Functional dissociations between four basic arithmetic operations in the human posterior parietal cortex: A cytoarchitectonic mapping study

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ABSTRACT

Although lesion studies over the past several decades have focused on functional dissociations in posterior parietal cortex (PPC) during arithmetic, no consistent view has emerged of its differential involvement in addition, subtraction, multiplication, and division. To circumvent problems with poor anatomical localization, we examined functional overlap and dissociations in cytoarchitectonically defined subdivisions of the intraparietal sulcus (IPS), superior parietal lobule (SPL) and angular gyrus (AG), across these four operations. Compared to a number identification control task, all operations except addition, showed a consistent profile of left posterior IPS activation and deactivation in the right posterior AG. Multiplication and subtraction differed significantly in right, but not left, IPS and AG activity, challenging the view that the left AG differentially subserves retrieval during multiplication. Although addition and multiplication both rely on retrieval, multiplication evoked significantly greater activation in right posterior IPS, as well as the prefrontal cortex, lingual and fusiform gyri, demonstrating that addition and multiplication engage different brain processes. Comparison of PPC responses to the two pairs of inverse operations: division versus multiplication and subtraction versus addition revealed greater activation of left lateral SPL during division, suggesting that processing inverse relations is operation specific. Our findings demonstrate that individual IPS, SPL and AG subdivisions are differentially modulated by the four arithmetic operations and they point to significant functional heterogeneity and individual differences in activation and deactivation within the PPC. Critically, these effects are related to retrieval, calculation and inversion, the three key cognitive processes that are differentially engaged by arithmetic operations. Our findings point to distribute representation of these processes in the human PPC and also help explain why lesion and previous imaging studies have yielded inconsistent findings.

Addition, subtraction, multiplication, and division constitute the four basic arithmetic operations. There has been considerable behavioral research on the cognitive processes associated with these operations over the past several decades. Surprisingly, individuals use a variety of strategies when solving simple arithmetic problems suggesting that these operations are not entirely automatized even in adults (Campbell & Timm, 2000; Hecht, 1999; LeFevre et al., 1996; Siegler & Shrager, 1984). In particular, the rate of retrieval versus alternate calculation strategies differs widely across operations (Campbell, 2008). Retrieval is the dominant method for addition and multiplication, whereas subtraction and division rely more on alternate strategies such as counting and inversion. Campbell and Xue (2001) reported retrieval rates of 76% for addition and 96% for multiplication, but only 58% for subtraction and 57% for division in college-age adults (Campbell & Xue, 2001). These differences may be the consequence of addition and multiplication being taught prior to subtraction and division, their respective inverse operations, in most school curricula (Campbell, 2008). Problem solving using a related fact from previously learned inverse operations is clearly a more parsimonious strategy than memorizing facts for all four operations (Campbell & Alberts, 2009).

Although both addition and multiplication rely heavily on retrieval, they differ in their primary backup strategies. Whereas counting and decomposition are fairly efficient strategies for addition, it is less appropriate for multiplication (Hecht, 1999), which

can be solved by repeated addition or number series (7, 14, 21, etc.). Similarly, subtraction and division differ in their reliance on inversion for problem solving. Many dividends have a small set of unique multiplicative factors (e.g. the only factors of 35 are 5 and 7), thus making division more likely to be solved using multiplication (Rickard, 2005). In contrast, problems involving subtraction can be solved by invoking many alternate addends. In summary, these behavioral results suggest that retrieval is the primary method used by adults for solving simple addition and multiplication problems, whereas subtraction and division rely primarily on calculation and various backup strategies.

Behavioral differences in strategy use across operations suggest that the operations may have different neural correlates. Based on a case study of two patients with distinct cortical and subcortical lesions Dehaene and Cohen (1997) proposed that the posterior parietal cortex (PPC) was involved in calculation, whereas subcortical and left-lateralized frontal and temporal language regions were involved in math fact retrieval. However, other lesion studies have found dissociations between arithmetic operations within the parietal lobe and have suggested that both retrieval and calculation involve the PPC. Dagenbach and McCloskey (1992) reported that a patient with lesions in the left PPC performed better in subtraction than addition or multiplication problems, suggesting that compared to retrieval, calculation relies more on left PPC regions. In contrast, van Harskamp, Rudge, and Cipolotti (2002) described a patient with lesions to most of the left PPC who had preserved multiplication but impaired addition. Delazer and Benke (1997) reported a case of a left PPC tumor that damaged the supramarginal gyrus (Brodmann area 40), the angular gyrus (AG, BA 39) and underlying white matter, leaving the patient with no conceptual knowledge of arithmetic but preserved multiplication facts. Although there has been considerable effort in understanding the role of the PPC in mathematical cognition using lesion studies, this effort has been largely unsuccessful. The highly variable locations and laterality of the lesions as well as the limited number of operations examined in each study, makes drawing specific conclusions about the differential role of the PPC in the four basic arithmetic operations difficult.

Functional imaging studies have begun to provide more precise anatomical localization of PPC activity during each arithmetic operation. Multiplication and subtraction are the two operations that have most often been compared in studies seeking to examine differences between operations that predominantly use retrieval versus calculation strategies. Lee (2000) compared brain responses to single-digit multiplication and subtraction problems using fMRI and reported that multiplication elicited greater activation than subtraction in the left AG and supramarginal gyrus while subtraction elicited larger activation than multiplication, bilaterally, in the IPS. These findings led Lee (2000) and Dehaene, Piazza, Pinel, and Cohen (2003) to suggest that verbally based retrieval engaged the AG, whereas quantity based calculation differentially recruited the IPS. However the absence of a control condition precluded examination of brain activity produced by each operation separately. Other studies have failed to demonstrate differential AG activation for multiplication, compared to subtraction, and have instead found equivalent IPS activation for both operations. For example, Chochon, Cohen, van de Moortele, and Dehaene (1999) found that multiplication (multiplying a presented number by 3) was associated with left IPS activity while subtraction (subtraction a presented number from 11) was associated with bilateral IPS activity. A direct comparison of subtraction to multiplication revealed greater activation only in the right IPS. No brain regions showed greater responses to multiplication over subtraction.

Using positron emission tomography, Hayashi, Ishii, Kitagaki, and Kazui (2000) compared a counting control to continuous subtraction from 100 and to the recitation of the multiplication 'times

tables'. Although they did not compare activity directly, they found that the same areas were activated by the tasks, with more extensive activity for subtraction than multiplication. In particular, both operations activated bilateral inferior parietal areas and the left precentral and medial frontal gyri, whereas only subtraction activated right frontal areas. They attribute these differences to greater working memory demands in the subtraction task (Hayashi et al., 2000). Kawashima et al. (2004) presented single-digit addition, subtraction and multiplication problems with covert responses. Compared to a resting baseline all three operations showed left inferior parietal cortex activity, but subtraction and multiplication also demonstrated right inferior parietal cortex activity. In a direct comparison between operations, they found no significant activity differences anywhere in the brain. There was no separate control condition in their study. These early studies were limited by small sample sizes and lacked the overt behavioral responses needed to assess compliance and brain–behavior relationships. In addition, many of these studies often lacked adequate control conditions, limiting the interpretability of the findings.

Only two studies to date have examined brain responses to all four arithmetic operations using a within-subjects design (Fehr, Code, & Herrmann, 2007; Fehr, Code, & Herrmann, 2008). Fehr et al. compared brain responses to complex (two-digit) and simple (one-digit) problems with each of the four operations using visually (2007) and aurally presented (2008) stimuli. Using a conjunction analysis they found that complex, compared to simple, problems activated bilateral superior and middle frontal gyri and right precuneus across all operations. Brain activation between operations was not compared directly; therefore it is unclear whether there are any reliable differences between the operations. Simple problems were assumed to always be solved by retrieval of memorized math facts and were not reported. Furthermore, the use of a self-paced design with a fixed inter-stimulus interval of 2 s, without the jittering required to estimate distinct fMRI responses to each stimulus, precludes a clear functional dissociation of the brain regions involved in each operation. Zhou et al. (2007) found that when addition and multiplication problems were matched on difficulty, addition elicited greater activity in the IPS compared to multiplication but no differences were found in the AG.

Taken together, behavioral, lesion and functional imaging studies paint a conflicting view of functional dissociations between arithmetic operations, and the precise neural correlates of overlapping and distinct PPC responses across the four operations are as yet unclear. In this study we examine the functional overlap and dissociations in brain activity between the four operations, in the context of differential cognitive processes they evoke. Participants performed an arithmetic equation verification task with two operands, in each of the four operations: addition, subtraction, multiplication and division. A common non-arithmetic control task involving number identification was used to examine responses to each operation. By using a single-digit, two-operand task, we were able to limit the effects of working memory load and assess the neural responses elicited by each operation, controlling for sensory input, basic number processing, response selection and motor response (Menon, Mackenzie, Rivera, & Reiss, 2002; Menon, Rivera, White, Glover, & Reiss, 2000). To our knowledge, this is the first study to contrast brain responses to the four basic mental arithmetic operations effects in a single study.

In this study, we focused on three distinct areas of the PPC that have been consistently implicated in math cognition: the intraparietal sulcus (IPS), superior parietal lobule (SPL, BA 7) and angular gyrus (AG, BA 39) (Dehaene et al., 2003; Menon et al., 2000; Wu et al., 2009). Importantly, we employed the recently developed cytoarchitectonic probabilistic maps of the PPC, which provide a more anatomically precise and consistent basis for examining the differential profile of fMRI responses across the four opera-

tions. Using post-mortem human brains, Zilles and colleagues have parcellated these three structures through observer-independent analyses of cellular structure and organization. In the IPS, which was not part of Brodmann's original parcellation scheme, cytoarchitectonic mapping has identified three subdivisions: anterior hIP1 and hIP2 (Choi et al., 2006) and posterior hIP3 (Scheperjans et al., 2008). The AG (BA 39) is subdivided into the anterior and posterior subregions, PGa and PGp, respectively (Caspers et al., 2006). The SPL (BA 7) is divided into four areas: one immediately posterior to the post-central sulcus (SPL 7PC), an anterior area (SPL 7A), a posterior area (SPL 7P) and a medial area (SPL 7M) (Scheperjans et al., 2008). A previous probabilistic cytoarchitectonic mapping study of arithmetic involving both addition and subtraction operations found heterogeneous pattern of activation in the IPS and deactivation in the AG (Wu et al., 2009). Wu and colleagues also found that AG responses were more sensitive to task difficulty than other IPC regions. We use a similar approach here to quantify the profile of activation and deactivation in the IPS, AG and SPL.

Our investigation focused on four key hypotheses. Compared to subtraction, multiplication relies to a greater extent on retrieval and whereas subtraction involves more calculation (Campbell, 2008; Campbell & Xue, 2001). We therefore hypothesized that they would differentially engage the PPC, with greater IPS response during subtraction and greater left AG response for multiplication (Dehaene et al., 2003). A related question we address here is whether differences in IPS and AG response arise from activation or deactivation. Second, since both addition and multiplication are well-rehearsed and highly automatized in adults, we hypothesized that these two operations would show no differences in accuracy, reaction time or PPC response. Third, addition and subtraction constitute inverse operations and involve similar quantity manipulations on the number line. Yet subtraction is more cognitively demanding and less reliant on retrieval than addition. We hypothesized that subtraction would result in longer response times and greater IPS activations than addition. Finally, multiplication and division also constitute inverse operations in which multiplication problems are most directly solved by retrieval. We hypothesized that if these two pairs of operations are primarily solved by inversion they would evoke a similar pattern of differences. The alternate hypothesis we examine is that processing of inverse relations is operation specific.

1. Methods

1.1. Participants

Twenty participants (11 males, 9 females), between the ages of 18 and 30 ($M = 23.9$, SD = 3.28), were recruited from the Stanford University community. All participants gave written informed consent, and were treated in accordance with the APA "Ethical Principles of Psychologists and Code of Conduct". All protocols were approved by the Human Subjects Committee at Stanford University School of Medicine.

1.2. Experimental procedures

Participants performed blocks of alternating arithmetic and control trials. In the arithmetic trials, participants were asked to verify the validity of two-operand arithmetic equations, such as "2 + 4 = 6". Addition problems consisted of single-digit operands from 1 to 9 summing to less than 10. Multiplication problems consisted of all the combinations of single-digit operands from 1 to 9. Subtraction and division stimuli were inverses of these problems, respectively. This design allowed us to match reaction times (RT) between multiplication and subtraction, a key comparison of interest. This is because for educated adults, reaction times (RT) for small subtraction problems tends to lie between RTs for small and large multiplication problems (Campbell & Alberts, 2009; Campbell & Xue, 2001) whereas RTs on large subtraction problems, involving double-digit minuends, are much longer (Campbell & Alberts, 2009; Seyler, Kirk, & Ashcraft, 2003).

Invalid equations were constructed by adding or subtracting '1' or '2' from the correct answer (e.g., 2 + 4 = 7). For the number identification control stimuli, the arithmetic symbols were replaced by symbols randomly chosen from the following:

"@", "(", or "o". No symbol was repeated within a trial. Participants were asked to identify whether the number 5 was present in a string of stimuli (e.g. 6 @ 1 o 5).

The experiment consisted of two runs, one containing addition, subtraction and number identification blocks, and the second containing multiplication, division and number identification blocks. The order of the runs was randomized across participants. Each run consisted of 20 blocks alternating between arithmetic and number identification blocks and the arithmetic blocks alternated between addition and subtraction or multiplication and division. Each stimulus was presented for 2 s and blocks had 12 trials, lasting for 24 s. A run lasted 8 min. In each experimental block, half of the equations presented were valid, and the other half were invalid; the order of valid and invalid equations was randomized. In control blocks, half of the strings presented contained the numeral 5, whereas the other half did not; the order of presentation of these strings was randomized. Participants were randomly given different versions of the task in which either the addition, subtraction, or control block was presented first. The order of the experimental and control stimuli was also randomly selected. Similar randomization procedures were used in the run involving multiplication and division trials.

1.3. fMRI data acquisition

Images were acquired using a *GE* 3T Signa Scanner with the standard quadrature birdcage head coil. 28 axial slices, 4.0 mm thick, 1.0 mm skip, were imaged using a T2* Spiral in/out sequence (Glover & Lai, 1998) and a TR of 2 s. The task was programmed using Psyscope (Cohen, MacWhinney, Flatt, & Provost, 1993) on a Macintosh (Cupertino, CA) computer. Scan and task onsets were synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a 'CMU Button Box' microprocessor (http://poppy.psy.cmu.edu/psyscope). Stimuli were presented visually at the center of a screen using a custom-built magnet compatible projection system (Resonance Technology, CA). An external timer maintained an accuracy of stimulus presentation to within 1 ms.

1.4. fMRI data analysis

1.4.1. Preprocessing

The first five volumes were not analyzed to allow for signal equilibration effects. Images were reconstructed, by inverse Fourier transform, for each of the time points into $64 \times 64 \times 28$ image matrices (voxel size $3.125 \times 3.125 \times 4.5$ mm). A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan (Glover & Lai, 1998). Functional MRI data were pre-processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to correct for motion and errors in slice-timing, spatially transformed to standard stereotaxic space (based on the Montreal Neurologic Institute coordinate system), resampled every 2 mm using sinc interpolation and smoothed with a 6 mm full-width half-maximum Gaussian kernel to decrease spatial noise prior to statistical analysis.

1.4.2. Individual and group analyses

Statistical analysis was performed on individual and group data using a general linear model as implemented in SPM8. Individual subject analyses were first performed using a general linear model with task-related regressors as well as six movement parameters from the realignment procedure mentioned above. Task-related regressors were modeled as boxcar functions corresponding to each condition, and convolved with a hemodynamic response function and a temporal dispersion derivative to account for voxel-wise latency differences in hemodynamic response. Low-frequency drifts at each voxel were removed using a high-pass filter (0.5 cycles/min) and serial correlations were accounted for by modeling the fMRI time series as a first-degree autoregressive process (Friston et al., 1997). Voxel-wise *t*-statistics maps for each condition were generated for each participant, along with the respective contrast images. Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure (Holmes & Friston, 1998). Group-level activation was determined using individual subject contrast images and a second-level random-effects analysis of variance. Finally, significant clusters of activation were determined using a voxel-wise height threshold of $p < 0.01$, corrected for multiple spatial comparisons at the cluster level ($p < 0.01$) (Poline, Worsley, Evans, & Friston, 1997). For a priori regions of interest we used a stringent height threshold of $p < 0.001$, uncorrected.

At the group level, we used paired t-tests to compare brain activity for each arithmetic operation against the corresponding number identification tasks. The following between-operation comparisons were also performed at the group level: (1) (subtraction – number identification) versus (multiplication – number identification); (2) (addition – number identification) versus (multiplication – number identification); (3) addition versus subtraction; (4) multiplication versus division. The comparisons of each operation to the control task were also used to examine the relation between *behavioral* performance and brain activation for each of the four operations. Activation foci were superimposed on high-resolution T1-weighted images and their locations were interpreted using known neuroanatomical landmarks (Mai, Paxinoss, & Voss, 2007).
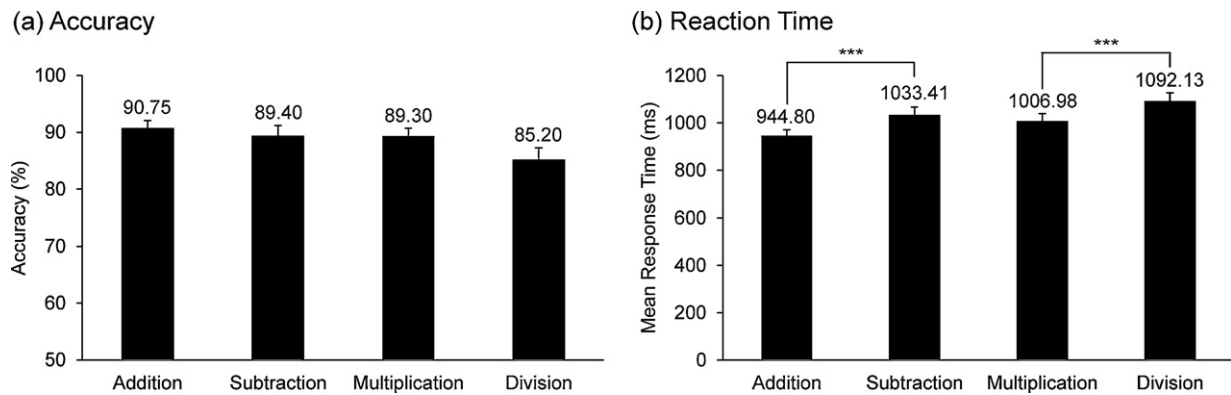
(a) Accuracy

(b) Reaction Time

Fig. 1. Behavioral performance during addition, subtraction, multiplication and division tasks. (a) Accuracy and (b) mean reaction time for each of the four arithmetic operations. Bonferonni corrected post-hoc comparisons of the estimated marginal means on the contrasts of interest (addition versus subtraction, multiplication versus division, addition versus multiplication and subtraction versus multiplication) showed that there were no between-operation differences in accuracy. Reaction times were faster for addition, compared to subtraction, and for multiplication, compared to division (***$p < 0.001$).

1.4.3. PPC regions of interest

Regions of interest (ROI) analyses were based on the cytoarchitectonically distinct maps of three IPS (hIP3, hIP1 and hIP2), two AG (PGp and PGa) and four SPL (7P, 7M, 7A, 7PC) regions. In the order listed, these ROIs run successively along the caudal to rostral axis of the PPC. Detailed information about the anatomical boundaries of these maps has been published elsewhere (Caspers et al., 2006; Choi et al., 2006; Scheperjans et al., 2008). Quantitative analysis of activations in each of the cytoarchitectonic probabilistic maps was performed using the SPM Anatomy Toolbox (Eickhoff et al., 2005). The spatial distribution of regional activations were characterized by three metrics – the percentage of a specific cytoarchitectonic region that belonged to an activated cluster, the percentage of an activation cluster that was in a specific region, and probability that a peak in the cluster was assigned to a region (Eickhoff et al., 2007, 2005; Scheperjans et al., 2008; Wu et al., 2009). The overlap between specific cytoarchitectonically defined PPC subdivisions and each functional ROI, from the general linear model analysis, was determined using the MarsBar toolbox (Brett, Anton, &Valabregue, 2002) and the average *t*-score was computed in these overlapping voxels. Flat maps of cytoarchitectonically defined PPC subdivisions and functional ROIs were generated using Caret (Van Essen et al., 2001) and displayed using the PALS atlas (Van Essen, 2005).

2. Results

2.1. Behavior

Fig. 1 summarizes the accuracy and reaction times for each of the four arithmetic operations. Repeated measures ANOVA were used to examine differences in accuracy and reaction time between the operations. For accuracy, there was a significant difference between the operations ($F(3, 57) = 3.029$, $p = 0.037$). However, post-hoc pair-wise comparisons of estimated marginal means revealed no significant differences between the operations (all $ps > 0.2$, Bonferroni corrected). Average RTs for correct trials were computed after removing trials more than two standard deviations away from each participant's mean reaction time. A repeated measures ANOVA for reaction times showed significant differences between the operations ($F(3, 57) = 16.827$, $p < 0.001$). Post-hoc pair-wise comparisons of estimated marginal means revealed that addition and multiplication were significantly faster than their respective inverses ($p < 0.001$), whereas multiplication did not differ from addition ($p = 0.197$) or subtraction ($p = 1.000$).

2.2. PPC responses to each individual operation

Here we focus on PPC regions that showed greater task-related activation (calculation > number identification control) and deactivation (number identification control > calculation) (Table 1 and Figs. 2–4). Supplementary Table S1 summarizes results at the whole-brain level.

2.2.1. Addition

No PPC regions showed significant activation during addition. However, significant deactivations were detected in the right AG and adjoining supramarginal gyrus. Specifically, quantitative mapping using the SPM Anatomy Toolbox revealed that 45% of the right PGa and 30% of the right PGp showed deactivations. The right superior parietal lobule also deactivated encompassing 17% of the SPL 7A and 8% of the SPL 7P.

2.2.2. Subtraction

All three left IPS regions showed significant activations with a posterior to anterior gradient, with 37% hIP3, 23% of hIP1 and 23% of hIP2 activated above baseline. Two left SPL regions were also activated, encompassing 33% of 7PC and 8% of 7A. Activation peaks were detected in all these areas except for hIP2. Interestingly, there was no significant activation in the right IPS or SPL. There was significant and wide spread deactivation of the right PGp (54%) and PGa (50%).

2.2.3. Multiplication

There were significant bilateral activations in the PPC during multiplication. In the left hemisphere, all three IPS regions showed prominent activations with decreasing response in a posterior to anterior direction (96% of hIP3, 66% of hIP1 and 56% of hIP2). Less extensive activations were observed in SPL regions 7PC, 7A, and 7P as well as PGa. A similar pattern was observed in the right IPS and SPL. In contrast, 52% of the right PGp and 29% of the right PGa were deactivated during multiplication. Prominent deactivations were also observed in the medial aspects of SPL in subdivision 7M.

2.2.4. Division

There were significant bilateral activations in the PPC during division. In the left hemisphere, 100% of hIP3, 81% of hIP1, and 70% of hIP2 were activated, again reflecting a posterior to anterior gradient. In the left SPL, a similar posterior to anterior gradient was observed with 66% of 7P, 57% of 7PC, 52% of 7A being activated. 21% of PGa also showed significant activation above the control task. A similar pattern was observed in the right IPS and SPL. Peaks were detected bilaterally in hIP3. The medial SPL region 7M showed significant deactivation in both hemispheres. Both AG subdivisions PGa and PGp showed large deactivations in the left and right hemispheres.
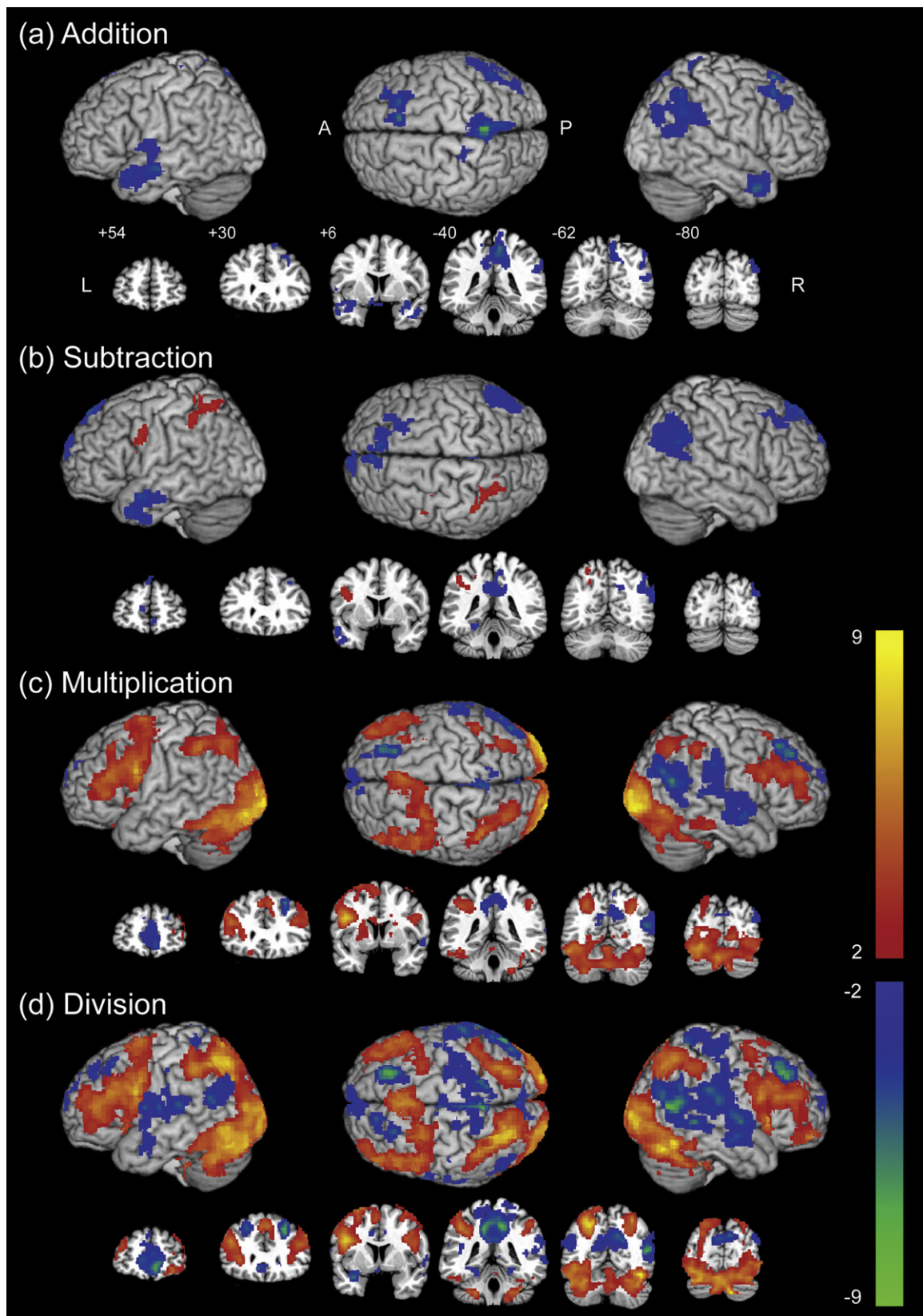
Fig. 2. Brain activation and deactivation during the four arithmetic tasks. Surface rendering and coronal sections of brain regions that showed significant activation (red) and deactivation (blue) are shown for (a) addition, (b) subtraction, (c) multiplication, and (d) division, compared to a common number identification control task. Each cluster was significant at height $p < 0.01$, corrected for spatial extent at $p < 0.01$.

Table 1
Probabilistic labeling of posterior parietal cortex (PPC) activation and deactivation during the four arithmetic tasks.

Comparison	Region	Size of cluster	% of region activated	% of cluster in region	Peak activation coordinates			Probability of peak in assigned region (%)
					X	Y	Z	
Addition								
Identification – calculation	R SPL 7A	200	16.8	5.7	6	−60	60	30
	R SPL 7P	57	8.3	1.6	6	−68	60	40
	R PGa	448	44.7	28.3	48	−54	34	60
	R PGp	353	30.3	22.3	48	−64	16	40
Subtraction								
Calculation – identification	L hIP3	103	37.7	13.1	−28	−54	42	30
	L SPL 7PC	62	32.8	7.8	−34	−50	68	20
	L hIP2	56	23.0	7.1				
	L hIP1	105	22.9	13.3	−34	−44	38	40
	L SPL 7A	148	8.4	18.8	−28	−58	58	90
Identification – calculation	R PGp	630	54.0	40.9	40	−76	30	40
	R PGa	505	50.4	32.8	48	−52	32	50
Multiplication								
Calculation – identification	L hIP3	264	96.3	10.5	−30	−64	42	20
	L hIP1	301	65.7	12.0	−40	−44	44	30
	L hIP2	136	56.3	5.4				
	L SPL 7PC	73	38.7	2.9	−58	−34	52	10
	L SPL 7A	332	18.3	12.8	−26	−52	44	10
	L SPL 7P	92	17.0	3.7				
	L PGa	126	15.3	5.0				
	R hIP3	196	65.7	15.3	30	−52	46	50
	R hIP1	131	57.2	10.2	30	−62	34	10
	R hIP2	48	32.7	3.7				
	R SPL 7PC	48	11.9	3.7				
	R SPL 7A	60	5.1	4.7				
Identification – calculation	R SPL 7M	103	59.2	2.1				
	L SPL 7M	68	48.0	1.3				
	R PGp	601	51.6	39.0	50	−64	18	40
	R PGa	294	29.3	19.0	62	−56	16	70
Division								
Calculation – identification	L hIP3	278	99.5	1.1	−26	−58	46	50
	L hIP1	381	81.4	1.5				
	L hIP2	172	69.7	0.7				
	L SPL 7P	363	65.5	1.4				
	L SPL 7PC	110	57.4	0.4				
	L SPL 7A	935	52.1	3.6				
	L PGa	178	21.2	0.7	−26	−72	50	20
	R hIP3	271	91.1	11.2	34	−52	44	60
	R hIP1	148	64.8	6.1	40	−42	36	30
	R hIP2	87	59.5	3.6				
	R SPL 7A	429	36.8	17.7	32	−62	54	50
	R SPL 7P	232	35.0	9.6	26	−68	44	10
	R PGp	78	6.7	3.2				
Identification – calculation	L SPL 7M	84	63.6	0.5				
	R SPL 7M	101	60.5	0.5				
	R PGp	565	48.5	3.0	50	−66	14	30
	R PGa	387	38.6	2.1				
	L PGp	351	32.3	40.8	−48	−72	38	70
	L PGa	138	16.8	16.1	−50	−58	20	30

Posterior parietal cortex (PPC) regions that showed significantly greater activation (calculation > identification) and deactivation (identification > calculation) during each of the four arithmetic operations. For each significant cluster, the probabilistic region, percentage of activation in the region, percentage of cluster that was in the region, peak MNI coordinate, and the probability of the peak being in the region are shown. Each cluster was significant after correction for height ($p < 0.01$) and extent ($p < 0.01$). Cytoarchitectonically defined probability maps were used to interpret the locations of the cluster and peaks within subdivisions of the intraparietal sulcus (IPS), angular gyrus (AG), and supramarginal gyrus (SMG). Only subdivisions where greater than 5% of the voxels were significantly activated are reported.

2.3. Individual differences in PPC response

Accuracy was close to ceiling on all four tasks and there was little variability in accuracy across participants so this analysis focused on individual differences in reaction time. Here we focus on individual differences in PPC response (Fig. 5 and Table 2); Supplementary Table S2 summarizes results at the whole-brain level.
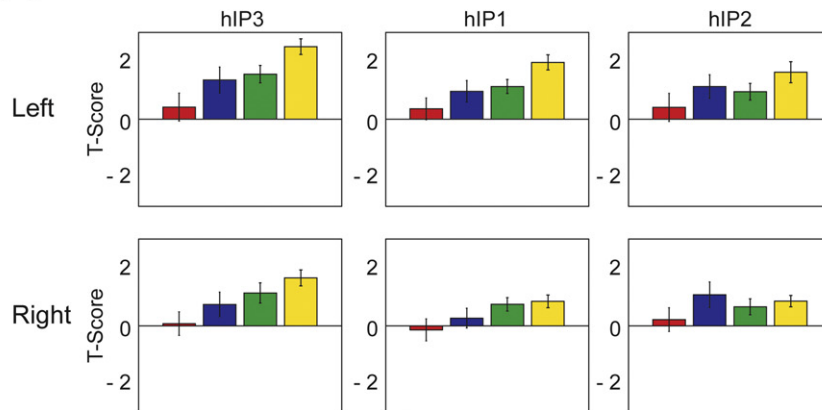
2.3.1. Addition and subtraction

RT was not significantly correlated with activation in the addition or subtraction tasks in the PPC or elsewhere in the brain.
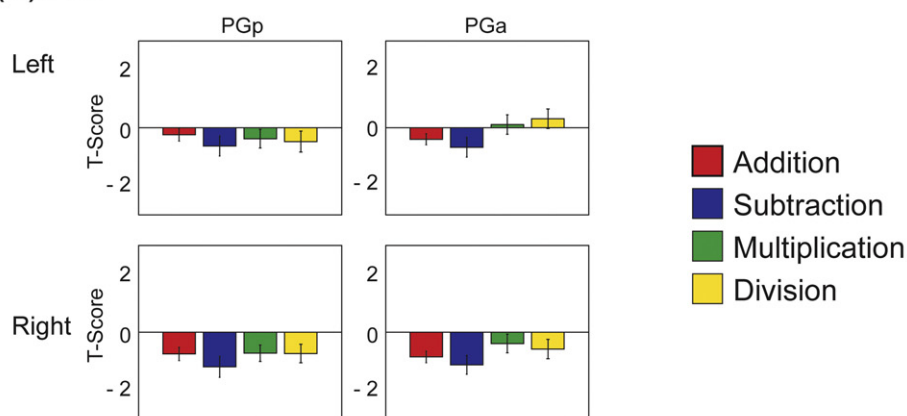
2.3.2. Multiplication

Reaction times were negatively correlated with activity in the right PGa ($r = −0.818$, $p < 0.001$). This cluster covered 27% of PGa and 6% of the hIP2 and extended to cover large portions of the supra-
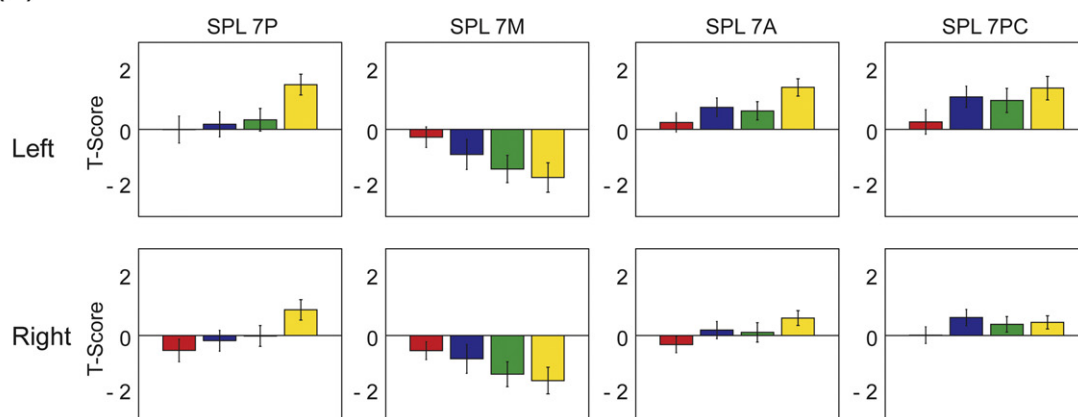
Fig. 3. Signal strength of activation and deactivation in the cytoarchitectonically defined regions of the posterior parietal cortex (PPC). (a) Intraparietal sulcus regions (IPS – hIP3, hIP1, and hIP2), (b) angular gyrus (AG – PGp and PGa), and (c) superior parietal lobule (SPL – 7P, 7PC, 7M and 7A) during addition, subtraction, multiplication and division. The three left and most right IPS areas showed positive task-related activation during all four operations. Both AG regions showed consistent deactivation in the right hemisphere, whereas the left PGp and PGa either showed deactivation or non-significant effects. SPL regions 7P, 7PC and 7A responses were at or above baseline, whereas, SPL7M showed consistent deactivation for all four operations. Within the IPS, AG and SPL, the respective subdivisions are organized in a posterior to anterior direction.

marginal gyrus (Fig. 5b, Table 2). Longer reaction times resulted in greater deactivation of these regions. Reaction times were also positively correlated with left AG response ($r = 0.763$, $p < 0.001$). This cluster covered 9% of the left PGp and 6% of the left PGa.

2.3.3. Division

No brain regions showed negative correlations with reaction time. Reaction time was positively correlated with activity in the left PPC ($r = 0.811$, $p < 0.001$). This cluster covered 35% of the left SPL

7P, and 7% of the left PGa. Longer reaction times resulted in greater activation of these regions.

2.4. Between-operation differences in the PPC

Our analysis focused on four cognitive processes. To contrast retrieval and calculation in arithmetic we first compared brain responses to (i) multiplication versus subtraction. We then examined retrieval processes associated with (ii) multiplication and
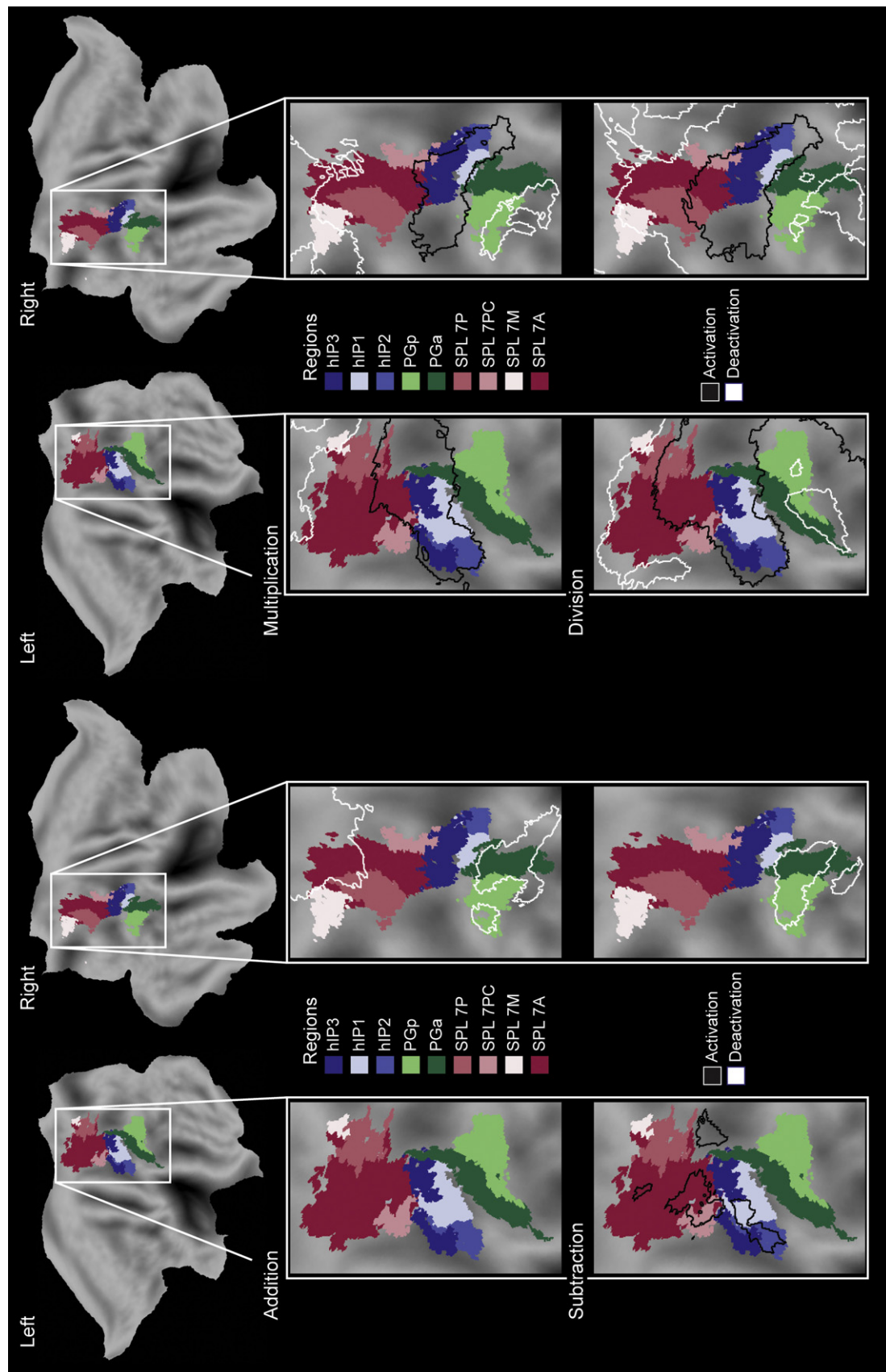
Fig. 4. Surface maps of activations and deactivations in cytoarchitectonically defined PPC regions. Surface maps of each cytoarchitectonic subdivision of the IPS, AG and SPL were created by projecting these regions onto the PALS atlas (Van Essen, 2005) using Caret (Van Essen, 2005). Task-related activations (white outline) and deactivations (black outline) are projected onto these surface maps for each arithmetic operation. Across operations, overlapping activations were detected in the left IPS and adjoining SPL, whereas deactivations overlapped in the right AG and were most variable in medial SPL area 7M.
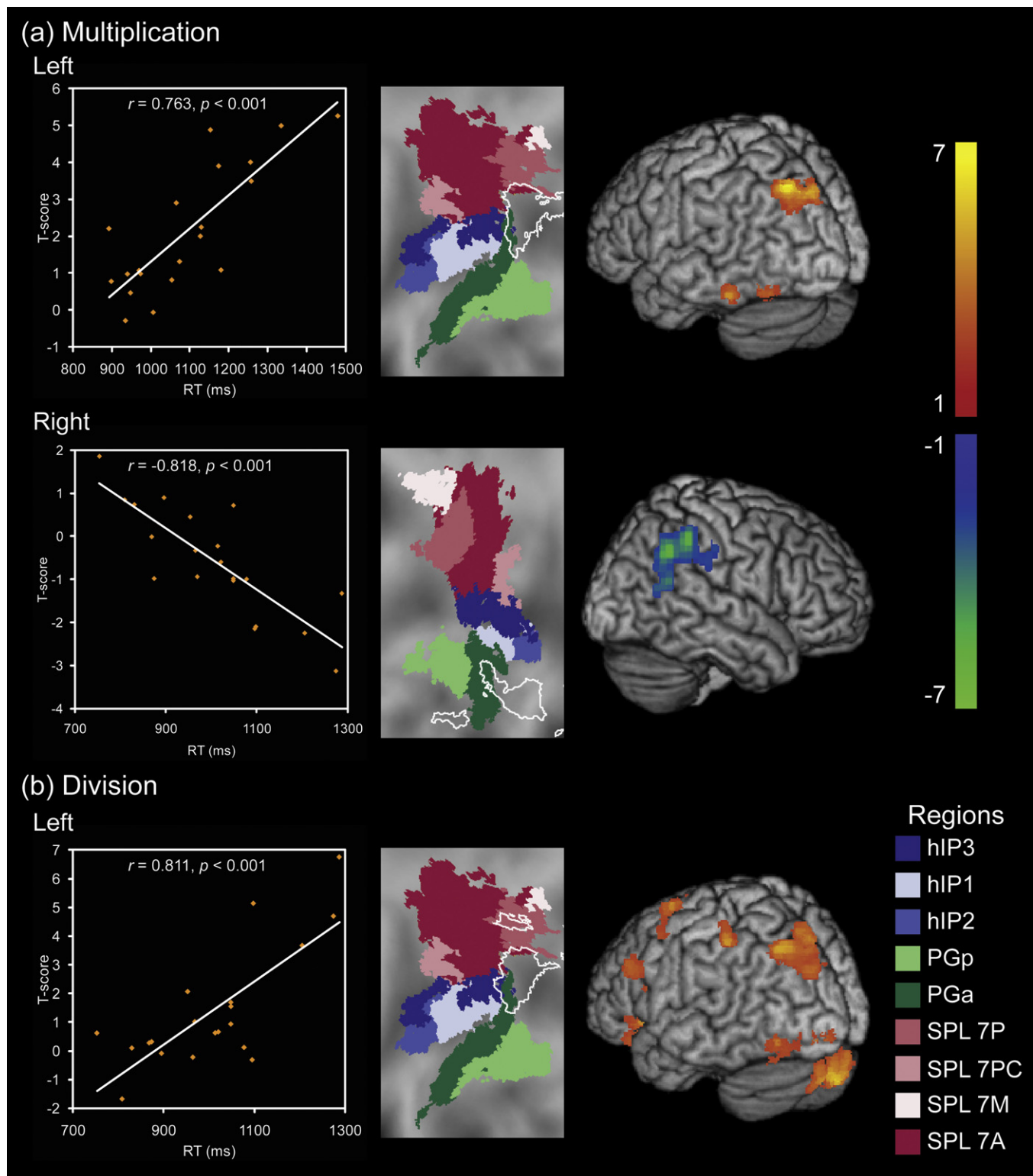
Fig. 5. Brain regions where activation and deactivation was significantly correlated with reaction time (white outline). (a) For multiplication, reaction times were positively correlated with activation in the left AG region PGp and negatively correlated with right PGa and hIP2, extending into the posterior supramarginal gyrus. Correlation maps are shown outlined in white on surface maps of cytoarchitectonically defined PPC regions and as surface renderings. (b) For division, reaction times were positively correlated with activation in the left PGp. Each cluster was significant at height $p < 0.01$, corrected for spatial extent at $p < 0.01$.

addition. We investigated differences in PPC activation across two pair-wise inverse operations: (iii) addition versus subtraction, and (iv) multiplication versus division. Here we focus on the PPC (Figs. 6 and 7). Supplementary Table S3 summarizes results at the whole-brain level.

2.4.1. Multiplication versus subtraction

No differences in activation between multiplication and subtraction were observed in the left PPC. Multiplication elicited greater activation than subtraction in right PPC, covering 18% of the right PGa, 16% of the right PGp, 16% of the right hIP1 and 7%
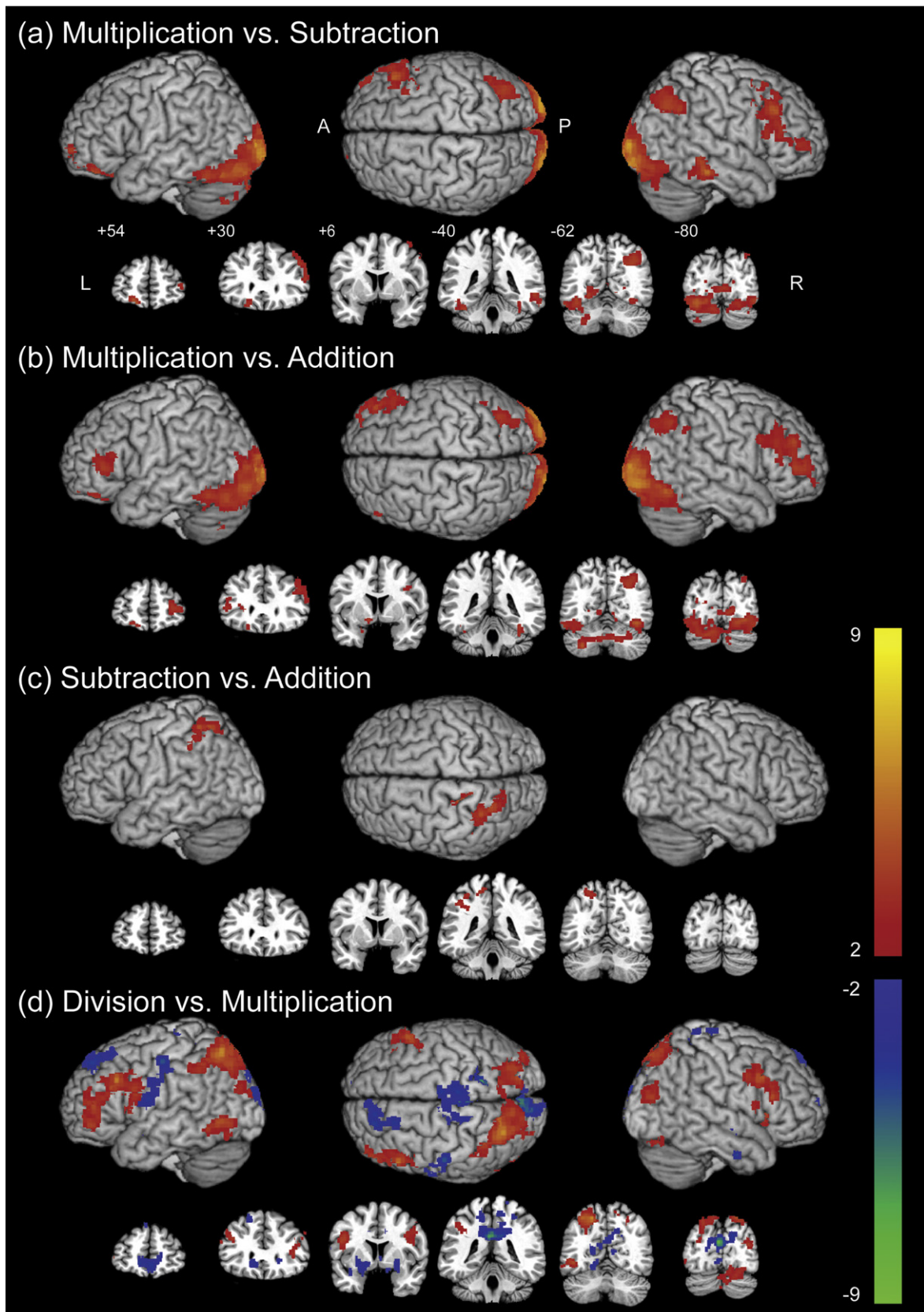
Fig. 6. Brain regions that showed significant differences in activation between operations. Surface rendering and coronal sections of brain regions that showed significant activation (red) and deactivations (blue) are shown for (a) multiplication versus subtraction, (b) multiplication versus addition, (c) subtraction versus addition and (d) division versus multiplication. Each cluster was significant at height $p < 0.01$, corrected for spatial extent at $p < 0.01$.
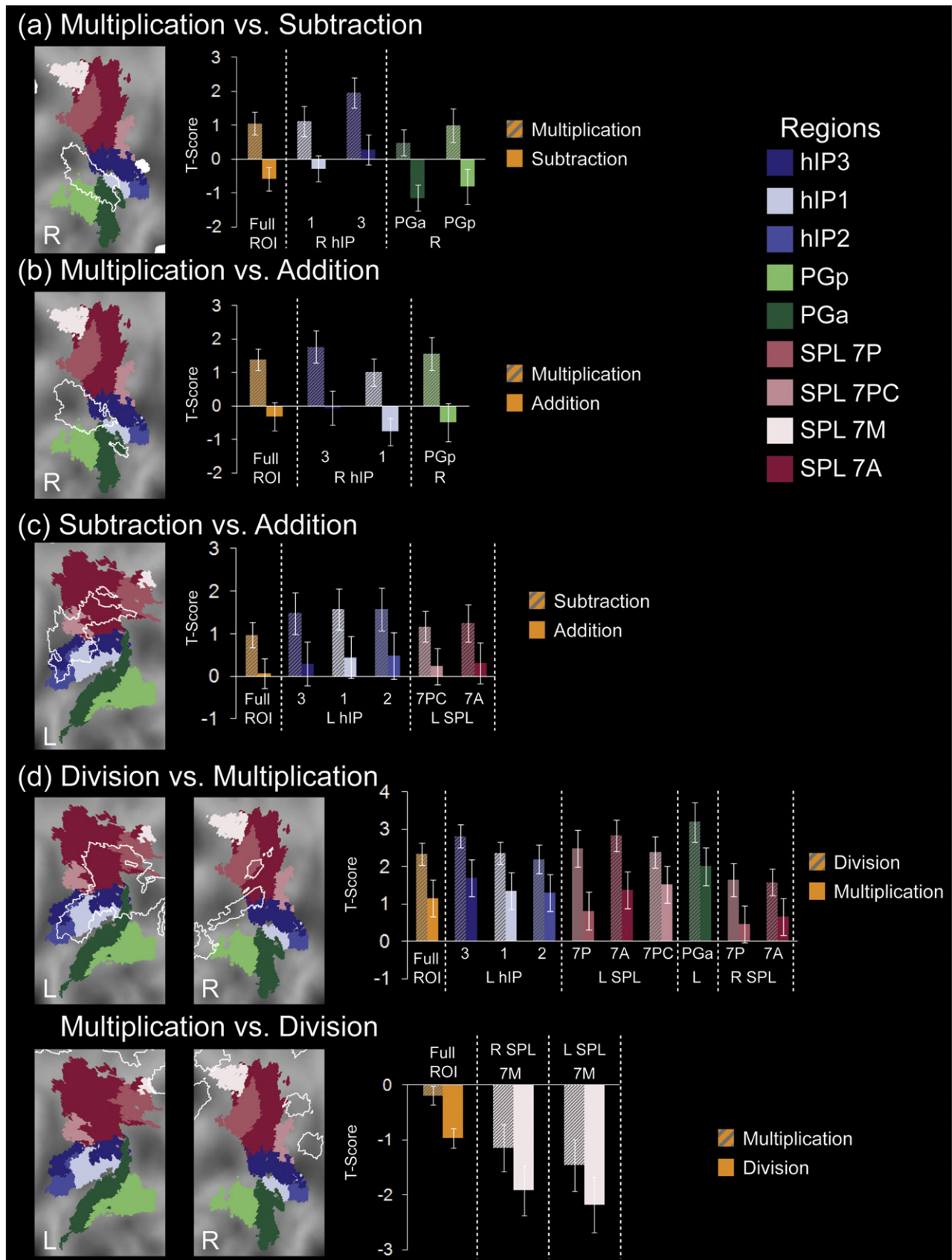
Fig. 7. Surface maps of brain regions that showed significant differences in activation (white outline) in cytoarchitectonically defined PPC regions. (a) Multiplication versus subtraction, (b) multiplication versus addition, (c) subtraction versus addition, and (d) division versus multiplication. Graphs display average *t*-score for the entire functional cluster (orange) as well as voxels that overlapped with each cytoarchitectonic subdivision of the PPC. Only subdivisions where greater than 5% of the voxels were significantly activated are shown. Other details as in Fig. 4.

Table 2
Probabilistic labeling of PPC regions which were significantly correlated with reaction time during multiplication and division. Both positive and negative correlations are shown. Other details as in Table 1.

Operation	Region	Size of cluster	% of region activated	% of cluster in region	Peak activation coordinates			Probability of peak in assigned region (%)
					X	Y	Z	
Multiplication – positive	L PGp	92	8.5	13.1				
	L PGa	50	6.1	7.2	−30	−74	48	40
Multiplication – negative	R PGa	268	26.7	22.2	54	−54	18	40
	R hIP2	9	5.9	0.7	42	−32	30	10
Division – positive	L SPL 7P	191	35.1	21.1	−6	−78	50	70
	L PGa	54	6.6	6.0	−26	−74	48	30

of the hIP3. We then examined the profile of responses within this cluster that overlapped with each of these four IPS and AG subdivisions. In the hIP1 and hIP3, multiplication showed activation above baseline, whereas subtraction did not. Multiplication showed weak activation of PGp and PGa, whereas subtraction showed strong deactivation. No PPC regions showed greater activation to subtraction, compared to multiplication.

2.4.2. Multiplication versus addition

No differences in activation between multiplication and addition were observed in the left PPC. Multiplication elicited greater activation in right PPC, encompassing 20% of the hIP3 and 12% of the hIP1% and 7% of the PGp. Differences in these regions were driven by activation during multiplication and deactivation during addition in PGp and hIP1. No PPC regions showed greater activation during addition, compared to multiplication.

2.4.3. Addition versus subtraction

No PPC regions showed greater activation to addition, compared to subtraction. Subtraction resulted in greater left PPC activations relative to addition, which encompassed 35% of hIP3, 22% of hIP1, 14% of hIP2, 36% of SPL 7PC and 14% of SPL 7A. These results were driven by differences in activation above the control task.

2.4.4. Multiplication versus division

Division showed significantly greater activation in the left IPS, encompassing 71% of the left hIP3, 64% of the left hIP1, and 30% of the left hIP2. Greater activation was also observed bilaterally in the SPL, encompassing 58% of left 7P, 39% of left 7A, 12% of left 7PC, 41% of right 7P and 13% of SPL 7A. Left PGa showed greater activation during division. These results were driven by differences in activation above the control task. Multiplication showed greater activation than division in the medial parietal lobe, with 12% of left SPL 7M and 8% of right SPL 7M, but these differences were driven by greater deactivation for division than multiplication.

2.5. (Division – multiplication) versus (subtraction – addition)

An ANOVA revealed significant interaction between the two pairs of inverse operations in left SPL 7P ($p < 0.001$, uncorrected), as shown in Supplementary Fig. S1.

3. Discussion

We examined functional overlap and dissociation in brain responses to four basic arithmetic operations, with a particular focus on cognitive processes that modulate PPC responses. We show that cytoarchitectonically defined subdivisions within the PPC (Caspers et al., 2006; Choi et al., 2006; Scheperjans et al., 2008)

provide a more precise method for relating structure and function in the human PPC. This in turn helps to examine functional dissociations with the PPC underlying basic mathematical problem solving operations. Below, we describe functional dissociations and regional heterogeneities in relation to activation and deactivation in specific cytoarchitectonically defined subdivisions of the IPS, AG and SPL. We next describe how responses in these regions are modulated by fact retrieval, calculation and inversion across operations.

3.1. Functional overlap and dissociations in the IPS

The IPS is the PPC region most consistently implicated in numerical and mathematical information processing (Dehaene et al., 2003; Menon et al., 2000). Activity in the IPS is modulated by difficulty in magnitude comparison and arithmetic problem solving (Ansari, Dhital, & Siong, 2006; Delazer et al., 2003; Menon et al., 2002; Pinel, Dehaene, Riviere, & LeBihan, 2001; Rosenberg-Lee, Lovett, & Anderson, 2009; Zago et al., 2008). All four operations, except addition, activated the IPS above the number identification control task. Activations were most prominent in the posterior IPS regions hIP3 and hIP1 (note that in the nomenclature defined by Caspers et al. (2006), hIP1 is posterior to hIP2). Subtraction primarily activated left hIP3, whereas multiplication and division showed extensive bilateral activations of hIP3 and hIP1. Across the four conditions and three IPS regions, activations showed a distributed pattern of responses rather than discrete operation specific foci (Figs. 2 and 6). An important finding highlighted by the precise cytoarchitectonic mapping of the PPC is that IPS responses do not necessarily scale with task difficulty. Although RTs did not differ between subtraction and multiplication, IPS activation was significantly greater during multiplication. These results suggest that IPS responses are independent of task difficulty. Furthermore, this result challenges the view that subtraction engages the IPS to a greater extent because of its greater reliance on calculation.

Anatomical and physiological connectivity analysis provides insights into the neural processing subserved by these regions. We have recently suggested that IPS acts as an intermediate station for relaying salient visual information into the dorsal attention and working memory network (Uddin et al., 2010). Using DTI and resting-state functional connectivity we found differential connectivity patterns for these regions (Uddin et al., 2010). Specifically, the hIP3 has greater connectivity to striate and extrastriate cortex and hIP1 has greater connectivity with inferior and middle frontal gyri. Consistent with this finding, greater activation of the hIP1 during multiplication and division was accompanied by greater activation of the prefrontal cortex. This pattern of responses suggests that the anterior IPS (hIP1) relies more on prefrontal control mechanisms during multiplication and division problem solving, in comparison

to addition and subtraction and is consistent with the results of a recent meta-analysis which found strong activity in prefrontal cortex regions involved in working memory during arithmetic tasks (Arsalidou & Taylor, 2011).

3.2. Functional heterogeneity in the AG: activation and deactivation

In contrast to the IPS which showed greater activation, the AG showed prominent reductions in activation, or deactivation, relative to the number identification control task during all four operations. Although we cannot directly assess signal levels relative to a rest baseline in our study, previous studies have consistently found deactivation relative to rest baseline in the AG during arithmetic problem solving (Grabner et al., 2007; Mizuhara, Wang, Kobayashi, & Yamaguchi, 2005; Zhou et al., 2007). Deactivations were most prominent in the right AG. One emerging view of AG function comes from research into the default mode network, a set of brain regions that consistently shows reduced activity during cognitive tasks, compared to rest (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). In addition to the two midline areas, the ventral medial prefrontal cortex and the posterior cingulate cortex, the default mode network also includes lateral parietal areas within the AG (Uddin et al., 2010). Consistent with this observation, we found significant deactivation, relative to the control task, medially and bilaterally in all these areas for all four operations, except the addition task which only deactivated the right AG. Most nodes of the default mode network typically show greater deactivation with increased task difficulty (Daselaar, Prince, & Cabeza, 2004; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Wu et al., 2009). Three analyses from our study suggest that this is not always the case. First, even though addition and subtraction differed on reaction time, these operations did not differ in the level of AG deactivation. Second, a similar finding held for multiplication and division. Third, even when there were no reaction time differences between multiplication and subtraction, there were differences in AG deactivation between the operations. Taken together, our analysis suggests that AG deactivations depend on the operation, independent of behavioral difficulty as assessed by differences in reaction time.

AG responses were sensitive to individual differences in mathematical ability. Previous studies have suggested that increased AG deactivation is associated with poorer math performance (Wu et al., 2009) and abilities (Grabner et al., 2007), but no studies have examined how individual differences in AG activation and deactivation differ across the four arithmetic operations. In our study, we found that AG responses were correlated with reaction time during multiplication and division, but not during addition or subtraction (Fig. 5). A different pattern of individual differences emerged for these two operations. For multiplication, the right and left AG showed an opposing pattern of effects with slower participants showing greater deactivation in the right AG and greater activation in the left AG. For division, only the left AG showed significant effects with slower participants showing greater activation. Most participants showed positive task-related responses, rather than deactivation in the left PGa bordering the supramarginal gyrus, during both multiplication and division. These results point to further heterogeneities in the AG as well as functional dissociations between the left and right AG. Interestingly, individual differences and differences between operations were most prominent close to functional boundaries between PPC regions. The functional circuits underlying these effects remain to be investigated, but one possible explanation is that individual variation in functional connectivity appears to correlate best with the transitional areas between the task positive and task negative areas, rather than the peaks of network activity (Mennes et al., 2010).

3.3. Functional heterogeneity in the SPL

While the IPS and AG have been the focus of most investigations in mental arithmetic, the SPL is also known to be consistently activated across a wide range of studies (Dehaene et al., 2003). Since the boundary between the SPL and dorsal aspects of the IPS has not been adequately differentiated in previous studies, quite often activations in these regions tend to be arbitrarily assigned to the SPL. The use of cytoarchitectonic maps of the SPL and IPS allows us to more clearly distinguish activations in these regions than has been possible so far.

Our analysis demonstrates that the SPL shows a pattern of heterogeneity different from the IPS and AG. All operations, except addition, showed significant responses in the SPL compared to the number identification control task. Notably, while the lateral SPL subregions (7A, 7PC and 7P) showed task-related activations in each operation, medial SPL subregion 7M showed prominent deactivations. However, unlike the IPS and AG, which showed heterogeneous responses, both between and within operations and bilaterally, SPL 7M had monotonically increasing deactivation with operation reaction times. SPL 7M is part of the midline structures comprising the default mode network (Greicius et al., 2003). Scheperjans et al. (2008) have noted that medial parietal areas tend to have less inter-individual response variability than lateral structures, perhaps accounting for the strong effects noted in this region. Recently, Margulies et al. (2009) used resting-state functional connectivity measures to parcellate the medial parietal cortex in both humans and monkeys. They propose that the 'cognitive' dorsal posterior area with connections to the lateral frontal areas and the IPS can be distinguished from a 'limbic' ventral area (essentially posterior cingulate cortex), with connections to midline frontal areas and angular gyrus. Although the exact mapping of these areas to 7A, 7P and 7M is unclear, it does match our findings of task-related activation in 7A and deactivation in 7M. Finally, we note the specific engagement of the SPL by division relative to other operations. Division strongly activated SPL 7A and 7P bilaterally, whereas the other operations activated it weakly (left 7A) or not at all (right 7A, bilateral 7P, Fig. 3c). Moreover, division was also the only operation to show significant correlation with performance in SPL (left 7P). Together, these results suggest that activation in SPL regions 7A, 7P and 7PC is modulated differently from deactivation in SPL 7M across operations.

3.4. Retrieval versus calculation: contrasting subtraction and multiplication

The IPS has been the focus of four previous investigations of differential PPC responses during subtraction and multiplication. The main reason for contrasting these operations is that they encapsulate two key cognitive processes in arithmetic: calculation and fact retrieval, respectively. Previous studies have yielded conflicting findings with little agreement on the precise anatomical localization of between-task differences. In the IPS, greater activity for multiplication (Kawashima et al., 2004) and subtraction (Hayashi et al., 2000; Lee, 2000) have both been reported. On the other hand, Chochon et al. (1999) found no differences in the IPS. However, because most of these studies did not acquire behavioral data concurrently with fMRI data it is unclear whether the observed IPS differences are due to differences between operations or the result of task difficulty. Our study overcomes several limitations of previous studies by carefully matching task difficulty across the two operations, along with the use of more appropriate control tasks and larger samples compared to previous studies. Critically, by restricting the range of addition and subtraction problems, we were able to ensure that RTs on subtraction and multiplications were comparable. In particular, subtraction problems with minuends in

the range of 11–18 have RTs 450–850 ms longer than problems in the range used in our study (Campbell & Alberts, 2009; Campbell & Xue, 2001; Seyler et al., 2003).

Although there were no differences in either accuracy or reaction time between the conditions, we found that multiplication, compared to subtraction, showed greater activation in the right IPS regions hIP3 and hIP1, as well as the right AG. Critically, no differences were observed in the left hemisphere. In order to further delineate the profile of differences between multiplication and subtraction, we examined responses in each cytoarchitectonically defined IPS and AG region that overlapped with the significant areas on the multiplication versus subtraction comparison. Although a large extent of the right PGp showed significant deactivation relative to the control task for both multiplication (52%) and subtraction (50%), a direct comparison of the two operations identified a subregion within the right PGp and adjoining PGa which showed activation above the control task for multiplication and deactivation for subtraction (Fig. 7e). Thus, although both operations deactivate the PGp, relatively circumscribed subregions of the PGa and PGp, bordering the IPS, showed activations above baseline only in the multiplication task. Taken together, these results hint at further heterogeneities within the AG above and beyond those demarcated by its cytoarchitectonic boundaries. Furthermore, it should be noted that these differences between operations were found in the right AG. These findings do not provide support for a differential role for left AG mediated verbal fact retrieval during multiplication as proposed by the "triple-code" model (Dehaene et al., 2003).

3.5. Fact retrieval in multiplication versus addition

Addition and multiplication are two operations that rely most heavily on retrieval of well-learned math facts in adults (Campbell, 2008; Campbell & Xue, 2001). The two operations were well matched for accuracy. Addition problems were solved slightly faster than multiplication problems, perhaps because the addition problems were from a restricted range. RT difference between these operations was about 62 ms. Previous behavioral studies by Campbell and colleagues have shown that addition problems with sums greater than 10 also show faster RTs than the corresponding multiplication problems (Campbell & Alberts, 2009; Robert & Campbell, 2008), so matching addition and multiplication problems on RT while simultaneously matching RTs on subtraction and multiplication problems is non-trivial. Despite the lack of significant differences in RT, there were substantial differences in brain response to the two problem types. In contrast to addition, which produced no activity above the number identification control task, the multiplication task showed significant activation bilaterally in the PPC as well as the prefrontal cortex. A direct comparison between the two tasks revealed significantly greater activation in the right PPC, covering 20% of hIP3, 12% of hIP1 and 7% of PGp (Fig. 7d, Table 3). Critically, it should be noted that PPC differences within the AG were restricted to the right hemisphere suggesting that verbally mediated retrieval of multiplication is not the main source of processing differences in the two tasks. Interestingly, functional differences in the AG were driven by deactivation for addition and activation for multiplication, further weakening the case for a strong role for the AG in verbal retrieval of math facts.

Retrieval is used more consistently for multiplication because alternative computational strategies are more time consuming than those for addition. Consistent with these observations, we found greater ventrolateral and dorsolateral prefrontal cortex activation during multiplication than addition (and subtraction), brain regions which have been implicated in controlled memory retrieval (Badre & Wagner, 2002). Interestingly these differences

were strongest in the right hemisphere, consistent with a recent meta-analysis of arithmetic tasks (Arsalidou & Taylor, 2011) which found that activity during multiplication tasks was strongly right-lateralized in prefrontal cortex. Taken together, these findings challenge the view that multiplication relies primarily on left-lateralized language areas.

3.6. Processing inverse arithmetic operations

We focus here on distinctions between the two pair-wise inverse operations: addition versus subtraction and multiplication versus division. An important question is whether processing of inverse relations is operation specific. Subtraction is not as automated as addition (Campbell & Alberts, 2009; Campbell & Xue, 2001), despite the fact that problem solving by inversion is essential part of understanding mathematical concepts (Bryant, Christie, & Rendu, 1999). Consistent with this model, we found that participants were significantly slower at solving subtraction than addition verification problems. Subtraction also resulted in greater activation of the left IPS and SPL; interestingly, there were no differences in the prefrontal cortex or any other brain regions for subtraction problems, compared to addition.

Behavioral studies have suggested that inversion is the primary backup strategy for division (Campbell & Xue, 2001). One view holds that division is facilitated by the automatic activation in memory of the multiplicative factors of dividends (Rickard, 2005). Reaction time differences of 86 ms observed between division and multiplication was identical to reaction time differences between subtraction and addition. Thus, if both subtraction and division depended equally on inversion, we might predict similar patterns of differences between division and multiplication on the one hand and those between subtraction and addition on the other. However, activation differences between division and multiplication were more widespread, than between subtraction and addition, in the left IPS and SPL, and included additional regions in the right IPS and SPL. Moreover, activation differences were also observed in the ventrolateral and dorsolateral prefrontal cortex, fusiform gyrus, basal ganglia and the cerebellum – areas that did not show any activation differences between subtraction and addition. Further, multiplication also showed greater activity than division, and these differences were driven by greater deactivation for division than multiplication in SPL 7M, bilaterally. No such differences were observed in addition compared to subtraction.

What accounts for these extensive differences in brain activation when there are no behavioral differences between pairs of inverse operations? Dube and Robinson (2010) found that one-quarter of university undergraduates tested failed to solve problems of the form $a \times b \div b$ by cancelling the final two terms, suggesting that they did not understand conceptually the inverse relationship between multiplication and division. This suggests that participants may not readily use inversion strategies to solve related inverse problems. One possibility here is that the verification format of tasks used in our study may interfere with the automatic activation of the multiplicative factors (Rickard, 2005).

Finally, multiplication and division were the only operations to show individual differences in brain response related to performance. While both multiplication and division showed positive correlations with reaction time in the left PGa, only division showed prominent brain–behavior relationships in the SPL. No such effects were observed in the case of subtraction and addition. Taken together, these results suggest that strategies used to solve division problems are much more complex than strategies used to solve subtraction problems. These results further suggest that processing of inverse relations is operation specific.

Table 3
Probabilistic labeling of posterior parietal cortex (PPC) responses in four key between-operation comparisons. Other details as in Table 1.

Comparison	Region	Size of cluster	% of region activated	% of cluster in region	Peak activation coordinates			Probability of peak in assigned region (%)
					X	Y	Z	
Multiplication – subtraction	R Pga	176	17.5	17.8	44	−64	56	30
	R PGp	191	16.3	19.3	40	−68	38	30
	R hIP1	36	15.5	3.6	40	−56	36	20
	R hIP3	20	6.6	2.0				
Multiplication – addition	R hIP3	59	19.9	7.0	34	−64	44	20
	R hIP1	27	11.9	3.2	28	−60	36	10
	R PGp	78	6.7	9.2				
Subtraction – addition	L SPL 7PC	67	35.8	6.5				
	L hIP3	96	35.1	9.4				
	L hIP1	101	22.1	9.9	−34	−46	44	30
	L hIP2	35	14.3	3.4	−44	−40	42	20
	L SPL 7A	245	13.9	23.8	−26	−58	58	50
Division – multiplication	L hIP3	196	71.4	5.5	−32	−50	42	40
	L hIP1	295	64.4	8.4				
	L SPL 7P	315	58.0	8.9	−10	−76	56	60
	L SPL 7A	679	38.6	19.3	−28	−68	56	40
	L hIP2	71	29.4	2.0				
	L PGa	113	13.7	3.2				
	L SPL 7PC	22	11.7	0.6				
	R SPL 7P	273	41.2	7.8	20	−82	54	20
	R SPL 7A	147	12.6	4.2	30	−76	56	20
Multiplication – division	L SPL 7M	16	11.8	0.2				
	R SPL 7M	14	8.1	0.2				

4. Limitations

There are multiple trade-offs in stimulus selection and RT matching across the four operations. In general, it is not possible to achieve behavioral matching to test all possible hypotheses comparing across the four operations (Campbell & Alberts, 2009; Campbell & Xue, 2001; Robert & Campbell, 2008). For multiplication versus subtraction, a key comparison in our study, there were no significant performance differences. Addition and multiplication showed modest, but not significant, RT differences likely arising from the use of smaller problems for addition and subtraction relative to multiplication and division. However, as noted above, if we had used the full range of addition and subtraction problems, RTs on the latter could have been up to 850 ms longer (Seyler et al., 2003) and problem difficulty would significantly confound interpretation of brain responses. Furthermore, this stimulus set enabled us to examine how inverse operations are processed across the two pairs of operations – because the RT difference across these pairs was almost exactly 86 ms in both cases. This would have been impossible if we had used the full complement of single-digit subtraction problems.

Another potential limitation of this study is the use of verification rather than production tasks. We have framed differences between subtraction and multiplication in the context of retrieval and calculation strategies. However, familiarity may also influence performance on verification tasks like the one used here (Zbrodoff & Logan, 1990). To minimize familiarity effects, incorrect answers were created by adding or subtraction '1' or '2' from the correct value, following research showing larger discrepancies greatly increase rejection speed (Ashcraft & Battaglia, 1978; De Rammelaere, Stuyven, & Vandierendonck, 2001; Yagoubi, Lemaire, & Besson, 2003). However, for multiplication and division these values are implausible based on the multiplication table. For example, $6 \times 5 = 31$ can be rejected because products ending in 1 never appear in the 6 or 5 times table. If this were the case, we would expect multiplication and division to be more rapidly solved than addition and subtraction, respectively, which we did not observe. Additional

behavioral studies are needed to construct a more balanced set of stimuli across the four operations in order to further evaluate, and advance our understanding of similarities and differences in the neural representations of cognitive processes underlying various arithmetic operations.

A final limitation of our experimental design was the lack of a passive fixation ("rest") block. Thus, we cannot directly assess the direction of brain responses for each operation relative to a rest baseline, and also the lack of activity for addition. We suspect that both addition and the number identification task activated the IPS, as has previously been shown for number identification (Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003).

5. Conclusion

We have presented the most detailed study yet of the involvement of the PPC across the four basic arithmetic operations. When compared against a common number identification task that controls for sensorimotor processing, these operations show prominent functional overlap as well as functional dissociations within the PPC. Overlap across the operations was most prominent in activation of the left posterior IPS and in deactivation of the right posterior AG. We demonstrate that PPC subdivisions are differentially modulated by the four arithmetic operations and we point to significant functional heterogeneity and individual differences in activation and deactivation of these regions. Critically, these differences were related to retrieval, calculation and inversion, the three key cognitive processes that are differentially engaged by arithmetic operations. Our findings provide new insights into the functional organization of specific cytoarchitectonic divisions within the PPC, and further suggest that brain of responses associated with calculation and retrieval processes cannot be uniquely mapped to specific PPC regions. More generally, our study helps shed new light on the neural basis of contradictory findings in the lesion literature by demonstrating that the four basic arithmetic operations rely on a complex profile of distributed responses within the PPC, involving differential levels of activation and deactivation

across distinct subdivisions of the IPS, SPL and AG. How distributed representations in the PPC contribute to arithmetic information processing and problem solving remains to be investigated, and will most likely require novel multivariate approaches (Kriegeskorte, Mur, & Bandettini, 2008).

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2011.04.035.

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