notation (e.g., symbolic Arabic numerals, non-symbolic dot patterns). Although the majority of findings reported to date supports the hypothesis of abstract number representations in the IPS, it is important to note that the empirical evidence underlying this assumption rests on adult data (for a different view, again based on adult data, see Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007). Because findings derived from mature brain systems are not readily applicable to developing brain systems (Karmiloff-Smith, 1997; Kaufmann & Nuerk, 2005) it might be misleading to assume that also in children numbers are represented in an abstract format in the IPS. To the present no developmental studies are published that systematically investigate the question of notation-specificity in numerical cognition. Please note that Holloway and Ansari (2010) asked participating children and adults to solve both symbolic and non-symbolic number comparison tasks, but focused their analyses on (age-dependent)

common activation patterns across notation rather than investigating notation-dependent activation differences. Thus, our first research question is as follows: Are activations pertaining to symbolic and non-symbolic magnitude processing distinguishable in children? In case children's neural responses are sensitive to notation, activation patterns for symbolic and non-symbolic number processing should be distinct rather than overlapping. In young children intraparietal activation elicited by non-symbolic magnitudes might be more pronounced than that elicited by symbolic magnitudes because the access from symbolic processing to magnitude may still not be completely developed. Therefore, one can expect that non-symbolic magnitudes should activate the intraparietal cortex more consistently in children than symbolic magnitudes.

2. *Influence of age on non-symbolic number processing, comparison of typically developing children and adults*: How consistent are age-related parietal activation differences in response to non-symbolic number processing? Findings in the literature suggest that adults produce stronger parietal fMRI responses than children (Ansari & Dhital, 2006; Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon, Brannon, Carter, & Pelphrey, 2006; Cantlon et al., 2009; Holloway & Ansari, 2010; Kaufmann et al., 2006). Nonetheless, it remains to be tested whether reported activation foci in parietal regions overlap across the few studies published thus far. Moreover, children may recruit parietal brain regions that lie more anterior to parietal regions generally activated by adults (Kaufmann et al., 2008). Finally, children might need to recruit compensatory mechanisms (as reflected by additional frontal activations) in order to achieve comparable performance levels to adults (Ansari et al., 2005; Cantlon et al., 2009; Kaufmann et al., 2006; Kucian, von Aster, Loenneker, Dietrich, & Martin, 2008; Rivera, Reiss, Eckert, & Menon, 2005).
3. *Influence of math competency on number magnitude processing*: Which activation differences—within and outside the parietal lobes—are consistently found between children with good and poor calculation skills (dyscalculia)? Based on the scarce literature to date it can be hypothesized that dyscalculic children have a dysfunctional parietal number processing system (Kaufmann et al., 2009b; Kovas et al., 2009; Kucian et al., 2006; Mussolin et al., 2010; Price et al., 2007). However, findings are inconsistent as regards the exact localization of parietal dysfunction and moreover, are conflicting as to whether parietal activation differences are related to hypo- or hyperactivations.
4. *Neural correlates of calculation in children*: Which neural networks are consistently found to be activated by children upon performing simple calculations? Based on the literature we propose that children need to recruit distributed fronto-parietal networks to solve calculation tasks (Chen et al., 2006; Davis et al., 2009a; Kawashima et al., 2004; Kucian et al., 2006; Meintjes et al., 2010; Mussolin et al., 2010; Rivera et al., 2006). However, as studies are not directly comparable as regards experimental paradigms and methodologies employed the question remains which brain regions—within and outside the parietal lobes—are reported consistently across studies to be involved in simple calculation processes.

Although the above-stated questions have begun to be tackled in the literature, it remains obscure whether results of single studies are indeed reliable and stable. Employing a quantitative meta-analysis might help us to get a better overview of the results and furthermore, help us to better understand the meanings of the findings reported in these single studies. Activations obtained by the meta-analyses presented below denote regions that have been found to be significantly involved in the tasks of interest much more often than chance. Here, we use calculation procedures that involve coordinate-based activation likelihood estimation (ALE, Turkeltaub, Eden, Jones, & Zeffiro, 2002; for the updated version see Laird et al., 2005). We employ the version GingerALE (BrainMap®, see http://brainmap.org/index.html). A detailed description of the methodology underlying the GingerALE software will be provided in the Methods section.

METHODS

To identify relevant fMRI studies on both number magnitude comparison and calculation, we performed Medline searches with the keywords "number magnitude & children," "calculation & children," "dyscalculia," and "imaging." Criteria for the selection of fMRI studies were the following: (1) functional imaging data on at least one group of children should be provided in the study, (2) stimuli should be symbolic or non-symbolic magnitudes (i.e. dots, number of objects on the display), (3) tasks should be either magnitude comparison or calculation, and (4) studies reported the activation coordinates in a standard stereotaxic space (Talairach or MNI/Montreal Neurological Institute). All studies matching these criteria have been included in the present meta-analysis.

On the basis of the mentioned criteria, 19 fMRI studies were included in statistical analyses. Interestingly, the first published study dates back to 2005, the youngest being as recent as 2010. Fourteen of these studies provided information on number magnitude comparison (186 control children, 63 dyscalculics and 98 adults without dyscalculia) and seven provided data on calculation (126 control children, 18 dyscalculics and 18 adults without dyscalculia). Two studies were included in both meta-analyses (Kucian et al., 2006; Meintjes et al., 2010) since these studies examined magnitude processing and calculation. As it seems that in Kucian et al. (2008) the data set of children's fMRI responses to calculation is identical to the one reported in Kucian et al. (2006; which use an identical task and report an identical number of control children), we chose to enter only one data set reported by Kucian and collaborators (2006) into the meta-analysis on calculation. Data are current with April 15, 2010. We did not include a recent study from Kaufmann et al. (2009a) since the paradigm employed in this study slightly differs from the ones used in studies comprising the data pool for the present meta-analysis. Likewise, from the findings reported by Davis et al. (2009b) only data pertaining to control children were included into our study (i.e., meta-analysis IV) while data from dyscalculic children could not be included since in our meta-analysis III (targeted at examining the effects of math competency) all studies used a number comparison task rather than a calculation paradigm. The selected studies and their main characteristics are listed in Tables 1 and 2.

Four different meta-analyses were run. To guarantee statistical independence between the studies of the meta-analyses, one single contrast from each study was included in each meta-analysis. The meta-analyses used the peak coordinates of activation clusters identified by group comparisons or comparisons with a control task (see below the detailed description of contrasts entering each meta-analysis). In preparation for the meta-analyses, MNI-coordinates were transformed into Talairach space using icbm2tal (Lancaster et al., 2007).

TABLE 1
Overview of Individual Studies Included in the Meta-Analysis on Number Magnitude Comparison

Paper	*Task (Contrast)*	*Stimulus*	*Children Without DD (Children With DD) [Adults Without DD]*	*Mean Age/SD in Years (Age Range in Years)*[a]	*Meta-Analysis*[b]
Ansari et al., 2005	Number comparison (small > large distance)	symbolic	12 (—) [12]	Control children 10.4/*SD* n.a. (range 9.2–11.11); adults 19.8/*SD* n.a. (range 19.1–21.10)	I
Ansari & Dhital, 2006	Number comparison (small > large distance)	non-symbolic	9 (—) [9]	Control children 10.4/*SD* n.a. (range 9.11–11.11); adults 19.8/*SD* n.a. (range 18.8–21.10)	I, II
Cantlon et al., 2006	Number comparison (small > large distance)	non-symbolic	8 (—) [12]	Control children 4.75/*SD* n.a. (range 4.25–4.95); adults 25/*SD* n.a. (range 21–37)	I, II
Cantlon et al., 2009	Number comparison (small > large distance)	non-symbolic/symbolic	14 (—) [14]	Control children 7.2/*SD* .58 (range n.a.); adults 24/*SD* 3.05 (range n.a.)	II
Holloway & Ansari, 2010	Number comparison (> spatial judgment)	non-symbolic/symbolic	19 (—) [19]	Control children 8.25/*SD* n.a. (range 6.8–9.3); adults 23.5/*SD* n.a. (range 18.4–28.25)	II
Kaufmann et al., 2006	Number comparison (small > large distance)	non-symbolic	12 (—) [—]	Control children 9.6/*SD* n.a. (range 8–12)	I
Kaufmann et al., 2008	Number comparison (> spatial judgment)	non-symbolic	12 (—) [12]	Control children 8.6/*SD* 1.2 (range n.a.); adults 33.2/*SD* 8.6 (range n.a.)	I, II
Kaufmann et al., 2009b	Number comparison (> spatial judgment)	non-symbolic	9 (9[c]) [—]	Control children 9.7/*SD* 1.6 (range n.a.); children with DD 9.6/*SD* 1.1 (range n.a.)	III
Kovas et al., 2009	Number comparison (> color judgment)	non-symbolic	13 (13[d]) [—]	Control children 10/*SD* n.a. (range n.a.); children with DD 10/*SD* n.a. (range n.a.)	I
Kucian et al., 2006	Number comparison (> gray scale)	non-symbolic	20 (18[c,e]) [—]	Control children 10.6[f]/*SD* n.a. (range n.a.); children with DD 11.2/*SD* 1.3 (range n.a.)	I

Kucian et al., 2008	Number comparison (> gray scale)	non-symbolic	20 (—) [20]	Control children 10.6[f]/*SD* n.a. (range n.a.); adults 27.2/*SD* 5.0 (range n.a.)	II
Meintjes et al., 2010	Number comparison (> Greek letter identification)	symbolic	15 (—) [—]	Control children 10.5/*SD* 1.2 (range 8.2–12.6)	I
Mussolin et al., 2010	Number comparison (> color comparison)	symbolic	15 (15[c]) [—]	Control children 10.9/*SD* 1.6 (range n.a.); children with DD 10.5/*SD* 1.6 (range n.a.)	III
Price et al., 2007	Number comparison (small > large distance)	non-symbolic	8 (8[c]) [—]	Control children 12.06/*SD* .53 (range n.a.); children with DD 11.43/*SD* .59 (range n.a.)	III

DD = developmental dyscalculia; SD = standard deviations; n.a. = not available.

[a] Standard deviations (of mean ages) and age ranges are provided whenever possible and are stated as given in the respective publications (i.e., with no, one or two decimal places).

[b] *Meta-analysis I:* Symbolic versus non-symbolic number magnitude processing in typically developing children (please note that Kaufmann et al. [2009b] and Price et al. [2007] are not included in meta-analysis I because the latter studies report group differences while the remaining studies included in meta-analysis I report contrasts against baseline); *Meta-analysis II:* Influence of age on non-symbolic number processing, comparison of typically developing children and adults (please note that Kaufmann et al. [2009b] was not included in meta-analysis II because the study did not meet the inclusion criteria of directly contrasting children vs. adults); *Meta-analysis III:* Influence of math competency on number magnitude processing.

[c] Although in these studies dyscalculia diagnosis is based on the discrepancy criterion (i.e., average intellectual abilities and impaired arithmetical achievement), the authors used different tests to assess intelligence and arithmetic skills and moreover, across studies different definitions of "impaired arithmetic achievement" are used. For instance, while some consider a significant performance discrepancy between average IQ and below-average performance on a standardized test of arithmetic skills (discrepancy of 1.5 *SD*: Kaufmann et al., 2009b; Price et al., 2007; no explicit statement about extent of performance discrepancy: Kucian et al., 2006), other authors take a two-year delay in mathematical ability— combined with average intellectual abilities—as diagnostic criteria for DD (Mussolin et al., 2010).

[d] Note that the 13 children included in this study were "low achieving" children that might not warrant a diagnosis of DD. Thus, data from this study was not included in meta-analysis III.

[e] Data from this study was not included in meta-analysis III because the authors did not report direct comparisons between children with and without DD.

[f] Please note that both groups consist of children attending 3rd and 6th grade (mean age control children 3rd grade 9.2/*SD* .2; 6th grade 12.0/*SD* .3; dyscalculic children 3rd grade 10.1/*SD* .6; 6th grade 12.3/*SD* .6). Nonetheless, analyses of functional magnetic resonance imaging (fMRI) data are collapsed across the two age groups.

TABLE 2
Overview of Individual Studies Included in the Meta-Analysis on Calculation

Paper	*Task (Contrast)*	*Stimulus*	*Children Without DD (Children With DD) [Adults Without DD]*	*Mean Age/SD in Years (Age Range in Years)*[a]	*Meta-Analysis*[b]
Chen et al., 2006	Calculation (> viewing/listening digits)	symbolic	16[c] (—) [—]	Experts 11.75/*SD* 1.39 (range n.a.); non-experts 12.29/*SD*.38 (range n.a.)	IV
Davis et al., 2009a	Calculation (> Greek letter identification)	symbolic	27 (—) [10]	Control children 8.1/*SD* .4 (range 7.1–9.4); adults 30.7/*SD* 7.3 (range 25–49)	IV
Davis et al., 2009b	Calculation (> Greek letter identification)	symbolic	24 (24[d])[—]	Control children and children with dyscalculia 8.2/*SD* 2.9 (range 8.1 to 9.1)[e]	IV
Kawashima et al., 2004	Calculation (> 0 detection in digit string)	symbolic	8 (—) [8]	Control children 11.6/*SD* 1.6 (range 9–14); adults 44.1/*SD* 3.1 (range 40–49)	IV
Kucian et al., 2006	Calculation (> gray scale)	symbolic	20 (18) [—]	Control children 10.6[f]/*SD* n.a. (range n.a.); children with DD 11.2/*SD* 1.3 (range n.a.)	IV
Meintjes et al. 2010	Calculation (> Greek letter identification)	symbolic	14 (—) [—]	Control children 10.5/*SD* 1.2 (range 8.2–12.6)	IV
Rivera et al., 2005	Calculation (> fixation)	symbolic	17[g] (—) [—]	Control children and adults 13.67/*SD* n.a. (range 8.53–19.03)	IV

DD = developmental dyscalculia; SD = standard deviations; n.a. = not available.

[a] Standard deviations (of mean ages) and age ranges are provided whenever possible and are stated as given in the respective publications (i.e., with no, one or two decimal places).

[b] *Meta-analysis IV:* Neural correlates of calculation in children.

[c] In this study all participating children were average calculators but differed with respect to their expertise in abacus calculation. The experts ($n = 8$) practiced abacus operation and abacus mental calculation for 5.5 years on average (0.5 to 1 hour daily), while the non-experts ($n = 8$) had no experience with abacus operation/calculation.

[d] As already mentioned in the methods section, only data pertaining to control children were included into meta-analysis IV. Data from dyscalculic children ($n = 24$) could not be used for meta-analysis III (investigating math competency) since the remaining studies entering meta-analysis III employed a number comparison rather than a calculation paradigm.

[e] Please note that Davis et al. (2009b) provide mean age and age ranges for the whole study group solely.

[f] Please note that both groups consist of children attending 3rd and 6th grade (mean age control children 3rd grade 9.2/*SD* .2; 6th grade 12.0/*SD* .3; dyscalculic children 3rd grade 10.1/*SD* .6; 6th grade 12.3/*SD* .6). Nonetheless, analyses of functional magnetic resonance imaging (fMRI) data are collapsed across the two age groups.

[g] In this study 8- to 19-year-old individuals were included. Although age was defined as covariate of interest, the authors did not indicate the exact ages of their participants (i.e., of different age groups).

In each meta-analysis, a separate ALE map was generated by modeling each input focus as the center of a Gaussian probability distribution. To examine statistical significance, each of these maps was contrasted with a noise map based on 10,000 sets of random foci. These random sets consisted of the same number of foci as the to-be-tested maps. When a cluster included several anatomically distinct regions, the reported local maxima for these subregions were also used. The noise maps make it possible to examine the probability of the ALE value of each voxel under the null-hypothesis that ALE values are distributed randomly and uniformly in the brain. For these analyses, GingerALE software version 1.2b1 (Laird et al., 2005) was used with a FWHM (full width at half maximum) of 10 mm and 10,000 permutations. To correct for multiple comparisons, FDR (false discovery rate) was set at $p = .05$ and the threshold for cluster extent was set at a volume of 120 mm^3 (equivalent to 15 voxels). These are standard values recommended by the authors of the software.

In *meta-analysis* I the neural correlates of symbolic (21 foci) and non-symbolic (53 foci) number magnitude comparison in control children have been examined (Table 1). Studies examining the neural correlates of number magnitude processing presented a very homogeneous baseline, since all of these studies utilized a number comparison task (i.e., requiring children to make number classifications). In two studies examining the neural correlates of symbolic number comparison, the contrast small > large distance was reported (Ansari et al., 2005; Kaufmann et al., 2006). In three studies examining the neural correlates of non-symbolic number comparison, the contrast small > large distance was reported (Ansari & Dhital, 2006; Cantlon et al., 2006, 2009). In four further studies neural activity yielded upon processing number comparison was subtracted from activity obtained by processing physical comparisons (Kovas et al., 2009: color judgment; Kaufmann et al., 2008: spatial judgment, Kucian et al., 2006: gray scale; Meintjes et al., 2010: Greek letter identification).

It is important to note that all but the Cantlon et al. (2006) study require children to produce active number-related responses. On the contrary, Cantlon et al. (2006) use a passive habituation paradigm without response requirement. We believe that the inclusion of the Cantlon et al. study is justified because children's (and adults') brains are capable to process number magnitude in a very automatic fashion (Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003). A consistent finding from habituation tasks manipulating number magnitude is that adults and children (as well as preverbal infants and some non-human species) are well able to detect changes in numerosity (for respective reviews of behavioral and electrophysiological studies: e.g., Cantlon, Platt, & Brannon, 2009; Feigenson, Dehaene, & Spelke, 2004). Furthermore, upon employing a passive viewing paradigm in an adult fMRI study, Ansari, Dhital, and Siong (2006) showed that the IPS supports numerical processing in the absence of an explicit response requirement. Taken together, number magnitude processing can be tapped by both active and passive designs and accordingly, we chose to include findings derived from both types of paradigms into the present meta-analysis.

Finally, we would like to stress that the activation clusters reported in meta-analysis I do not originate from direct comparisons between groups. The reason for presenting indirect comparisons rather than direct ones is based on a closer inspection of our data basis revealing that most studies did not perform a direct statistical comparison between the contrasts of interest (symbolic versus non-symbolic number processing). Please note that two studies reporting data from both symbolic and non-symbolic number processing (Cantlon et al., 2009; Holloway & Ansari, 2010) could not be included in meta-analysis I because the authors only report results of a conjunction analysis (i.e., common activation in response to symbolic and non-symbolic number comparison) which renders the investigation of notation-specific effects impossible. However, the research question to be answered in meta-analysis I is targeted at notation-specific effects or in other words, meta-analysis I aims at investigating whether children's brain activations in response to symbolic and non-symbolic number processing tasks are overlapping or distinct from each other.

In *meta-analysis II* a specific comparison between control children and adults regarding non-symbolic number comparison was examined (influence of age, see Table 1). Not enough studies reporting activation differences on symbolic number processing between children and adults were available. For this reason only comparisons involving non-symbolic number processing were examined. Two different types of contrast were evaluated in this meta-analysis, one showing the voxels more activated in children than in adults (13 foci) and one showing the voxels more activated in adults than in children (31 foci). In three studies reporting stronger activation in adults than in control children during non-symbolic number comparison, the contrast small > large distance was reported (Ansari & Dhital, 2006; Cantlon et al., 2006, 2009). In three further studies, activity related to number comparison was subtracted from physical comparisons (Kucian et al., 2008: gray scale comparison; Kaufmann et al., 2008, Holloway & Ansari, 2010: spatial judgment). Note that the contrasts reported by Holloway and Ansari (2010) and Cantlon et al. (2009) are age-dependent activation differences yielded by conjunction analyses including symbolic and non-symbolic number comparisons. The inclusion of the latter two studies is justified since reported activations derived from employing conjunction analyses include activations produced by non-symbolic number processing. In one of those studies reporting stronger activation in control children than in adults during non-symbolic number comparison, the contrast small > large distance was reported (Cantlon et al., 2006). In a further study, fMRI responses related to number comparison were subtracted from those related to physical comparison (Kaufmann et al., 2008: spatial judgment).

In *meta-analysis III* the brain activation patterns shown by control children and dyscalculic children were compared (math competency, see Table 1). Two different contrasts were evaluated in this meta-analysis, one showing brain regions more activated in control children than in dyscalculics (6 foci, Table 3) and one showing the voxels more activated in dyscalculics than in control children (8 foci, Table 4). Importantly, in this meta-analysis the differentiation between symbolic and non-symbolic number magnitude comparison was not possible due to the very small number of studies on this topic. Two studies reported stronger activation in dyscalculics (Mussolin

TABLE 3
Areas Showing Stronger Activity in Control Children Than in Dyscalculics (Non-Symbolic and Symbolic Trials; $n = 2$ [Mussolin et al., 2010; Price et al., 2007])

Volume (mm^3)	*p-Value*	*x*	*y*	*z*	*Anatomical Label*
1984*	.008	−22	−62	50	Left precuneus (BA 7)
1760*	.007	34	−50	52	Right inferior parietal lobe (BA 40)
800	.007	−12	−28	46	Left frontal paracentral lobe (BA 6)
744*	.006	−36	−54	−14	Left fusiform gyrus (BA 37)
728*	.006	−14	54	−2	Left superior frontal gyrus (BA 10)
704	.007	30	36	36	Right middle frontal gyrus (BA 9)

* = local maximum of a bigger activation cluster. BA = Brodmann area.

TABLE 4
Areas Showing Stronger Activity in Dyscalculics Than in Control Children (Non-Symbolic and Symbolic Trials; $n = 2$ [Kaufmann et al., 2009b; Mussolin et al., 2010])

Volume (mm^3)	*p-Value*	*x*	*y*	*z*	*Anatomical Label*
824*	.006	−4	−44	66	Left postcentral gyrus (BA 5)
792	.007	46	−32	34	Right inferior parietal lobe (BA 40)
792	.007	28	−30	42	No gray matter found
768*	.006	0	32	44	Left superior frontal lobe (BA 8)
744	.006	30	−40	54	Right inferior parietal lobe (BA 40)
720	.007	−2	−20	−12	Left red nucleus (brainstem)
624	.006	6	−26	48	Right paracentral frontal lobe (BA 6)
616*	.006	−40	−58	42	Left inferior parietal lobe (BA 40)

* = local maximum of a bigger activation cluster. BA = Brodmann area.

et al., 2010; Kaufmann et al., 2009b) and two other studies reported stronger activation in control children than in dyscalculics (Mussolin et al., 2010, Price et al., 2007). Please note that the findings of Kovas et al. (2009) were not included in meta-analysis III because the latter authors used different diagnostic criteria (i.e., investigated children with mathematical disability rather than children with DD). Likewise, data reported by Kucian et al. (2006) could not be included because the authors did not report direct contrasts between children with and without DD.

In *meta-analysis IV* the fMRI correlates of calculation in non-dyscalculic children were examined. In total 167 foci of activation entered the analysis (Table 2). In contrast with the previous meta-analyses, the baseline contrasts differed substantially across the different studies included in this meta-analysis. Each study in this meta-analysis employed a different baseline contrast. Kawashima et al. (2004) compared calculation with detection of a 0 in the digit string, Kucian et al. (2006) compared calculation with gray scale judgment, Rivera et al. (2005) compared it with fixation, Chen et al. (2006) compared it with looking at or listening to digits and both Meintjes et al. (2010) and Davis et al. (2009a, 2009b) compared calculation with Greek letter identification. Only the contrast calculation > control condition has been investigated in this meta-analysis.

RESULTS

In the following, we will provide the results of the above described four meta-analyses. Anatomical regions and Brodmann areas (BA) are reported as provided by the GingerALE software.

Meta-Analysis I: Symbolic Versus Non-Symbolic Number Magnitude Processing in Children

Overall, eight studies were included in this analysis (see Table 1). Findings reveal that in children, the neural response to symbolic and non-symbolic number classifications barely overlap (Figure 1).

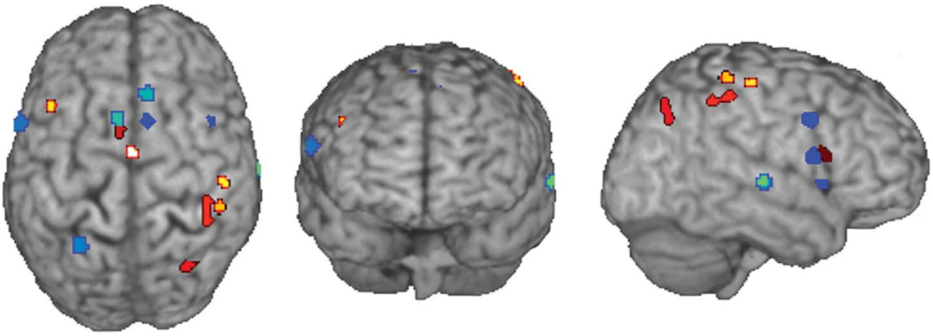

FIGURE 1 Consistent activation clusters produced by control children upon solving symbolic (i.e., Arabic digits) and nonsymbolic (e.g., dot or square patterns, finger patterns) number comparison tasks. Activations pertaining to symbolic number processing are denoted by blue blobs, while activations in response to non-symbolic number comparisons are visualized by red blobs. Please note that for both types of activation (i.e., blue and red) color codes vary according to activation extents, stronger activations being reflected by lighter colors. White and yellow color blobs denote the brightest variant of red (i.e., non-symbolic number processing). (color figure available online)

Symbolic number processing (blue blobs). Children consistently recruited bilateral parietal regions upon making symbolic number classifications. Two clusters of activation could be observed in the left and right anterior inferior parietal cortex (TC 40, –44, 54, BA 40; TC -52, –26, 22, BA 40) and the left superior parietal cortex (TC –28, –60, 58, BA 7). The right precentral gyrus (TC 40, 6, 34, BA 9) and the medial and inferior frontal gyrus (TC 8, 20, 46, BA 8; TC 48, 8, 14, BA 44, respectively) were activated by symbolic number comparisons as well as the premotor cortex bilaterally (TC –8, 6, 54, BA 6; TC –60, 4, 20, BA 6; TC 8, 6, 50, BA 6), the right insula (TC 36, 12, 0, BA 13) and the anterior cingulate gyrus (TC 4, 12, 24, BA 33). Moreover, children's fMRI responses to symbolic number processing encompassed the right superior temporal gyrus (TC 66, –20, 0, BA 22) and extending to the left cingulate gyrus (TC –20, –42, 24, BA 31). Finally, also the posterior lobe of the cerebellum was found to be consistently activated across studies (cerebellar tuber: TC –36, –60, –24; cerebellar declive: TC 24, –56, –16; TC 0, –68, –12).

Non-symbolic number processing (red blobs). Within the parietal lobes, the following clusters of activation were observed: right inferior parietal lobe bordering the anterior intraparietal cortex (TC 40, –36, 46, BA 40; TC 46, –38, 56, BA 40), right postcentral gyrus (TC 48, –26, 54, BA 2), left angular gyrus (TC –28, –62, 36, BA 39), and left precuneus (TC –8, –66, 32, BA 7). Furthermore, non-symbolic number processing elicited bilateral activation in prefrontal regions (TC 44, 28, 20, BA 46) and in the premotor cortex (precentral gyrus: TC –6, 0, 56, BA 6; TC 0, –10, 52, BA 6) and middle frontal gyrus (TC –42, 14, 32, BA 9). In occipital cortex, activations were found in the extrastriate cortex bilaterally (TC –22, –58, –2, BA 19; TC 30, –68, 34, BA 19) and in the lingual gyrus (TC –20, –48, 0, BA 19). Finally, different foci of activation emerged in gray matter bilaterally such as the insula (TC 42, 12, 16, BA 13) and the left claustrum (TC –30, 10, 16; TC –24, 18, 10).

Meta-Analysis II: Influence of Age on Non-Symbolic Number Magnitude Processing

In total, six studies were subjected to data analysis (see Table 1). In both hemispheres, parietal activations are clearly distinguishable between children (blue blobs) and adults (red blobs; see Figure 2). Adults activated a broad network of cortical regions stronger than children (23 activation clusters) while children only activated 12 clusters stronger than adults. A possible explanation for the more pronounced activation observed in adults may be that adults might simply show less interindividual variability than children. In particular, adults showed stronger activation than children in inferior and superior parietal cortex bilaterally (TC –36, –48, 38, BA 40; TC 32, –48, 36, BA 40; TC 52, –30, 44, BA 40; TC 40, –44, 50, BA 40; TC –12, –72, 30, BA 7; TC –40, –56, 54, BA 7). Several clusters of activation also were observed in the right extrastriate cortex (TC 36, –74, 36, BA 19; TC 36, –76, –10, BA 19; TC 38, –76, 8, BA 19), in the right cuneus (TC 18, –94, 6, BA 18; TC 12, –76, 28, BA 18) and in the right fusiform gyrus (TC 42, –56, –16, BA 37). Moreover, activation in the left inferior frontal gyrus was found (TC –24, 16, –14, BA 47), as well as in the left superior temporal gyrus (TC –44, 12, –28, BA 38), the left precentral gyrus (TC –34, –18, 60, BA 4), posterior cingulate gyrus bilaterally (TC –2, –46, 38, BA 31; TC 12, –54, 28; BA 31; TC 4, –54, 16, BA 23), the right insula (TC 46, –18, 16, BA 13; TC 36, 16, 6, BA 13) and the right subcallosal gyrus (TC 2, 12, –10, BA 25).

Interestingly, in comparison to adults, children's parietal activations encompass more anterior brain regions (blue; Figure 2). Children activated the anterior intraparietal cortex bilaterally (TC 58, –34, 48, BA 40; TC –52, –38, 48, BA 40). Children also recruited additional regions in the

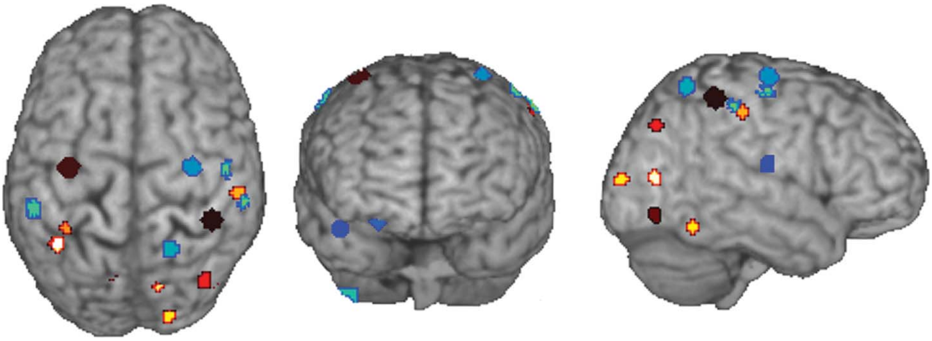

FIGURE 2 Age-dependency of neural activations obtained upon making non-symbolic number classifications. Activations produced by children are denoted in blue, those produced by adults are shown in red. Please note that for both types of activation (i.e., blue and red) color bars vary according to activation extents, stronger activations being reflected by lighter colors. White and yellow color blobs denote the brightest variant of red, while black blobs denote the darkest variant of red (i.e., adults). (color figure available online)

superior parietal lobule (TC 18, –60, 56, BA 7; TC –10, –70, 54, BA 7) and in the right postcentral gyrus (TC 48, –18, 56, BA 3). Children also activated the left superior temporal lobe (TC –44, 12, –28, BA 38), premotor cortex (TC 30, –18, 62, BA 6), left inferior frontal gyrus (TC –24, 16, –14, BA 47), subcallosal gyrus (TC 2, 12, –10, BA 25), the right insula (TC 46, –18, 16, BA 13) and the posterior cingulate gyrus (TC 4, –54, 16, BA 23).

Meta-Analysis III: Influence of Math Competency on Number Magnitude Processing

We merged data across symbolic and non-symbolic tasks, because otherwise the number of studies would have been too small in order to yield relevant results. Hence, three studies were included in the statistical analysis (Tables 1, 3 and 4). Consistent activations across studies were found for both sides of the contrast. Control children produced stronger activations than their dyscalculic peers in the left precuneus (BA 7), activation being centered on the left posterior IPS (see Table 3). Another activation cluster was found in the right inferior parietal lobe (BA 40) and in close vicinity to the posterior IPS. Furthermore, controls showed stronger activations in the left paracentral frontal lobe (BA 6), the left superior frontal gyrus (BA 10), the right middle frontal gyrus (BA 9: DLPC) and the left fusiform gyrus (BA 37). As can be seen from Table 4, dyscalculic children produced stronger fMRI responses in the left postcentral gyrus (BA 5) as well as in the left and right inferior parietal lobes. In the right inferior parietal lobe, activation was centered on the supramarginal gyrus (SMG, BA 40), closely neighboring the anterior IPS, while activation in the left inferior parietal lobe was adjacent to the lateral IPS. Finally, stronger activation clusters in dyscalculics were found in the superior frontal lobe (BA 8) and the paracentral frontal lobe (BA 6) on the right.

Meta-Analysis IV: Calculation Skills in Children

Data points from seven different studies were entered into this analysis (Table 2). As depicted in Figure 3, a broad network of neuronal regions is activated when children perform calculations. Seventeen clusters of activation were obtained. Consistent bilateral activations were observed in

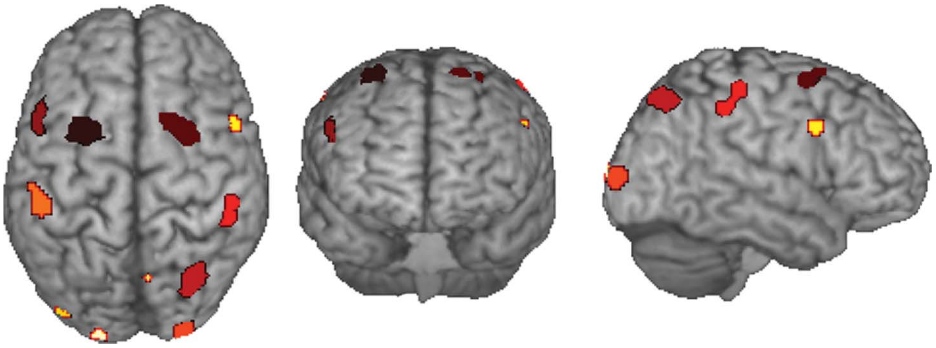

FIGURE 3 Consistent activation clusters produced by children upon solving simple calculation tasks. (color figure available online)

the inferior parietal lobe extending to the intraparietal cortex (TC –32, –54, 40 and TC 44, –42, 40, BA 40; TC –48, –34, 46, BA 40), the posterior superior parietal cortex (precuneus: TC 8, –66, 42, BA 7; TC 30, –70, 46, BA 7) and the right angular gyrus (TC 32, –60, 32, BA 39). Moreover, activation was observed in the inferior frontal gyrus (TC 50, 8, 32, BA 9; TC –46, 14, 26, BA 9) and premotor cortex, bilaterally (TC –26, 4, 56; TC 0, 16, 46, BA 6; TC 24, 4, 52, BA 6). Further activation clusters emerged in the left and right insula (TC –32, 24, 2, BA 47; TC 34, 16, 6, BA 13), left inferior temporal gyrus (TC –50, –50, –12, BA 20) and in large portions of striate and extrastriate cortex bilaterally (TC 24, –98, 6, BA18; TC –36, –86, 8, BA 19).

DISCUSSION

Although receiving increased scientific interest during the past few years, fMRI studies on the development of numerical cognition are scarce: At the time of writing this article, 19 fMRI papers have been found that provide sufficient data for calculating a meta-analysis of fMRI activation. In order to acknowledge the componential nature of the calculation system (meaning that different tasks rely on different types of number representations, different number formats and moreover, bear on quite different processing demands), we had to calculate four different meta-analyses. Importantly, the coordinate-based activation likelihood estimation (ALE) meta-analyses presented here allow calculating statistical significance of consistent activation foci across studies by contrasting ALE maps (that are generated by modeling each input focus as the center of a Gaussian probability distribution) with a noise map based on random foci. The main findings of the four meta-analyses conducted here are discussed in detail below.

Meta-analysis I aimed at identifying brain regions supporting symbolic and non-symbolic number magnitude comparison in control children (i.e., typically developing children with average calculation skills). In particular, we were interested in examining whether the assumption of an abstract number representation in the IPS (as postulated by Dehaene's neurofunctional calculation model that is based on adults) holds true for developing brain systems as well. Overall, the findings of meta-analysis I are not compatible with the notion of an abstract number representation in children (implying that the IPS should respond equally to symbolic and non-symbolic number magnitudes) but rather disclose that in children number notation (symbolic Arabic numbers versus nonsymbolic dot/square/finger patterns) influences the location of cerebral activation patterns in and outside the parietal lobes. At this point, we wish to stress that recently even in the adult literature the notion of exclusively abstract number representations has been seriously challenged (Cohen Kadosh & Walsh, 2009). In the present meta-analysis of developmental fMRI studies, symbolic number magnitude processing was found to produce bilateral parietal activations (including the left PSPL and the right IPS), while activations in response to non-symbolic processing were confined to the right parietal lobe (bordering the IPS). Within the right IPS, neural responses to non-symbolic number magnitude were located more anterior (i.e., in the anterior IPS) than those obtained by symbolic number processing. Interestingly, intraparietal activation foci in response to symbolic number processing (TC 40, –44, 54) are situated near the core of the IPS (as reported previously for adults by Dehaene et al., 2003; mean TC 41, –47, 48/SD 7, 7, 5), while activations in response to non-symbolic number processing are found adjacent to the anterior IPS (TC 40, -36, 46) and extending to the postcentral gyrus (TC 48, –26, 54). Previously, Kaufmann et al. (2008) suggested that activations in postcentral gyrus and neighboring anterior IPS may reflect a link between fingers and number processing (for a similar hypothesis, see Butterworth, 2005; Gracia-Bafalluy & Noël, 2008). Interestingly, the findings of meta-analysis I introduce a novel aspect to the latter discussion since results disclose notation-specific effects on parietal activations. In particular, children's need to recruit brain regions that possibly reflect reliance on finger-based number representations (i.e., the anterior IPS and neighboring postcentral gyrus) emerges upon processing of non-symbolic (but not so upon symbolic) number magnitudes. A potential explanation for a closer link between non-symbolic (rather than symbolic) number processing and finger-based number representations is that compared with symbolic Arabic digits, non-symbolic stimuli (i.e., dot/square patterns, finger patterns) are more likely to elicit finger-based solution strategies.

As regards lateralization of brain activations, the results of our developmental meta-analysis reveal that in children both symbolic and non-symbolic processing yield right parietal fMRI signals, while the left parietal lobe seems to be responsive mainly to symbolic number processing. A plausible—although thus far speculative—explanation for the latter finding is that in children symbolic number processing (that requires a greater level of abstraction compared with non-symbolic number processing) is preferentially supported by the left hemisphere (for similar findings in adults, see Piazza, Pinel, Le Bihan, & Dehaene, 2007; however, see Cohen Kadosh et al., 2007). Nonetheless, when looking at the individual studies included in the meta-analysis, it becomes clear that the picture is more complex than suggested by the findings of our meta-analysis: While some developmental fMRI studies report that children display right-lateralized parietal activations (non-symbolic NDE: Cantlon et al., 2006; symbolic NDE: Kaufmann et al., 2006), others observe that children recruit bilateral parietal brain regions (non-symbolic NDE: Kaufmann et al., 2008; Kucian et al., 2008; symbolic NDE: Mussolin et al., 2010). Compared with adults, one study fails to find suprathreshold parietal activation in children (symbolic NDE: Ansari et al., 2005), while another study reports that compared with adults children display deficient activations in right (intra)parietal regions (conjunction of symbolic and non-symbolic number comparison: Holloway & Ansari, 2010) and yet another finding proposes that children—relative to adults—exhibit less robust left (intra)parietal involvement (conjunction symbolic and non-symbolic NDE: Cantlon et al., 2009). Notably, also in the adult literature the question of lateralization is discussed controversially (for an overview, see Ansari, 2007).

Effects of notation were not restricted to parietal regions. Rather, symbolic and non-symbolic stimuli also yielded partially distinct activation patterns in frontal brain regions. Only non-symbolic—but not so symbolic—processing was found to be supported by the inferior (BA 45: pars triangular) and middle frontal gyrus (BA 46: DLPC). The exact functional role of the inferior frontal gyrus is discussed controversially to date. While some researchers postulate that BA 45 (in tandem with BA 44) plays a crucial role in semantic retrieval (Gabrieli, Poldrack, & Desmond, 1998) other authors propose that BA 45 is important for distinguishing task-relevant from task-irrelevant mental representations (Thompson-Schill, D'Esposito, & Kan, 1999). The exact functional significance of a notation-specific effect on BA 45 (and BA 46 that has been traditionally thought to support attentional and working memory processes) remains obscure. Nonetheless, a possible explanation might be that compared with symbolic magnitudes (Arabic digits) non-symbolic number magnitudes (dot/square patterns) are visually more complex and thus impose higher processing demands. Alternatively, these frontal areas (including the DLPC) are recruited because counting (of non-symbolic dot patterns) may require working memory (for respective adult findings, see Piazza, Giacomini, Le Bihan, & Dehaene, 2003). If not always, this might be the case at early stages of learning to count. Notably, the latter explanation is further supported by our finding of strong and distributed activations in striate and extrastriate regions upon processing non-symbolic (but not symbolic) number magnitudes. Finally, also the cerebellum and subcortical regions were found to respond selectively to symbolic (posterior lobe of cerebellum) and non-symbolic stimuli (claustrum). In the absence of systematic studies investigating the roles of the cerebellum and the claustrum in numerical cognition we defer from interpreting notation-specific effects on these brain structures.

Meta-analysis II was targeted at investigating age dependent activation differences between proficient children and adults regarding non-symbolic number comparison. Results of meta-analysis II propose that across studies, age modulates the exact localization of parietal activations. In particular, results suggest that children activate more anterior intraparietal regions, while intraparietal activations of adults are more posterior and stronger in the right hemisphere. In the right IPS (as well as regarding left postcentral regions), children's activations were slightly more anterior to those observed in adults. A plausible explanation—which to the present awaits empirical foundation—is that compared with adults (and despite comparable skill level) children still recruit procedural (possibly finger-based) strategies upon solving simple number tasks (Kaufmann et al., 2008; see earlier discussion).

A small cluster of activation was found in BA 47 of the inferior frontal gyrus of both children and adults. The finding of comparable frontal activations across development is not in line with previously reported results suggesting that number-related activations in frontal brain regions are stronger in children than in adults (Ansari et al., 2005; Ansari & Dhital, 2006; Cantlon et al, 2008; Holloway & Ansari, 2010; Kaufmann, 2006, 2008; Kucian et al., 2008; Rivera et al., 2005; but see Wood, Ischebeck, Koppelstaetter, Gotwald, & Kaufmann, 2009). For instance, the findings of Rivera et al. (2005) nicely show the negative correlation between age and extent of frontal activation during calculation: with increasing age frontal activations become less strong upon solving simple addition and subtraction problems. Likewise, Kaufmann et al. (2005, 2006) show that children produce significant medial and inferior frontal activations including the right DLPC and the left anterior cingulate cortex when making simple number classifications (for different findings, see Kucian et al., 2008). Notably, children's need to stronger recruit frontal brain regions (compared with adults) has been reported for symbolic number comparison (Ansari et al., 2005; Kaufmann et al. 2006), for non-symbolic number comparison (Ansari & Dhital, 2006; Kaufmann et al., 2008), for the conjunction of symbolic and non-symbolic number comparison (Cantlon et al., 2009) and for simple exact calculation alike (Kucian et al., 2008). Further support for age-dependent (ontogenetic) activation differences, possibly reflecting increasing functional specialization of (intra)parietal cortex for number processing, comes from the primate literature (Nieder, 2005, 2009). Upon considering the accumulating evidence from both human and non-human brain imaging studies for compensatory (age-dependent) recruitment of frontal brain regions upon processing number magnitudes, the restriction of consistent frontal (supportive) activations to a rather small cluster in inferior frontal cortex (that is furthermore comparable to adults frontal activations) is rather surprising at a first glance. However, upon closer inspection of the individual studies mentioned earlier, the reason for the lack of activation consistency becomes readily apparent. Though all the aforementioned studies report that children need to recruit frontal brain regions (possibly in an effort to compensate for yet suboptimal number magnitude processing skills) the exact localization within frontal cortices varies substantially between studies. Thus, though across studies frontal (neighboring) activations were reported, the absence of activation overlap prevents the ALE procedure from pinpointing additional frontal regions that are consistently activated across studies. The latter discrepancy (i.e., failure to find consistent and extended frontal activations despite recruitment of frontal brain regions is repeatedly reported in the developmental literature on numerical cognition) stresses the importance of conducting quantitative and statistically based meta-analyses. In particular, our findings disclose that activation patterns reported in single studies might not be consistent. Also, such analyses enable us to corroborate previous predictions about children's recruitment of procedural strategies that are reflected—among others—in strong reliance on frontal brain regions.

In the third meta-analysis (III), we sought to identify brain regions that are consistently but differently activated by children with and without dyscalculia on the number comparison task (data merged across symbolic and non-symbolic tasks). Results reveal that fronto-parietal fMRI responses of children with and without dyscalculia are quite distinguishable. Compared with dyscalculics, controls produced stronger activations in the left precuneus (activations centered on the IPS), the right inferior parietal lobe (activations being in close vicinity to the posterior IPS) and the right DLPC. Also the opposite contrast (i.e., dyscalculics > controls) yielded significant bilateral fronto-parietal activations, that were located in neighboring regions: Dyscalculics were found to recruit more strongly right superior frontal regions that lie more posterior than the left superior frontal regions found to be activated by controls. Within the parietal lobes, stronger activations produced by dyscalculics include the inferior parietal lobes bilaterally: On the right, activation foci lie in the SMG bordering the anterior IPS (while inferior parietal activations produced by controls are located more posterior and medial), while on the left, activations produced by dyscalculics border the lateral IPS. Furthermore, dyscalculics (but not controls) recruit the left postcentral gyrus upon making simple number classifications. Probably the most interesting finding is that controls recruit the left posterior IPS upon solving number tasks, while dyscalculics activate the right SMG (bordering the right anterior IPS) and the left postcentral gyrus. Thus, it can be concluded that dyscalculics fail to produce suprathreshold activations in the left IPS (for similar findings on an adult case of acquired acalculia, see Ashkenazi, Henik, Ifergane, & Shelef, 2008). In adult number processing, the left SMG (together with the left angular gyrus) has been assigned a key role in arithmetics (e.g., Menon, Rivera, White, Glover, & Reiss, 2000; Rivera et al., 2005). Contrary to the adult literature, the present meta-analysis discloses that dyscalculic children recruit the right (instead of the left) SMG. A potential explanation for the hemispheric differences in SMG activation may be that the adult studies cited above employed calculation tasks, while in the present meta-analysis, only number comparison tasks (across notation) were included. Hence, it is plausible to speculate that the left SMG may be conjointly activated with language-related number processing (solution of simple additions etc.), while the right SMG (and neighboring areas) may be preferentially tuned to processing of non-symbolic number magnitudes (for a similar account based on adult data, see Cappelletti, Lee, Freeman, & Price, 2010). Moreover, (intra)parietal activations produced by dyscalculics were more anterior (reaching as far as the postcentral gyrus) than those displayed by control children. In our view, a plausible explanation for the more anterior activation has been mentioned previously in meta-analysis II. There, we suggest that compared with adults, children need to rely more strongly on finger-based number representations upon processing simple number tasks (Butterworth, 2005; Kaufmann et al., 2008). In a similar vein, we propose that children with dyscalculia (and low math proficiency) need to invest more efforts than their average calculating peers to solve simple number tasks. Activations in the anterior IPS and in the postcentral gyrus as displayed by dyscalculic children may reflect enhanced reliance on compensatory mechanisms and more specifically, may reflect the recruitment of finger-based number representations.

Furthermore (and apart from fronto-parietal activation differences), controls showed stronger activations compared with dyscalculics in left fusiform gyrus, while dyscalculics produced stronger fMRI responses than controls in the left brainstem. Brainstem activations are difficult to interpret. However, number-related activations in the fusiform gyrus have been repeatedly reported in adults (for an overview, see Dehaene et al., 2003) and have been suggested to reflect the processing of number symbols (see also McCandliss et al., 2003).

Taken together, convergent findings across the few developmental fMRI studies published thus far are twofold at least: First, compared with average calculating children those with dyscalculia tend to have less robust number-related activations in the IPS possibly reflecting a dysfunctional intraparietal number system (deficient bilateral IPS: Kaufmann et al., 2006; Mussolin et al., 2010; deficient right IPS: Price et al., 2007). Second, children with dyscalculia seem to recruit either more distributed brain regions (possibly reflecting compensatory strategies; e.g., Kaufmann et al., 2008; Kucian et al., 2006; Price et al., 2007) or alternatively, display deficient recruitment of frontal brain regions that—in typically developing children—are found to support domain-general processing (Mussolin et al., 2010).

Finally, the focus of meta-analysis IV was to identify neural correlates that are consistently recruited by typically developing children when solving simple calculations. The adult literature on calculation provides rather convergent findings. Activations upon performing calculation procedures are reported in inferior and middle frontal as well as in inferior occipital brain regions (e.g., Delazer et al., 2005; Grabner et al., 2009; Ischebeck et al., 2009), some studies reporting additional activation in the cerebellum (Delazer et al., 2005; Grabner et al., 2007), the basal ganglia (Grabner et al., 2009; Ischebeck et al., 2009), the temporal gyrus (Delazer et al., 2005; Grabner et al., 2009), and the insula (Grabner et al., 2007; Ischebeck et al., 2009). Similarly, in the present meta-analysis of developmental fMRI studies, consistent activations were found in distributed and rather symmetric networks encompassing fronto-parietal and occipital brain regions bilaterally. In particular, children produced consistent activations in inferior and superior parietal cortices (including the IPS bilaterally and the right SMG). (Intra)parietal activations were extensive, reaching from the anterior to the posterior IPS (encompassing the precuneus). IPS activations most likely reflect number-related processing as previously reported in adults (e.g., Cohen Kadosh et al., 2008; Dehaene et al., 2003) and in children (Chen et al., 2006; Davis et al., 2009a; Kawashima et al., 2004; Kucian et al., 2006; Rivera et al., 2005). Because the developmental fMRI literature on numerical cognition is scarce at present, any attempt to further elucidate segregated regions within the parietal lobes (i.e., specific functions of the IPS and the SMG) needs to remain rather speculative. As mentioned previously, in adult studies the SMG is thought to support computational arithmetic (Menon et al., 2000; Rivera et al., 2005) while the IPS has been assigned a key role for number magnitude processing per se (Dehaene et al., 2003). According to Dehaene et al. (2003), posterior superior parietal regions mediate visual-spatial attention on the mental number line. Possibly, the findings of the present meta-analysis revealing strong involvement of the posterior IPS bilaterally (including the PSPL) may be interpreted as reflecting children's need to navigate on the mental number line upon performing arithmetic calculations. Likewise, recruitment of the anterior IPS also may reflect children's compensatory efforts to solve the arithmetic tasks at hand.

Extra-parietal consistent activations emerged in frontal and occipital regions as well as in the insula. Though insular activations are also reported in the adult literature on calculation (Grabner et al., 2007; Ischebeck et al., 2009), the functional role of the insular cortex in numerical cognition remains obscure to the present. In frontal brain regions, activations are found in the inferior frontal gyrus (extending to DLPC) and the premotor cortex. Previously, frontal involvement has been interpreted as reflecting effortful processing which, among others, places high demands on working memory and monitoring abilities (Ansari et al., 2005; Ansari & Dhital, 2006; Cantlon et al., 2006, 2009; Rivera et al., 2005; Kaufmann et al., 2006; Kucian et al., 2008). As children's arithmetic competencies are yet not automatized but rather require conscious and effortful processing, it is not surprising to learn that in children, calculation is strongly supported by (pre)frontal regions known to mediate supporting functions such as attention, working memory and monitoring. Finally, ALE maps reveal consistent activations in occipital regions (including striate and extrastriate cortex), most likely reflecting either strong demands on visual processing or differences in the baseline between the different studies.

Potential limitations of our study are as follows: Due to the small number of studies that report activation foci resulting from direct comparisons of the contrasts of interest, the findings of our meta-analysis I (comparing activation patterns in response to symbolic vs. non-symbolic number processing) rest on indirect comparisons. Though findings of meta-analysis I should be considered preliminary and future studies with larger data pools are needed to further corroborate our argumentation, we want to emphasize that our findings are based on a well-established statistical approach (i.e., the ALE method) and thus can be considered reliable. Nonetheless, we can't guarantee that results would remain exactly the same if activation maps derived from direct contrasts could have been used. Another potential limitation of our study is the rather small number of studies contributing to our data pool. However, since the vast majority of neuroscientific studies of numerical developmental rests on adult calculation models that might not be apt to fully explain children's performance on number processing and calculation tasks (Kaufmann & Nuerk, 2005) we believe that the time was ripe to conduct the present meta-analyses. Indeed, our findings provide first empirical evidence pinpointing crucial differences between adult and developing brain systems (see below paragraph for a summary of respective findings). Finally, a further issue warranting a cautious interpretation of findings is the fact that children's fMRI responses are known to be rather variable (Cantlon et al., 2006, Figure 4; for similar findings in adults, see Cohen Kadosh et al., 2008, Figure 1). Although we acknowledge that interindividual variability might hamper data interpretation we would like to emphasize that the ALE method employed in our meta-analyses is a well-established statistical approach that enables us to examine whether across different studies the overlap of functional activity observed in a given brain region emerges with a significantly larger probability than expected by pure noise.

FORMULATION OF A TENTATIVE DEVELOPMENTAL CALCULATION MODEL

Despite acknowledging the preliminary nature of the results presented in this article we suggest that our findings (disclosing crucial neurofunctional differences between mature and developing brain systems upon performing numerical tasks) could serve as a valid baseline for the formulation of a tentative developmental calculation model. In what follows we summarize the

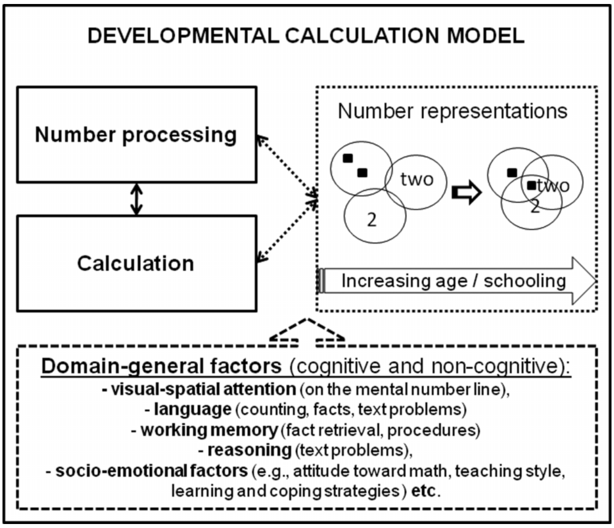

FIGURE 4 Schematic representation of a tentative developmental calculation model based on the findings of the present meta-analyses of developmental functional magnetic resonance imaging (fMRI) studies. Please note that the assumption of initially distinct number representations for symbolic and non-symbolic notations that—with increasing age and schooling—overlap has been adopted from Kucian and Kaufmann (2009, Figure 1).

most relevant findings of our meta-analyses and discuss how these findings converge or do not converge onto adult calculation models. As to the present Dehaene's model is the most popular neurofunctional calculation model and moreover, the one that is most frequently cited in the developmental fMRI literature as well, we confine the following analyses to this model.

Most notably, the findings of meta-analysis II reveal that across studies children consistently produce fMRI responses that are distinct from those produced by adults. The latter finding is especially remarkable because age effects on brain activation became apparent in non-symbolic number tasks requiring subjects to either make numerical classifications on object sets (i.e., dot/square patterns) or to passively detect numerosity changes across sequentially presented dot/square patterns. Interestingly, brain activations were distinguishable between children and adults, even though children found the tasks quite easy (out of the six studies included in meta-analyses II three report response accuracies higher than 90% [Ansari & Dhital, 2006; Kaufmann et al., 2008; Kucian et al., 2008], in one study children were 80% correct [Cantlon et al., 2009], one study [Holloway & Ansari, 2010] fails to provide the accuracy raw data and another study [Cantlon et al., 2006] employed a passive viewing paradigm without response requirement). Taken together, the finding of age-dependent differences in brain activation upon performing simple number tasks seriously questions the applicability of adult calculation models for developmental studies.

A second important finding is that in children symbolic and non-symbolic number processing tasks elicit quite distinct activations in parietal (and extra-parietal) brain regions (meta-analysis

I). The latter finding clearly is not compatible with the notion that the IPS hosts an abstract number representation (Dehaene et al., 2003) but rather suggests that in developing brain systems notation affects the exact localization of parietal (and extra-parietal) cerebral activations. Recently, Dehaene's view of an abstract number representation in the IPS has also been challenged by findings reported by Cohen Kadosh et al. (2008) showing that also in adults mental number representations in parietal cortex may be notation dependent (for a detailed discussion on the issue of abstract versus non-abstract number representations, see Cohen Kadosh & Walsh, 2009). Upon providing a developmental perspective on Cohen Kadosh and Walsh (2009), Kucian and Kaufmann (2009) propose that children's increasing expertise may cause a gradual shift from non-abstract (i.e., notation-dependent) to abstract (notation-independent) numerical representations.

Finally, meta-analyses IV discloses that children recruit distributed networks encompassing frontal, parietal and occipital brain regions bilaterally. Despite the fact that also the adult fMRI literature reveals that calculation is a complex process supported by both parietal and extra-parietal regions, it is rather surprising to find that to the present adult calculation models fail to fully acknowledge the important influence of supporting (domain-general) functions such as working memory, attentional and spatial skills, among others.

Figure 4 provides a schematic presentation of our attempt to sketch a developmental calculation model resting on the findings described above. Please note that results derived from meta-analysis III (disclosing effects of math competency on brain activation patterns) are not considered in our tentative model on typical developmental trajectories of numerical cognition. Moreover, at this point we wish to defer from incorporating the neural correlates of children's numerical skills into our developmental model. What the results of the present meta-analyses tell us is that children (compared with adults) produce less strong activations in number-supporting parietal regions. The latter finding of an age-dependent increased functional specialization of the IPS nicely fit the idea that the development of numerical processing involves "zooming" on the IPS. Similarly, activation differences in parietal regions between children with and without dyscalculia may reflect suboptimal functioning of number-relevant parietal regions in dyscalculic children. And finally, recruitment of additional extra-parietal regions (as found upon contrasting children vs. adults but also upon contrasting children with and without dyscalculia) likely reflects compensatory supporting mechanisms such as working memory, monitoring, updating, and so on.

Importantly, the differentiation between number processing and calculation has been proven useful in the standardization process of the German-language version of the dyscalculia test TEDI-MATH (Kaufmann et al., 2009c). The TEDI-MATH is a multi-componential calculation test for elementary school children. Upon employing faceted-smallest-space-analysis (FSSA) the administered tasks grouped into two clusters that are best conceptualized as components representing number processing and calculation (see also Krinzinger, Kaufmann, Wood, Nuerk, & Willmes, submitted). The rather clear distinction in two clusters (components) emerged across all age groups.

Taken together, results of the present meta-analyses of developmental fMRI studies on numerical cognition disclosed that children's activation patterns are clearly modulated by notation (symbolic vs. non-symbolic), task (number comparison vs. calculation), and competence level (children vs. adults; children with and without dyscalculia). Overall, recruitment of anterior intraparietal regions (which in some contrasts extend to postcentral gyrus), (pre)frontal regions, large portions of striate and extrastriate regions may be interpreted as reflecting effortful (number) processing. The latter assumption applies to typically developing children, but even more so to atypically developing children suffering from developmental dyscalculia.

Upon considering the rather small data base, we want to stress that the results of the meta-analyses reported here need to be interpreted with care. Nonetheless, we believe that beyond being timely, our endeavor to calculate statistically based meta-analyses of developmental fMRI studies in the realm of numerical cognition has the potential to contribute substantially to a better understanding of the neural structures and processes underlying the development of number representations and calculation abilities. Furthermore, we hope that the formulation of a tentative developmental calculation model may initiate future research endeavors targeted at refining the proposed model to eventually become a true and comprehensive *developmental* calculation model.

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