Numerical ordering and symbolic arithmetic share frontal and parietal circuits in the right hemisphere

André Knops [a,b,c,*], Klaus Willmes [b,c]

[a] Department of Psychology, Humboldt University, Berlin, Germany
[b] Section Neuropsychology, Neurological Clinic, University Hospital Aachen, Germany
[c] Interdisciplinary Centre for Clinical Research within the Faculty of Medicine at the RWTH Aachen University, Germany

A B S T R A C T

A prominent proposal in numerical cognition states that our mental calculation abilities are grounded in the approximate number system (ANS). Recently, it was proposed that this association is mediated by numerical ordering abilities. As a first step in elucidating the neural correlates of this link this study tested which areas in the human brain carry information common to both calculation and numerical ordering. While lying in an MR scanner 17 healthy participants (a) decided whether or not a given number triplet was presented in numerically ascending order, and (b) solved simple addition and subtraction problems. Standard general linear model analyses revealed a largely overlapping network in fronto-parietal regions for both tasks. By analyzing the spatial information over voxels using a whole-brain searchlight algorithm we identified a right hemispheric network comprising areas along the intraparietal sulcus and in the inferior frontal cortex which was similarly involved in order judgments and symbolic arithmetic. Functional and anatomical characteristics of this network make it a candidate for linking the ANS to mental arithmetic.

© 2013 Elsevier Inc. All rights reserved.

Introduction

Converging evidence suggests that the system enabling the estimation of the number of objects in a given set represents a crucial prerequisite for the development of adequate symbolic calculation skills (Piazza, 2010). When asked to estimate the number of items in a given set, estimations increase linearly with set size. Importantly, variability of the estimates increases proportionally with cardinality, yielding a constant coefficient of variation and thus conforming to Weber's law. Due to its imprecision this system is referred to as the approximate number system (ANS). The ANS represents numerical magnitude information in a language independent analog fashion. Humans share this system with other animals such as rats (Meck and Church, 1983), monkeys (Merten and Nieder, 2009; Nieder, 2012), birds (Emmerton and Renner, 2006), and even fish (Agrillo et al., 2007, 2009), implying a common evolutionary origin. In line with this claim, 6-months old babies already show numerical discrimination performance that is mainly defined by the ratio of the to-be-compared numerosities (Izard et al., 2009; Xu et al., 2005). Since symbolic number representation and its mental operations, e.g. mental arithmetic, are rooted in the ANS it 'inherits' certain characteristics and correlates with the acuity of the ANS. For example, when asked to distinguish two symbolic numbers, adults are faster and less error prone when the ratio of the two numbers is high, i.e. their numerical distance is large (Moyer and Landauer, 1967).

At the neural level, neuroimaging studies using functional magnetic resonance imaging (fMRI) repeatedly found the intraparietal sulcus (IPS) to be linked with the ANS and with mental arithmetic tasks. Voxels in the IPS have been found to decrease in activity upon repeated presentations of similar numerosities. Interestingly, this adaptation effect occurred irrespective of notation (dot patterns or Arabic numerals) (Piazza et al., 2004, 2007). Similarly, multi-voxel pattern analysis (MVPA) has been applied to fMRI data to decode the numerical information in a given display (Eger et al., 2009). Based upon activity in the IPS, the classifier was able to reliably distinguish between numerosities, underlining the crucial role of this brain region in representing numerical magnitude. Most importantly, however, Eger et al. (2009) were able to generalize from symbolic to non-symbolic numbers suggesting that the number representation is (at least partially) format independent. Recently, it has been shown that symbolic and non-symbolic mental arithmetic exhibit similar cognitive biases (Knops et al., 2009b). In problems with identical results, participants preferred larger outcomes for addition problems than subtraction problems, an effect referred to as the operational momentum effect. In a related fMRI study Knops et al. (2009a) demonstrated that symbolic and non-symbolic addition and subtraction activate largely overlapping portions of the bilateral IPS. By training a classifier on saccade-related activity in the posterior superior parietal lobe (PSPL) the authors were able to predict the type of mental operation (i.e. addition or subtraction) irrespective of notation (Knops et al., 2009a). Together, this implies that (i) symbolic calculation uses cortical

* Corresponding author at: Department of Psychology, Humboldt Universität zu Berlin, Rudower Chaussee 18, Berlin, 12489, Germany.
E-mail address: andre.knops@hu-berlin.de (A. Knops).

circuits of the ANS that evolved for processing of non-symbolic magnitude information and (ii) that mental calculation may (at least partially) rely on the dynamic interplay between subsystems of the parietal cortex, i.e. hIPS and PSPL.

Measures of the ANS acuity correlate with mathematical performance, both retrospectively and cross-sectionally (Halberda et al., 2008, 2012). Higher ANS acuity goes along with better symbolic mathematical performance. Moreover, delayed development of the ANS during childhood appears functionally related to developmental dyscalculia. The ANS acuity of 10-year old children suffering from developmental dyscalculia was significantly lower than IQ-matched controls and comparable to the ANS acuity of kindergarteners, i.e. displaying a developmental delay of approximately five years (Piazza et al., 2010).

The exact mechanisms and mediating skills that help build symbolic mathematics onto the ANS in the course of childhood remain elusive. Recently, the role of ordering abilities for the acquisition of numerical concepts has attracted attention. Lyons and Beilock (2011) tested university students on (a) a number comparison task in non-symbolic notation to measure ANS acuity, (b) an order judgment task using Arabic numerals, and (c) a mental arithmetic task involving all four basic mathematical operations (addition, subtraction, multiplication and division). Supporting the idea that symbolic calculation is grounded in the ANS (Halberda et al., 2012; Piazza et al., 2010), they observed a positive relation between ANS acuity and arithmetic performance, i.e. the better participants were in distinguishing dot patterns the better they scored in the mental arithmetic task. Second, they observed a positive correlation between ordering ability and mental arithmetic, which remained significant even after controlling for ANS acuity, working memory and other putative confounding variables. In a subsequent mediation analysis the authors demonstrated that the correlation between ANS acuity and arithmetic capacities was entirely mediated statistically by the capacity to judge the numerical order of Arabic numbers. Therefore, symbolic ordering ability may represent a stepping stone for exact calculation abilities to build up on the ANS.

To date no study has investigated the neural correlates of ordering abilities and arithmetic in the same participants. A number of studies investigated the relation between numerical and ordinal stimulus information. Fias and colleagues found that a letter position task ('which letter is later in the alphabet?') and a number comparison task lead to overlapping activations in bilateral IPS (Fias et al., 2007). Ischebeck et al. (2008) found that the bilateral anterior lateral portions of the IPS (area hIP2 according to probabilistic cytoarchitectonic maps (Caspers et al., 2008) as implemented in the Düsseldorf–Jülich histological atlas) were more active when participants generated exemplars from ordered sequences such as months or numbers as opposed to exemplars from classes without inherent order (i.e. animals). Outside the numerical domain, serial order has been investigated in the domains of (a) language processing and (b) working memory. Meyer, Obleser, Anwander and Friederici (2012) distinguish between storage and ordering of linguistic material. While left temporo-parietal regions are involved in storing linguistic information, Broca's area is involved in ordering them to avoid agent-object confusion, i.e. to correctly understand who is doing what to whom (Kim et al., 2009). Similarly, Broca's area has been shown to code for ordinal information in transitive learning paradigms where participants have to infer and maintain the ordinal structure of a new stimulus list (Van Opstal et al., 2009). Maintenance of order information in working memory elicited activation in right parietal cortex (Majerus et al., 2010). In these studies participants are presented with a series of items (faces or words) which they had to memorize. After a delay period participants were presented with two test items and had to judge whether they (a) previously appeared in the same order (order) or (b) whether both items were previously presented (identity). When contrasting order against identity (collapsing across faces and words), activation in right parietal cortex was observed. These results provide evidence for a modality-independent network including right anterior IPS underlying serial order processing.

The present study aims at investigating the neural correlates of order processing and mental arithmetic in a within-participant design, to further specify the link between the ANS and mental arithmetic. No brain imaging studies so far have investigated the relationship between ordering abilities and mental arithmetic. This study therefore establishes the first step in defining which brain mechanisms and networks are involved in linking the ANS to symbolic calculation via ordering abilities.

From a theoretical point of view, areas that functionally link the processing of order information to mental arithmetic must meet several criteria: First, the area must be active in both ordering and mental arithmetic (criterion 1). Second, the spatial activation pattern elicited by ordering should be similar to the spatial pattern elicited by mental arithmetic and this correlation should be consistently found in the majority of participants (i.e. be significant at the group level; criterion 2). Third, we hypothesized that those arithmetic operations, which are more demanding in terms of numerical competencies and for which ordering abilities are more important, also exhibit a stronger correlation with ordering ability (criterion 3). We reasoned that subtraction (compared to addition) may rely more on ordering abilities due to a stronger involvement of backward counting in combination with the importance of serial position of operands in non-commutative subtraction. The current study includes addition and subtraction problems as well as a numerical ordering task, thus allowing us to test, which areas in the brain meet these criteria and may potentially link symbolic calculation to ordering abilities.

Materials and methods

Participants

After having given their written informed consent, fMRI data was acquired from 21 healthy participants while they were performing two tasks (see below). All participants had normal or corrected-to-normal vision and reported no history of neurological or psychiatric illness. Participants were paid 10€ per hour for their participation. This study was approved by the local Ethics Committee of the Medical Faculty, RWTH Aachen University.

Four subjects were excluded from subsequent analysis due to missing task compliance (1), extensive head motion artifacts during scanning (2), or because participants quit the procedure before the session had ended (1). All subsequent analyses are based on data from 17 participants (8 male participants; mean age: 24.9 years [min–max: 20–31 years]).

Stimuli and procedure

Participants engaged in two tasks, a calculation task and a task to assess ordering ability (order).

In the calculation task participants were visually presented with addition and subtraction problems in Arabic notation followed by two response choices and had to indicate the correct result by pushing a button on the corresponding side (left or right). Addition and subtraction problems were randomly intermixed. For each participant the sequence was generated anew. All operands and results were two-digit numbers (21–89). Problems were created such that they would not contain tie numbers (e.g. 66), operands with identical units (e.g. 56 + 46), parts of multiplication tables (e.g. 24 + 12), or result in a decade number (e.g. 24 + 36 = 60). In order to prevent participants from basing their decision on the information of the unit position only we presented the correct results along with a response alternative (ra) that was computed by adding a constant (co) to the correct result (cr) as $ra = cr + co$ with co being member of the set $\{-10, -2, 2, 10\}$. Half of the problems comprised carrying (e.g. 59 + 13 = 72) or borrowing (e.g. 62 − 13 = 49), resulting in 4 stimulus groups (addition no carry, addition carry, subtraction no borrowing, subtraction borrowing). Problems size (defined as the sum of all three numbers in a given problem, i.e. operand 1 + operand 2 + result) was carefully matched

between all stimulus categories. Mean problem size varied only slightly between conditions (minimum: 133.75 [addition without carry], maximum: 134.88 [addition problems with carry]; mean: 134.44). Each of these categories contained 32 stimuli, resulting in 128 calculation problems.

Calculation problems were presented in a slow event-related design. Each trial started with the presentation of a fixation cross in the center of the screen for 1000 ms, followed by the subsequent presentation of the first operand, the operator, the second operand, and an equal sign. All elements of one problem were temporally separated by the presentation of a blank screen for 200 ms. The response alternatives were presented to the left and right of the center of the screen after a blank screen would allow the participants to calculate the result of the current problem for the mean duration of 3500 ms (randomly varied between 3100 ms and 3900 ms in steps of 100 ms). Responses were presented until a response was made or for a maximum of 1700 ms. Individual trials were separated by an interval of 10,000 ms to allow for complete recovery of the BOLD response between trials. The calculation task was divided into four blocks, each lasting approximately 10.5 min. A trial is schematically depicted in Fig. 1 (top). In total the calculation task took 45 min on average.

For the order task participants were shown three single-digit numbers between one and nine, horizontally arranged and had to indicate whether or not the three numbers were numerically ascending from left to right (left button = no; right button = yes). Half of the number triplets were numerically ascending (e.g. 1 4 9). The rest of the triplets were either numerically descending (50%; e.g. 8 5 2) or did not conform to a monotonic function (50%; e.g. 5 2 8). In order to control for low-level visual activity and activity related to response preparation, response selection and response execution we included a control condition in which participants had to indicate on which side a symbol sequence (e.g. § Þ Þ) contained two identical symbols.

The order task was presented as a block design with number triplets and symbol triplets alternating between blocks. Each block started with an instruction presented for 5000 ms, followed by a fixation cross for 400 ms, and the first number/symbol triplet presented for 1500 ms. If a participant's response latency in a given trial was smaller than 1500 ms, the letter/symbol triplet was replaced by a blank screen for the rest of the 1500 ms period. After 800 ms the next triplet was presented. Fig. 1 (bottom) schematically depicts two trials from the ordering task (left) and the control task (right). A block contained 16 triplets and lasted 41,800 ms. Individual blocks were separated by a low-level baseline condition for 20,000 ms, where only the German word for break ("Pause") was presented on screen, allowing participants to recover and prepare for the upcoming block. A total of 8 blocks was presented, 4 number blocks, and 4 symbol blocks. Total duration of the order task was approximately 8.2 min.

Apparatus and imaging parameters

Functional images were acquired on a 3T Siemens TrioTim MR system with a standard head coil. Transversal multi-slice T2*-weighted images were obtained with a gradient echo planar imaging sequence (TE = 28 ms; TR = 1800 ms; in plane resolution = 3×3 mm^2; slice thickness = 3 mm; slice spacing = 3.99 mm; matrix = 64×64; slices = 30; flip angle = 67°) covering the whole brain for all participants studied. During the calculation task 4×349 volumes were acquired, while in the order task 280 volumes were acquired. The first four volumes of each session were discarded to allow tissue to reach steady state magnetization. A high-resolution T1-weighted three-dimensional anatomical image was also acquired (TE = 2.98 ms; TR = 2300 ms; 256×256 matrix; voxel dimensions = $1 \times 1 \times 1$ mm^3; 176 slices; flip angle = 9°).

All visual stimuli were administered via MR compatible video goggles (VisuaStimDigital) by Resonance Technology Inc. (http://www.mrivideo.com). Stimulation protocols were controlled by Presentation software (Neurobehavioral Systems).
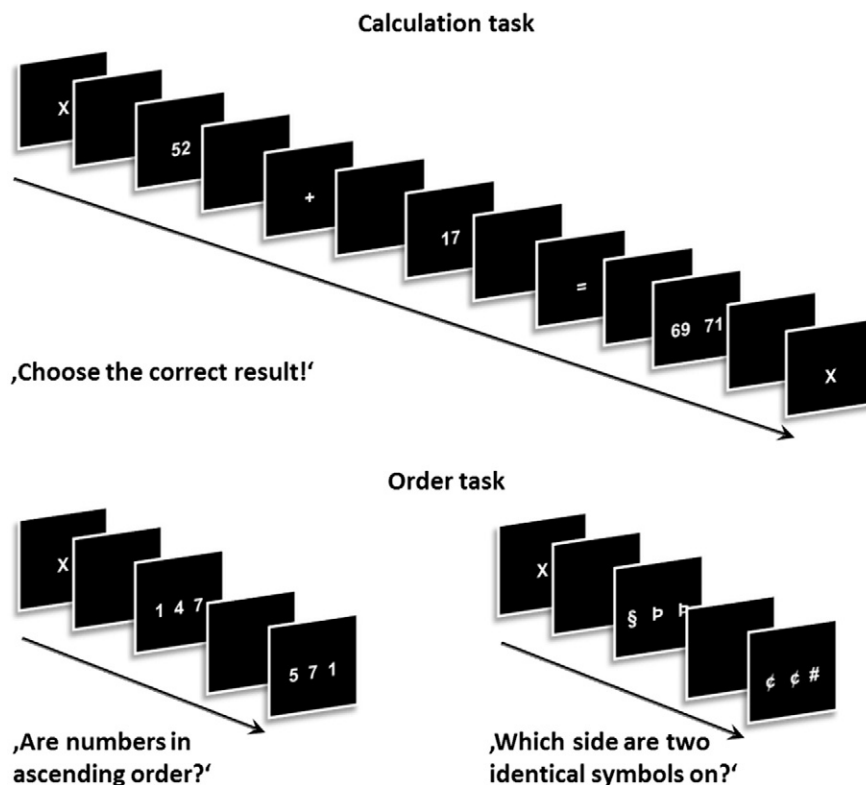

Fig. 1. Schematic depiction of a trial in the calculation task (top) and the ordering task (bottom).

fMRI data analysis

Images were analyzed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging; http://www.fil.ion. ucl.ac.uk/spm/). The functional images were corrected for slice acquisition delays, re-aligned to the first scan of the first run to correct for within- and between-session motion, co-registered with the anatomical image, and normalized to the MNI template using the Segment module in SPM8. Thus, for each participant a probability map of several tissue types (gray matter, white matter, and cerebro-spinal fluid) was available. Spatial smoothing with a Gaussian kernel (FWHM = $6 \times 6 \times 8$ mm^3, i.e. 2 times the voxel size) was applied only for the GLM analyses. All correlation analyses (see below) were computed using unsmoothed data.

In the calculation task, for each participant and session a general linear model was defined, which included 2 regressors at the onset of the second operand (addition vs. subtraction) and 6 individual motion parameters from preprocessing to capture remaining signal variations due to head motion. The canonical hemodynamic response function and its temporal derivative were used to model the BOLD response. To visualize the network of brain regions underlying addition and subtraction, both conditions were contrasted against baseline.

In the order task, each block was modeled by a standard hemodynamic response function (and its temporal derivative), resulting in a model with 3 regressors: number triplet, symbol triplet (high-level baseline), and pause (low-level baseline). To visualize the network of brain regions underlying processing of order information the number triplets were contrasted against the symbol triplets at the participant level.

Recent multivariate analysis approaches of brain imaging data emphasize that different tasks, conditions and even stimulus categories give rise to distinct and recognizable patterns of activation, even in situations when the classical General Linear Model (GLM) approach is not sensitive enough to reveal amplitude differences (Haxby et al., 2001; O'Toole et al., 2007). To go beyond the mere report of overlapping activity, we use across voxel correlations (AVC) to investigate the relationship between ordinal and cardinal information in the context of mental arithmetic. AVC are computed by sampling from the voxels in a given region of interest the parameter estimates for two conditions in a first step and computing the Pearson correlation coefficient across voxels in a second step (Peelen et al., 2006). We extend this approach in two important ways. First, rather than limiting the analysis to certain predefined regions of interest and potentially missing important information from other regions, we apply a search light algorithm to the whole brain. Second, unlike previous studies that used AVC analyses (Andres et al., 2012; Peelen et al., 2006), we limited the search space to gray matter voxels rather than including theoretically uninformative information from white matter voxels.

AVCs were computed using a searchlight algorithm. Before computing the AVCs, the models described above were computed using unsmoothed data to maintain the maximal amount of spatial information present in the original data. All other aspects of preprocessing were identical to the standard GLM analyses. Every voxel inside a participant-specific mask covering the whole brain served as a seed voxel once. Around the seed voxel a sphere was created (radius = 5 voxels) and Pearson correlation coefficients between conditions were calculated across these voxels using the parameter estimates ('beta') of the linear contrasts described above. Inside a given sphere only those voxels were selected, which contained gray matter tissue, as defined by the gray matter probability map created during preprocessing by SPM8. To obtain a participant specific binary gray matter mask the individual gray matter probability maps were thresholded at 0.2 and resampled to match the spatial resolution of the functional data. The correlation between two given conditions was assigned to the respective seed voxel. For further statistical analyses correlations were Fisher Z′-transformed (Fisher, 1921). Statistical significance of correlation maps at the group level was tested by feeding the Z′-maps into the standard second-level one-sample *t*-test routine

in SPM, applying a FDR-corrected alpha of p < .05. Similarly, (dependent) individual subject AVC correlations between subtraction and order condition (respectively addition and order condition) were compared at the group level by computing the difference of both Z′-transformed AVC correlations per voxel and feeding the resulting individual subject Z′-difference maps into the standard (second level) one-sample *t*-test routine in SPM. For visualization purposes standard correlation coefficients ($-1 <= r <= 1$) are mapped onto a standard mesh (Van Essen, 2005) using Caret software (Van Essen et al., 2001).

The following contrasts were computed. For calculation we separately contrasted both addition and subtraction against baseline (addition > baseline; subtraction > baseline) and against each other (addition > subtraction; subtraction > addition). For the order task we contrasted order versus symbol condition (order > symbol).

For the AVC analyses, order was correlated with both arithmetic operations (r[addition, order]; r[subtraction, order]). We also contrasted the two correlation maps against each other (r[subtraction, order] > r[addition, order]).

For all analyses the participant specific contrast images were tested for significance at the group level by standard t-tests. False discovery rate (FDR (Genovese et al., 2002)) in combination with a minimal cluster size threshold (k) of 10 voxels was used to correct for multiple testing at p < .05.

Behavioral analysis

Before submitting reaction times (RTs) to subsequent analyses, outliers (RTs outside a range of ± 2.5 standard deviations around a participant's mean) were discarded from the data. All reaction times were analyzed using repeated measures ANOVA, and post-hoc analyses were conducted using one sample t-tests. Error rates (ER) were analyzed likewise after they had been arc-sine transformed (2arcsin $\sqrt{}$ error rate).
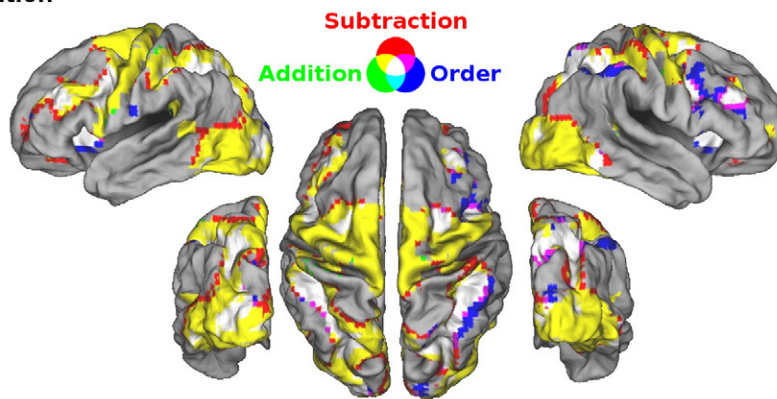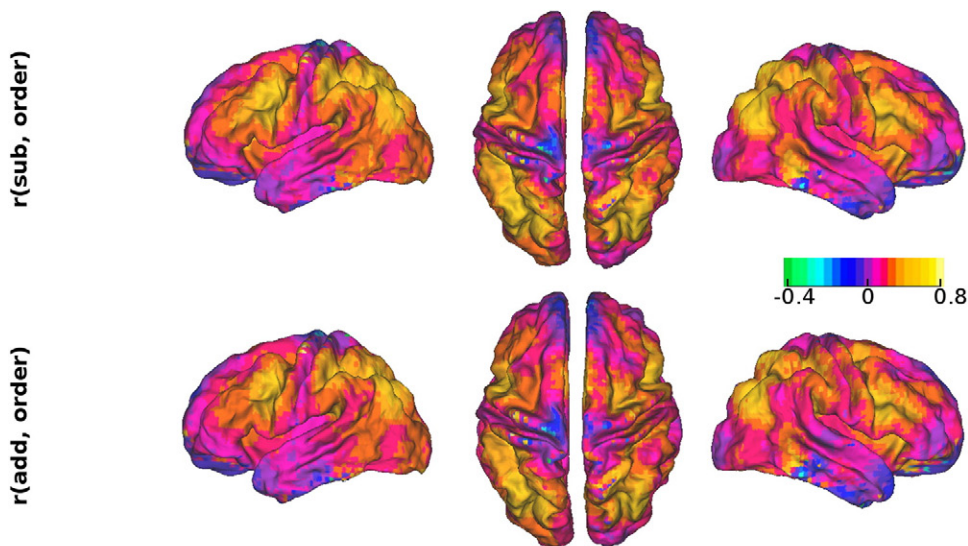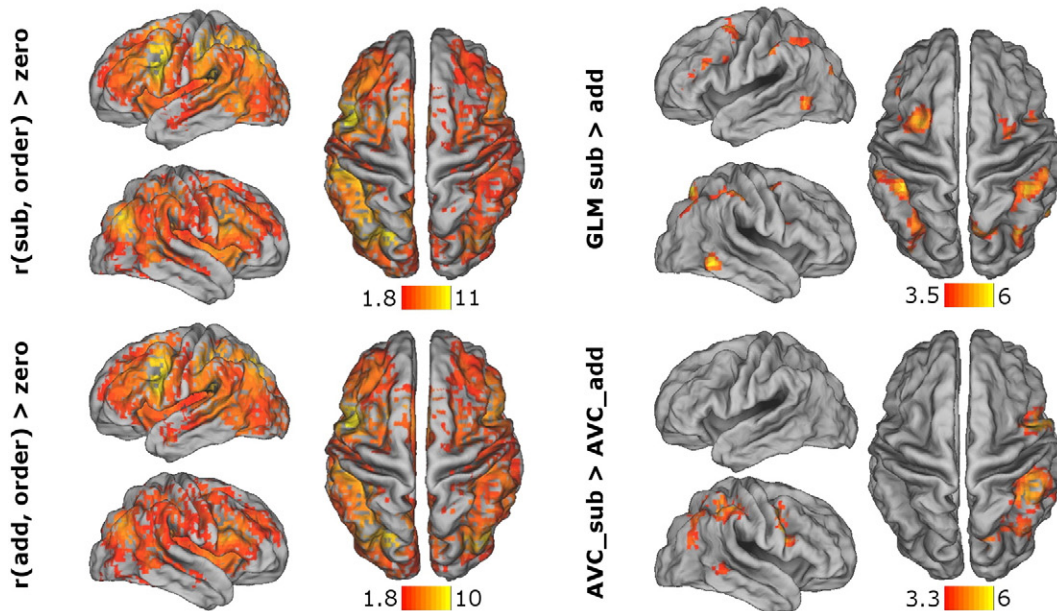
Results

Behavioral results

In the calculation task participants were significantly faster and more accurate in responding to addition (700 ms; 9%) than to subtraction (761 ms; 14.9%) problems (RT: $F(1, 16) = 15.85$, $p = .001$; ER: $F(1, 16) = 13.42$, $p = .002$) and responded faster/more accurately to problems without carrying/borrowing (705 ms; 9.7%) than to problems with carrying/borrowing (757 ms; 14.3%; RT: $F(1, 16) = 10.24$, $p = .006$; ER: $F(1, 16) = 4.64$, $p = .047$). As indicated by the significant interaction between carrying and operation (RT: $F(1, 16) = 12.73$, $p = .003$; ER: $F(1, 16) = 4.76$, $p = .044$) this difference was mainly due to slower RTs, respectively more errors in subtraction problems involving borrowing (subtraction borrowing vs. subtraction no borrowing; RT: $t(16) = 4.039$, $p = .001$; ER: $t(16) = 3.4$, $p = .004$); for addition problems carry vs. no carry had no effect; RT: $t(16) = .165$, $p = .87$; ER: $t(16) = .71$, $p = .486$).

In the order paradigm participants responded significantly faster to the symbol condition than to the number triplets (569 ms vs. 875 ms, respectively; $t(16) = -11.59$, $p < .001$). Order of the triplets had a significant impact only on accuracy (RT: $F(2, 32) = 1.691$, $p < .201$, Greenhouse–Geisser $\varepsilon = .98$; $F(2, 32) = 43.542$, $p < .001$, Greenhouse–Geisser $\varepsilon = .878$). Triplets in non-monotonic order (e.g. 9 5 7) were responded to significantly less accurately (73.90%) than triplets in ascending (89.71%; ER: $t(16) = -6.082$, $p < .001$) or descending (95.22%; ER: $t(16) = -7.949$, $p < .001$) order, with descending triplets being significantly more accurately responded to than ascending triplets (ER: $t(16) = 4.268$, $p = .001$). In partial contrast to previous results (Lyons and Beilock, 2009) participants were more accurate but not faster when responding to symmetric triplets (e.g. 2 5 8; 879 ms; 92.7%) than when responding to asymmetric triplets (e.g. 1 3 9; 883 ms; 40.13%; RT: $t(16) = -0.25$, $p = .804$; ER: $t(16) = 13.83$, $p < .001$).

A GLM Activation

B Across Voxel Correlation

C Masking Contrasts

Fig. 2. (A) Activation data of subtraction (red), addition (green), and order task (blue) against baseline projected on top, lateral and back views of the brain (all FDR-corrected p < .05). Areas jointly activated by subtraction and additions are depicted in yellow. Overlap between all three contrasts is shown in white. (B) Projections of across voxel correlation (AVC) on lateral and top views of the brain are shown in top (r[subtraction, order] and bottom (r[addition, order] row. Correlation strength is color coded with negative correlations (e.g. in left motor cortex) being depicted in blue or green and positive correlations with 'warmer' colors (see color bar). (C) Contrasts at the group level that served as masks to determine those regions that met criteria 1 to 3. Color bars depict t-values from respective parametric maps in SPM. Top left: r(subtraction, order) > zero. Bottom left: r(addition, order) > zero. Top right: subtraction > addition (GLM). Bottom right: results from AVC contrast r(subtraction, order) > r(addition, order). All contrasts corrected for multiple testing at FDR p < .05 with a minimum cluster size k = 10.

Imaging results

Activation

Subtraction and addition activated a network which is well-described in the literature, consisting of parietal, prefrontal, inferior frontal, and (pre-)central areas. These networks were highly overlapping, as illustrated by the superposition of both maps onto a single surface template (see Fig. 2A).

The network activated by the contrast order > symbol revealed a similar parieto-frontal network comprising parietal, prefrontal, inferior frontal, and (pre-)central areas (see Fig. 2A, blue). Any overlap (shown in white in Fig. 2A) between both networks (calculation and ordering) can be regarded to meet criterion 1 from the Introduction section.

Criterion 3 stipulates that subtraction relies more on ordering abilities than addition. Hence, any region that is particularly engaged in mediating the relationship between the mental magnitude representation and calculation via ordering abilities should exhibit more activity in the contrast subtraction > addition (criterion 3). Note that computing this contrast also allows to 'subtract out' activation from low-level, visual, or response-related processes that are common to both arithmetic operations. In the contrast subtraction > addition activation was observed in bilateral parietal cortex along the IPS, superior frontal gyrus extending into precentral gyrus, left inferior and middle frontal gyrus along the inferior frontal gyrus, right inferior frontal cortex, and bilateral inferior and middle temporal cortex. Results are shown in Fig. 2C (top right) and anatomical locations of peak activations are listed in Table 1.

Across voxel correlation (AVC)

To test which regions exhibit a similar spatial pattern of activation and hence a similar involvement of the constituting neural circuits in both conditions (criterion 2), we computed whole-brain AVC between both calculation networks (addition and subtraction separately) and the order contrast (order > symbol). Fig. 2B depicts the AVC between addition and order (top row of Fig. 2B) and the AVC between subtraction and order (bottom row of Fig. 2B). These maps reveal that the involvement of bilateral parietal and bilateral dorso-lateral prefrontal cortex circuits in the order task resembles involvement in the calculation task and hence meets criterion 2. To evaluate which regions exhibit a coherently similar pattern between addition and subtraction on the one hand and order on the other, we submitted the individual correlation maps to a standard *t*-test in SPM. Results are shown in the left column of Fig. 2C. Large parts of gray matter tissue exhibit significant overlap in spatial pattern of activation elicited by addition and subtraction on the one hand and ordering ability on the other hand, as evidenced by significantly positive correlation coefficients. For both addition and subtraction, the highest correlations were observed in left parietal regions including inferior and superior parietal cortex, angular gyrus, supramarginal gyrus, and precuneus, extending into middle and superior occipital gyrus. Peak correlations were also observed in the left supplementary motor area, extending into the left superior frontal lobe and cingulate cortex, left prefrontal regions including pars triangularis, Insula and Rolandic operculum, right inferior frontal cortex (pars triangularis, Rolandic operculum, Insula), right precuneus and right middle occipital gyrus extending into angular gyrus. Table 1 summarizes the peak correlations and their coordinates according to the automated anatomical labeling toolbox in SPM8 (Tzourio-Mazoyer et al., 2002). Note that in order to individuate the different peak correlations in SPM we raised the statistical threshold to p < .05 (family wise error [FWE] corrected).

According to criterion 3 any region that is particularly engaged in mediating the relationship between mental magnitude representation and calculation via ordering abilities should (a) exhibit more activity in the contrast subtraction > addition (see above) and (b) exhibit a more similar spatial pattern between subtraction and ordering than between addition and ordering. Areas that meet these conditions can be regarded as meeting criterion 3. Hence we contrasted the AVC(subtraction, order) > AVC(addition, order). Note that this goes
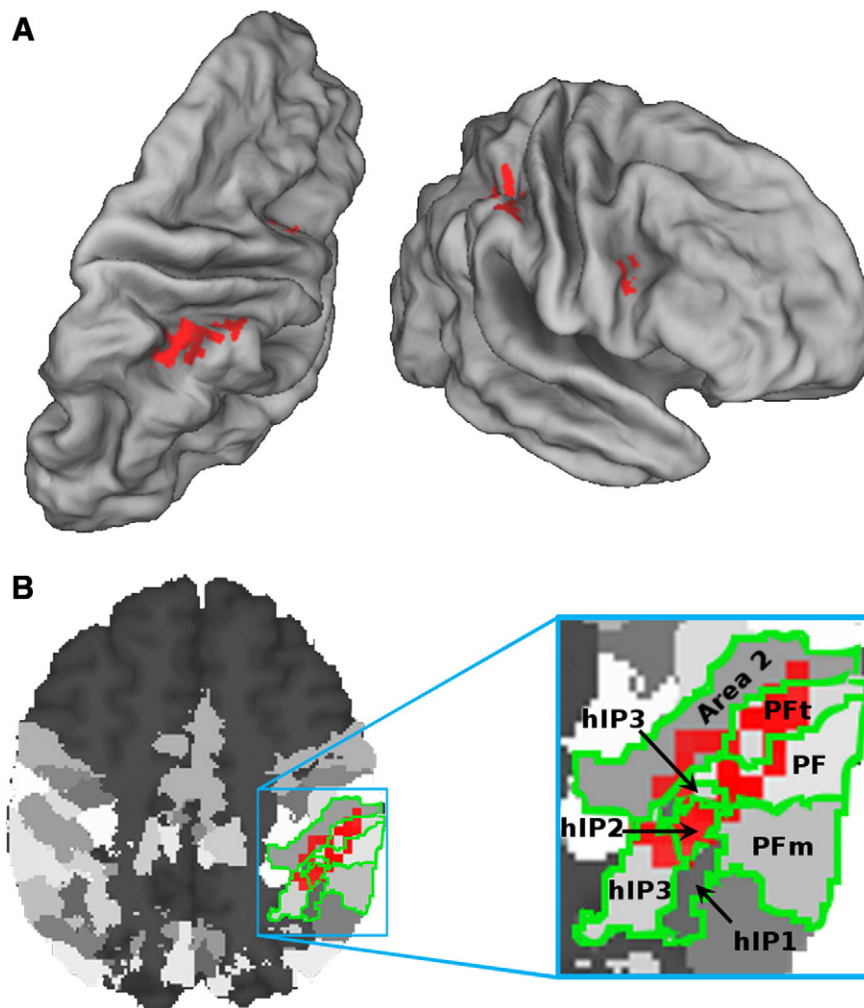
Table 1
Peak coordinates and anatomical labels of brain regions significantly activated in contrasts used as masks (all p < .05, FDR-corrected).

Contrast	Brain region	z-Score	Peak coordinates (MNI)		
			x	y	z
r(sub, order) > zero	L parietal, sup. temporal,	5.53	−21	−73	46
	L suppl. motor area, sup. frontal	5.51	−15	14	62
	L precentral, inf. frontal	5.47	−42	8	34
	R mid. occipital, angular gyrus	5.15	42	−76	34
	R precuneus	5.12	18	−67	30
	L insula	4.75	−39	5	10
	R inf. frontal	4.74	36	35	−10
	R inf. frontal	4.72	51	17	14
	R Insula	4.70	39	8	10
	R postcentral	4.37	42	−28	42
r(add, order) > zero	L precentral	5.70	−48	2	30
	L parietal, sup. temporal, occipital	5.56	−21	−73	46
	L suppl. motor area, sup. frontal	5.30	−18	17	54
	L insula	4.86	−39	5	10
	R inf. frontal	4.85	51	17	14
	R insula	4.79	39	8	2
	R precuneus	4.73	18	−67	30
	R mid. occipital, angular gyrus	4.71	42	−37	34
Subtraction > addition	L parietal	4.23	−45	−40	42
	R parietal, precuneus	4.16	18	−70	58
	R inf. & mid. temporal	4.14	60	−55	10
	R parietal	4.04	45	−40	50
	R mid. & sup. frontal, suppl. motor area	3.90	12	20	46
	L mid. & inf. temporal	3.85	−57	−61	−2
	L inf. & mid. frontal	3.69	−48	44	10
	R mid. & sup. frontal	3.62	33	−1	54
	R inf. frontal, precentral	3.54	51	8	22
	L precentral, mid. frontal	3.22	−39	8	34
r(sub, order) > r(add, order)	R precentral, inf. & mid. frontal	4.20	51	2	42
	R parietal, postcentral, angular gyrus	3.87	45	−43	50
	L post. cingulum	3.28	−3	−37	26
	R inf. & mid. temporal	3.07	63	−40	−2

inf.—inferior; L—left hemisphere; mid.—middle; post.—posterior; R—right hemisphere; sup.—superior; suppl.—supplementary.

beyond the notion that subtraction leads to more activation in a given region of interest (see above GLM contrast subtraction > addition). This would be trivial given that subtraction is often found to be more difficult than addition (see Behavioral results section). In contrast, here we search for regions that show higher similarity in activation pattern between subtraction and order as compared to addition and order and that are more activated for subtraction compared to addition. From a theoretical and statistical point of view these notions are independent, thus raising the bar for regions to fulfill these criteria. The contrast AVC(subtraction, order) > AVC(addition, order) yielded right lateralized activations in the precentral gyrus, inferior and middle frontal regions, parietal cortex and precuneus, and inferior and middle temporal areas, as well as one cluster located in left cingulate. Results are summarized in Table 1.

Finally, we combined the above analyses to further specify regions in the brain that would mediate the relationship between mental arithmetic and ordering abilities. To this end we inclusively masked the AVC contrast AVC(subtraction, order) > AVC(addition, order) by all contrasts described above (AVC[subtraction, order], AVC[addition, order], subtraction > baseline, addition > baseline, and subtraction > addition). Results are shown in Fig. 3 and anatomical location of peak activations is listed in Table 2. Only areas in right Brodmann area 44 (BA 44) and along the right IPS met the conditions imposed by criteria 1 to 3. The right parietal cluster included voxels along the fundus of the IPS (hIP1, hIP2, hIP3) and in the supramarginal gyrus (PF, PFt, PFm). At the anterior end this cluster extended into the post-central gyrus (BA 2). In Fig. 3B the parietal cluster is projected

Fig. 3. (A) Right hemispheric regions fulfilling all criteria (1–3) as defined in the Introduction section projected on posterior–superior (left) and lateral–frontal (right) views of the brain. (B) Projections on horizontal plane (z = 49.5) of cytoarchitectonically defined parcellation of the brain in SPM (Anatomy toolbox (Eickhoff et al., 2007)) with a zoom on the activated regions (blue box) on the right. Borders of labeled areas in right parietal lobe are depicted in green; all FDR-corrected (p < .05) and inclusively masked by the contrasts as specified in the text.

onto the cytoarchitectonically defined regions of the parietal cortex. The outlines of the relevant parietal regions are shown in green and labels are provided in the zoom inset in the right part of Fig. 3B.

Discussion

In this study we investigated which brain regions are jointly involved in the processing of order information and mental arithmetic and may thus serve as candidate regions linking the ANS to symbolic calculation abilities. Behaviorally, this link is mediated by the ability to analyze order information in a series of three numbers (Lyons and Beilock, 2011). Therefore, we administered an order judgment task

Table 2
Probabilistic labeling of parietal cortex and frontal cortex activation meeting criteria 1–3, as defined in the text.

Cluster	# voxels	Max	Labels [probability]	z-score	MNI peak coordinates		
					x	y	z
Parietal	65	1	hIP2_R [30]	5.09	45	−43	50
		2	hIP2_R [30]	4.86	51	−37	50
		3	hIP3_R [40]	4.47	33	−49	50
Frontal	16	1	Area 44_R [50]	4.69	54	11	22

and a symbolic calculation task to participants while measuring their BOLD response. We derived three criteria that such areas must meet. First, these areas need to be activated in both calculation and ordering. Second, the spatial activation pattern should be similar between ordering and calculation and this association should be significantly different from zero (i.e. no association) at the group level. Third, subtraction should exhibit stronger association with ordering ability than addition. Complementing standard GLM analyses with whole-brain across voxel correlations (AVC) confined to cortical gray matter, we analyzed the similarity of spatial patterns of activation between ordering and calculation and identified a circumscribed cortical network of right hemisphere regions that fulfilled these criteria. This network comprises the right anterior and lateral aspects of the IPS (hIP1, hIP2, and hIP3), extending into postcentral gyrus (BA 2) and supramarginal gyrus (PFt, PF, PFm), and right inferior frontal cortex (BA 44). This network might be considered a candidate for linking the ANS to symbolic calculation abilities.

Functional role of right parietal cortex

We identified a circumscribed right-hemispheric cluster in the anterior and lateral aspect of the IPS that appeared related to both ordering abilities and symbolic arithmetic. This is in accordance with results from previous studies on mental arithmetic where bilateral parietal activations have frequently been reported (Arsalidou and Taylor, 2011).

Most importantly, right parietal activation has been reported when contrasting subtraction versus addition using two-digit problems as the ones used here (Kong et al., 2005). Generating exemplars from ordered sequences such as months or numbers as opposed to exemplars from classes without inherent order (i.e. animals) has been reported to elicit activity in hIP2 (Ischebeck et al., 2008), a region we observed in the current study, too. Interestingly, the reported activation in right parietal cortex in the context of maintenance of order information in working memory (Majerus et al., 2010), too, coincided well with the localization of the parietal cluster in the current study. Hence the current results are in line with the previous results from different domains, i.e. numerical cognition and working memory. The current findings extend previous reports by showing that – within the same participants – ordering related activation in right anterior parietal cortex overlaps with mental calculation activation. Going beyond the report of mere overlap we show that the spatial pattern of activation is similar between calculation and ordering, with subtraction showing a closer resemblance than addition. Thus, for the first time the present study convincingly demonstrates the functional implication of overlapping neural circuits in right anterior parietal areas in both symbolic calculation and numerical order judgments.

Functional role of right-hemisphere BA 44

Besides a right parietal cluster a circumscribed cluster in right BA 44, the right-hemisphere homologue of Broca's area in the left hemisphere, fulfilled all criteria for linking ordering ability to mental arithmetic. Left hemisphere BA 44 is part of Broca's area and thus classically considered a language-related area. More specifically, left BA 44 is supposed to be involved in processing phonological and syntactical aspects of language (Poldrack et al., 1999). Friederici (2002, 2012) argues that left BA 44 processes syntactically complex sentences and hierarchical structures independent of semantics. Broca's area is involved in ordering linguistic information to avoid agent-object confusion (Kim et al., 2009) and also codes for ordinal information in transitive learning paradigms (Van Opstal et al., 2009). At the anatomical level this network is well reflected by the connectivity of BA 44. Via the arcuate fasciculus (AF) and/or the fasciculus longitudinalis superior (FSL) Broca's area connects to superior temporal sulcus (STS) and middle temporal gyrus (MTG), as well as to inferior parietal cortex. In the macaque brain area 44 directly projects to PFG (Petrides and Pandya, 2009), an area that corresponds to the caudal aspect of human supramarginal gyrus. Area 44 also receives input from area PG (Petrides and Pandya, 2009), an area located in the angular gyrus in the human brain (Caspers et al., 2006). Beyond ordering of linguistic information Broca's area has been considered to participate in the encoding of human action. Left-hemispheric lesions to Broca's area lead to impaired sequencing and ordering of action-related pictures (Fazio et al., 2009). Hence, the left hemisphere appears to contain a network including Broca's area (left BA 44) that is associated with processing of syntactical and ordinal features of language, action, and memory content.

While an extensive literature describes the functional and anatomical characteristics of left BA 44 (Broca's area), the functional role of its right hemisphere counterpart is described in much less detail. In the context of the current study it is important to note that mental arithmetic studies frequently reported activation in right BA 44 but either did not thoroughly discuss its functional significance (Grabner et al., 2009; Stanescu-Cosson et al., 2000) or mainly focused on parietal activation (Molko et al., 2003; Simon et al., 2002). For example, Simon et al. (2002) found the right BA 44 active in calculation versus letter naming, in grasping versus object naming, and in a phoneme detection task versus orthographic evaluation. BA 44 was also found to be significantly more active during procedural calculation than during arithmetic fact retrieval (Grabner et al., 2009). Analyzing the functional connectivity in the context of a non-symbolic subtraction task, Park et al. (2012) identified right BA 44 to be linked with activation in right parietal cortex. Our results are in line with these findings and, for the first time, offer the

opportunity to pinpoint the putative function of right BA 44 in the context of mental arithmetic.

Basic aspects of anatomical organization in BA 44 by and large seem to be similar between both hemispheres (Keller et al., 2009), hence similar networks may well exist in both hemispheres. Recent fiber tracking studies found left and right BA 44 to be connected with ipsilateral inferior parietal areas (PFt, PF, PFm, PGa, and PGp) and observed no hemispheric differences for those connections (Caspers et al., 2011). For the left hemisphere a network comprising Broca's area, left STS and left MTG has been associated with the processing of ordinal aspects of linguistic materials and action. Within this network left BA 44 seems to be associated with processing of syntactic and ordinal information while STS and MTG carry semantic information (Meyer et al., 2012). Based on the present findings we propose a similar right hemispheric network comprising right BA 44 and right IPS regions, which is associated with the processing of order information in the context of mental arithmetic. This network may operate on the spatial aspects of numerical information for two reasons. First, numerical magnitude has been proposed to be represented on a spatially oriented mental number line. Numerical magnitude information is thought to be represented in a place coding scheme, with noisy activation peaking at the respective position on the mental number line. The notion of a spatially organized mental magnitude representation has received empirical support from patient studies (Umiltà et al., 2009), behavioral (Dehaene et al., 1993) and neuroimaging studies (Koten et al., 2011). Hubbard et al. (2005) proposed to conceive of mental arithmetic as movements along the mental number line which are mediated by the dynamic interplay between PSPL and IPS. Second, areas PF, PFm, and PFt show strong anatomical connections to superior parietal cortex, including parietal areas 5M, 7PC, and 7A (Caspers et al., 2011). These regions seem to be involved in the processing of allocentric coordinates in spatial navigation (Zhang and Ekstrom, 2012) and (together with the retrosplenial cortex) in the "retrieval of object locations within the context of a stable reference frame (p. 14)". The dynamic interplay between these regions may thus provide information about the relative position of activations on a spatially organized mental magnitude dimension. Interestingly, the AVC between subtraction and ordering was significantly higher as compared to the AVC between addition and ordering. The activation pattern elicited by subtraction hence was more similar to the pattern found in the ordering task, implying that order information contributes more to subtraction than to addition. In combination with the notion that the spatially oriented mental number line plays a more crucial role in subtraction than in addition this suggests that order, too, is extracted from a spatially organized representation. Together our findings fit nicely with the idea that the IPS does not only represent numerical magnitude. Rather its functional scope needs to be augmented to serial position information of inherently ordered categories or memorized sequences.

Linking the ANS to symbolic calculation abilities

Ordering abilities are supposed to link symbolic calculation to the ANS (Lyons and Beilock, 2011). Can the present study help establishing the link between ANS and symbolic calculation abilities? As stated in the Introduction section, cumulating evidence suggests common neural circuits underlying an abstract numerical magnitude representation. This notion has received support from empirical work (Eger et al., 2009; Knops et al., 2009a; Piazza et al., 2004, 2007; Santens et al., 2010) and theoretical modeling studies (Verguts and Fias, 2004). For example, Knops et al. (2009a) demonstrated that symbolic and non-symbolic calculation activated largely overlapping areas in bilateral IPS. Moreover, they demonstrated that posterior parietal areas are equally involved in non-symbolic and in symbolic calculation. These studies point to an abstract magnitude representation which is accessed by different number notations in the context of various tasks, albeit along different routes (Santens et al., 2010) and with different precision for symbolic and

non-symbolic notation (but see Cohen et al. (2009) for a different view). If the notion of an abstract magnitude representation holds at the neural level, we would expect both symbolic (current study) and non-symbolic magnitude information to activate similar if not identical neural circuits. Indeed, the right parietal cluster reported here (peak coordinates: 45, −43, 50) has also been reported in several previous neuroimaging studies investigating non-symbolic magnitude representation: the mean coordinates (38.4, −45.5, 45.5) from a recent meta-analysis reviewing brain imaging studies investigating the processing of different magnitude dimensions (Cohen Kadosh et al., 2008), the peak activation (42, −46, 48) in a conjunction analysis of sequentially and simultaneously presented non-symbolic magnitude information versus control (Dormal et al., 2010), and the peak activation (42, −44, 52) of a right parietal cluster showing distance-dependent recovery from adaptation (Piazza et al., 2007) all fall well within the range of the parietal cluster reported here. Consequently, we think it is reasonable to assume that the very same or at least largely overlapping neural circuits are recruited for (1) processing abstract numerical magnitude, and, based upon the present study, (2) order processing as well as (3) symbolic addition and subtraction. We therefore tentatively propose the identified network as an ideally suited candidate region for linking the ANS with mental calculation abilities. This network may provide a neural instantiation of the "proposal that relative order in numerical symbols is a stepping stone between the ANS and higher math abilities (p. 257, Lyons and Beilock, 2011)".

Methodological considerations

From a methodological point of view the present study extends previous analyses of activation patterns by using across voxel correlations and thereby augments classical GLM analyses in two important ways. First, rather than limiting the analyses to certain (more or less subjectively chosen) regions of interest we extended the analysis of the spatial patterns of activation to the whole brain. In combination with standard GLM analyses or (depending on the design) decoding analyses, this new approach can substantially improve our understanding of brain imaging data and provide a more comprehensive view that goes beyond merely reporting overlapping activations in standard GLM analyses. Second, we used individual gray matter probability maps to limit our analysis to voxels which most likely reflect the activity of gray matter. The physiological basis of the BOLD response in white matter is unclear (Logothetis and Wandell, 2004) and hence activation data from voxels located in white matter are difficult to interpret theoretically. Great care should be taken to exclude those white matter voxels from further analysis—especially in the context of analyses that are based on the spatial pattern of activity such as decoding analyses or AVCs. In this vein, the analysis approach chosen in the current study helps to increase the validity of the reported results.

Conclusions

Extending and reconciling previous research from different domains in a within-participant design, we identified a cortical network comprising areas along the IPS and BA 44 in the right hemisphere which was jointly involved in numerical order processing and mental arithmetic. Beyond the observation of merely overlapping activations we also found similar spatial patterns of activation, as evidenced by significant across voxel correlations (AVC) in these areas. In standard GLM analysis subtraction led to higher activation as compared to addition in these areas. In AVC analysis, subtraction correlated more with order than addition did. From these findings we infer that this network may be associated with linking symbolic calculation to order processing. Based on cumulating evidence that associates the parietal part of the observed network to the approximate number system we propose that the observed network is a candidate for linking the ANS with symbolic calculation abilities. The observed right-hemispheric network might represent a numerical "homologue" of a left-lateralized network dedicated to order processing in language and thereby helps clarifying the role of right BA 44 in the context of mental arithmetic.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.09.037.

References

Agrillo, C., Dadda, M., Bisazza, A., 2007. Quantity discrimination in female mosquitofish. Anim. Cogn. 10 (1), 63–70. http://dx.doi.org/10.1007/s10071-006-0036-5.

Agrillo, C., Dadda, M., Serena, G., Bisazza, A., 2009. Use of number by fish. PLoS One 4 (3), e4786. http://dx.doi.org/10.1371/journal.pone.0004786.

Andres, M., Michaux, N., Pesenti, M., 2012. Common substrate for mental arithmetic and finger representation in the parietal cortex. Neuroimage 62 (3), 1520–1528. http://dx.doi.org/10.1016/j.neuroimage.2012.05.047.

Arsalidou, M., Taylor, M.J., 2011. Is 2 + 2 = 4? Meta-analyses of brain areas needed for numbers and calculations. Neuroimage 54 (3), 2382–2393. http://dx.doi.org/10.1016/j.neuroimage.2010.10.009.

Caspers, S., Eickhoff, S.B., Geyer, S., Scheperjans, F., Mohlberg, H., Zilles, K., Amunts, K., 2008. The human inferior parietal lobule in stereotaxic space. Brain Struct. Funct. 212 (6), 481–495. http://dx.doi.org/10.1007/s00429-008-0195-z.

Caspers, S., Eickhoff, S.B., Rick, T., von Kapri, A., Kuhlen, T., Huang, R., …, Zilles, K., 2011. Probabilistic fibre tract analysis of cytoarchitectonically defined human inferior parietal lobule areas reveals similarities to macaques. Neuroimage 58 (2), 362–380. http://dx.doi.org/10.1016/j.neuroimage.2011.06.027.

Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., Zilles, K., 2006. The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. Neuroimage 33 (2), 430–448. http://dx.doi.org/10.1016/j.neuroimage.2006.06.054.

Cohen Kadosh, R., Lammertyn, J., Izard, V., 2008. Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. Prog. Neurobiol. 84 (2), 132–147.

Cohen Kadosh, R., Walsh, V., 2009. Numerical representation in the parietal lobes: abstract or not abstract? Behav. Brain Sci. 32 (3–4), 313–328. http://dx.doi.org/10.1017/S0140525X09990938 (discussion 328–373).

Dehaene, S., Bossini, S., Giraux, P., 1993. The mental representation of parity and number magnitude. J. Exp. Psychol. Gen. 122, 371–396.

Dormal, V., Andres, M., Dormal, G., Pesenti, M., 2010. Mode-dependent and mode-independent representations of numerosity in the right intraparietal sulcus. Neuroimage 52 (4), 1677–1686. http://dx.doi.org/10.1016/j.neuroimage.2010.04.254.

Eger, E., Michel, V., Thirion, B., Amadon, A., Dehaene, S., Kleinschmidt, A., 2009. Deciphering cortical number coding from human brain activity patterns. Curr. Biol. 19 (19), 1608–1615.

Eickhoff, S.B., Paus, T., Caspers, S., Grosbras, M.H., Evans, A.C., Zilles, K., Amunts, K., 2007. Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. Neuroimage 36 (3), 511–521. http://dx.doi.org/10.1016/j.neuroimage.2007.03.060.

Emmerton, J., Renner, J.C., 2006. Scalar effects in the visual discrimination of numerosity by pigeons. Learn. Behav. 34 (2), 176–192.

Fazio, P., Cantagallo, A., Craighero, L., D'Ausilio, A., Roy, A.C., Pozzo, T., Fadiga, L., 2009. Encoding of human action in Broca's area. Brain 132 (Pt 7), 1980–1988. http://dx.doi.org/10.1093/brain/awp118.

Fias, W., Lammertyn, J., Caessens, B., Orban, G.A., 2007. Processing of abstract ordinal knowledge in the horizontal segment of the intraparietal sulcus. J. Neurosci. 27 (33), 8952–8956. http://dx.doi.org/10.1523/JNEUROSCI.2076-07.2007.

Fisher, R.A., 1921. On the probable error of a coefficient of correlation deduced from a small sample. Metron 1, 3–32.

Friederici, A.D., 2002. Towards a neural basis of auditory sentence processing. Trends Cogn. Sci. 6 (2), 78–84.

Friederici, A.D., 2012. The cortical language circuit: from auditory perception to sentence comprehension. Trends Cogn. Sci. 16 (5), 262–268. http://dx.doi.org/10.1016/j.tics.2012.04.001.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15 (4), 870–878. http://dx.doi.org/10.1006/nimg.2001.1037.

Grabner, R.H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., Neuper, C., 2009. To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. Neuropsychologia 47 (2), 604–608.

Halberda, J., Ly, R., Wilmer, J.B., Naiman, D.Q., Germine, L., 2012. Number sense across the lifespan as revealed by a massive Internet-based sample. Proc. Natl. Acad. Sci. U.S.A. 109 (28), 11116–11120. http://dx.doi.org/10.1073/pnas.1200196109.

Halberda, J., Mazzocco, M.M., Feigenson, L., 2008. Individual differences in non-verbal number acuity correlate with maths achievement. Nature 455 (7213), 665–668.

Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L., Pietrini, P., 2001. Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293 (5539), 2425–2430. http://dx.doi.org/10.1126/science.1063736.

Hubbard, E.M., Piazza, M., Pinel, P., Dehaene, S., 2005. Interactions between number and space in parietal cortex. Nat. Rev. Neurosci. 6 (6), 435–448.

Ischebeck, A., Heim, S., Siedentopf, C., Zamarian, L., Schocke, M., Kremser, C., Delazer, M., 2008. Are numbers special? Comparing the generation of verbal materials from ordered categories (months) to numbers and other categories (animals) in an fMRI study. Hum. Brain Mapp. 29 (8), 894–909.

Izard, V., Sann, C., Spelke, E.S., Streri, A., 2009. Newborn infants perceive abstract numbers. Proc. Natl. Acad. Sci. U.S.A. 106 (25), 10382–10385.

Keller, S.S., Crow, T., Foundas, A., Amunts, K., Roberts, N., 2009. Broca's area: nomenclature, anatomy, typology and asymmetry. Brain Lang. 109 (1), 29–48. http://dx.doi.org/10.1016/j.bandl.2008.11.005.

Kim, J., Koizumi, M., Ikuta, N., Fukumitsu, Y., Kimura, N., Iwata, K., …, Kawashima, R., 2009. Scrambling effects on the processing of Japanese sentences: an fMRI study. J. Neurolinguistics 22 (2), 151–166. http://dx.doi.org/10.1016/j.jneuroling.2008.07.005.

Knops, A., Thirion, B., Hubbard, E.M., Michel, V., Dehaene, S., 2009a. Recruitment of an area involved in eye movements during mental arithmetic. Science 324 (5934), 1583–1585.

Knops, A., Viarouge, A., Dehaene, S., 2009b. Dynamic representations underlying symbolic and nonsymbolic calculation: evidence from the operational momentum effect. Atten. Percept. Psychophys. 71 (4), 803–821.

Kong, J., Wang, C., Kwong, K., Vangel, M., Chua, E., Gollub, R., 2005. The neural substrate of arithmetic operations and procedure complexity. Brain Res. Cogn. Brain Res. 22 (3), 397–405. http://dx.doi.org/10.1016/j.cogbrainres.2004.09.011.

Koten Jr., J.W., Lonnemann, J., Willmes, K., Knops, A., 2011. Micro and macro pattern analyses of fMRI data support both early and late interaction of numerical and spatial information. Front. Hum. Neurosci. 5, 115. http://dx.doi.org/10.3389/fnhum.2011.00115.

Logothetis, N.K., Wandell, B.A., 2004. Interpreting the BOLD signal. Annu. Rev. Physiol. 66, 735–769. http://dx.doi.org/10.1146/annurev.physiol.66.082602.092845.

Lyons, I.M., Beilock, S.L., 2009. Beyond quantity: individual differences in working memory and the ordinal understanding of numerical symbols. Cognition 113 (2), 189–204. http://dx.doi.org/10.1016/j.cognition.2009.08.003.

Lyons, I.M., Beilock, S.L., 2011. Numerical ordering ability mediates the relation between number-sense and arithmetic competence. Cognition 121 (2), 256–261. http://dx.doi.org/10.1016/j.cognition.2011.07.009.

Majerus, S., D'Argembeau, A., Martinez Perez, T., Belayachi, S., Van der Linden, M., Collette, F., Maquet, P., 2010. The commonality of neural networks for verbal and visual short-term memory. J. Cogn. Neurosci. 22 (11), 2570–2593. http://dx.doi.org/10.1162/jocn.2009.21378.

Meck, W.H., Church, R.M., 1983. A mode control model of counting and timing processes. J. Exp. Psychol. Anim. Behav. Process. 9 (3), 320–334.

Merten, K., Nieder, A., 2009. Compressed scaling of abstract numerosity representations in adult humans and monkeys. J. Cogn. Neurosci. 21 (2), 333–346.

Meyer, L., Obleser, J., Anwander, A., Friederici, A.D., 2012. Linking ordering in Broca's area to storage in left temporo-parietal regions: the case of sentence processing. Neuroimage 62 (3), 1987–1998. http://dx.doi.org/10.1016/j.neuroimage.2012.05.052.

Molko, N., Cachia, A., Riviere, D., Mangin, J.F., Bruandet, M., Le, B.D., Dehaene, S., 2003. Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. Neuron 40 (4), 847–858.

Moyer, R.S., Landauer, T.K., 1967. Time required for judgements of numerical inequality. Nature 215 (5109), 1519–1520.

Nieder, A., 2012. Supramodal numerosity selectivity of neurons in primate prefrontal and posterior parietal cortices. Proc. Natl. Acad. Sci. U.S.A. 109 (29), 11860–11865. http://dx.doi.org/10.1073/pnas.1204580109.

O'Toole, A.J., Jiang, F., Abdi, H., Penard, N., Dunlop, J.P., Parent, M.A., 2007. Theoretical, statistical, and practical perspectives on pattern-based classification approaches to the analysis of functional neuroimaging data. J. Cogn. Neurosci. 19 (11), 1735–1752.

Park, J., Park, D.C., Polk, T.A., 2012. Parietal functional connectivity in numerical cognition. Cereb. Cortex. http://dx.doi.org/10.1093/cercor/bhs193.

Peelen, M.V., Wiggett, A.J., Downing, P.E., 2006. Patterns of fMRI activity dissociate overlapping functional brain areas that respond to biological motion. Neuron 49 (6), 815–822.

Petrides, M., Pandya, D.N., 2009. Distinct parietal and temporal pathways to the homologues of Broca's area in the monkey. PLoS Biol. 7 (8), e1000170. http://dx.doi.org/10.1371/journal.pbio.1000170.

Piazza, M., 2010. Neurocognitive start-up tools for symbolic number representations. Trends Cogn. Sci. 14 (12), 542–551.

Piazza, M., Facoetti, A., Trussardi, A.N., Berteletti, I., Conte, S., Lucangeli, D., Zorzi, M., 2010. Developmental trajectory of number acuity reveals a severe impairment in developmental dyscalculia. Cognition 116 (1), 33–41.

Piazza, M., Izard, V., Pinel, P., Le Bihan, D., Dehaene, S., 2004. Tuning curves for approximate numerosity in the human intraparietal sulcus. Neuron 44 (3), 547–555. http://dx.doi.org/10.1016/j.neuron.2004.10.014.

Piazza, M., Pinel, P., Le Bihan, D., Dehaene, S., 2007. A magnitude code common to numerosities and number symbols in human intraparietal cortex. Neuron 53 (2), 293–305.

Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. Neuroimage 10 (1), 15–35. http://dx.doi.org/10.1006/nimg.1999.0441.

Santens, S., Roggeman, C., Fias, W., Verguts, T., 2010. Number processing pathways in human parietal cortex. Cereb. Cortex 20 (1), 77–88. http://dx.doi.org/10.1093/cercor/bhp080.

Simon, O., Mangin, J.F., Cohen, L., Le, B.D., Dehaene, S., 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron 33 (3), 475–487.

Stanescu-Cosson, R., Pinel, P., van De Moortele, P.F., Le, B.D., Cohen, L., Dehaene, S., 2000. Understanding dissociations in dyscalculia: a brain imaging study of the impact of number size on the cerebral networks for exact and approximate calculation. Brain 123 (Pt 11), 2240–2255.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15 (1), 273–289. http://dx.doi.org/10.1006/nimg.2001.0978.

Umiltà, C., Priftis, K., Zorzi, M., 2009. The spatial representation of numbers: evidence from neglect and pseudoneglect. Exp. Brain Res. 192 (3), 561–569.

Van Essen, D.C., 2005. A population-average, landmark- and surface-based (PALS) atlas of human cerebral cortex. Neuroimage 28 (3), 635–662. http://dx.doi.org/10.1016/j.neuroimage.2005.06.058.

Van Essen, D.C., Drury, H.A., Dickson, J., Harwell, J., Hanlon, D., Anderson, C.H., 2001. An integrated software suite for surface-based analyses of cerebral cortex. J. Am. Med. Inform. Assoc. 8 (5), 443–459.

Van Opstal, F., Fias, W., Peigneux, P., Verguts, T., 2009. The neural representation of extensively trained ordered sequences. Neuroimage 47 (1), 367–375.

Verguts, T., Fias, W., 2004. Representation of number in animals and humans: a neural model. J. Cogn. Neurosci. 16 (9), 1493–1504.

Xu, F., Spelke, E.S., Goddard, S., 2005. Number sense in human infants. Dev. Sci. 8 (1), 88–101.

Zhang, H., Ekstrom, A., 2012. Human neural systems underlying rigid and flexible forms of allocentric spatial representation. Hum. Brain Mapp. http://dx.doi.org/10.1002/hbm.21494.