

Response-Selection-Related Parietal Activation during Number Comparison

Silke M. Göbel¹, Heidi Johansen-Berg², Tim Behrens²,
and Matthew F. S. Rushworth^{1,2}

Abstract

■ Neuroimaging studies of number comparison have consistently found activation in the intraparietal sulcus (IPS). Recently, it has been suggested that activations in the IPS vary with the distance between the numbers being compared. In number comparison, the smaller the distance between a number and the reference the longer the reaction time (RT). Activations in the right or left IPS, however, have also been related to attentional and intentional selection. It is possible, therefore, that activity in this region is a reflection of the more basic stimulus and response-selection processes associated with changes in RT. This fMRI experiment investigated the effect of numerical distance independently from RT. In addition, activations during number comparison of single-digit and double-digit stimuli were compared. During number comparison blocks, subjects had to indicate whether digits were greater or smaller than a reference (5 or 65). In control blocks, they were asked to perform a perceptual task (vertical line present/absent)

on either numerical or nonnumerical stimuli. Number comparison versus rest yielded a large bilateral parietal-posterior frontal network. However, no areas showed more activation during number comparison than during the control tasks. Furthermore, no areas were more active during comparison of numbers separated by a small distance than comparisons of those separated by a large distance or vice versa. A left-lateralized parietal-posterior frontal network varied significantly with RT. Our findings suggest that magnitude and numerical-distance-related IPS activations might be difficult to separate from fundamental stimulus and response-selection processes associated with RT changes. As is the case with other parameters, such as space, magnitude may be represented in the context of response selection in the parietal cortex. In this respect, the representation of magnitude in the human IPS may be similar to the representation of magnitude in other nonhuman primates. ■

INTRODUCTION

Neuroimaging studies of calculation have shown an involvement of the left intraparietal sulcus (IPS) and inferior parietal lobule (IPL) region during calculation (Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002; Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001; Zago et al., 2001; Burbaud et al., 2000; Cowell, Egan, Code, Harasty, & Watson, 2000; Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999; Rueckert et al., 1996). This is consistent with a large body of evidence that acalculia, difficulty with calculations, follows damage to similar regions (Dehaene, Piazza, Pinel, & Cohen, 2003; Cipolotti & van Harskamp, 2001; Dehaene, 2000; Butterworth, 1999).

Although particular parietal regions may be indispensable for calculation, the evidence is less clear for numerical magnitude. Many studies have not investigated numerical magnitude explicitly; however, it is clearly documented that patients with impaired calcu-

lation abilities often retain some appreciation of numerical magnitude (Cipolotti & van Harskamp, 2001; van Harskamp & Cipolotti, 2001). In addition, there are few reports of patients who are impaired in number comparison (Lemer et al., 2003; Butterworth, 1999; Delazer & Butterworth, 1997; Noël & Seron, 1993). The lesions have not been clearly documented in all of these patients, but in some cases the damage is outside the parietal cortex and both hemispheres are affected (Delazer & Butterworth, 1997; Hittmaier-Delazer et al., 1994; Warrington, 1982). Studies of split-brain patients indicate that magnitude representation is bilateral and present in both hemispheres (Cohen & Dehaene, 1996).

The lack of impairment in magnitude processing in many patients does not initially appear consistent with the results of brain imaging studies. Many of these studies have used number comparison tasks to investigate the representation of numerical magnitude. The task usually requires subjects to select between left- or right-hand key presses to indicate whether presented numbers are smaller or larger than a reference number. Most studies of number comparison report

¹Department of Experimental Psychology, University of Oxford, ²Functional Magnetic Resonance Imaging of the Brain (FMRiB) Centre

consistently increased activity in the IPS (Fias, Lammer-
tyn, Reynvoet, Dupont, & Orban, 2003; Le Clec'H et al.,
2000; Pesenti, Thioux, Samson, Bruyer, & Seron, 2000;
Pesenti, Thioux, Seron, & De Volder, 2000; Chochon,
Cohen, van de Moortele, & Dehaene, 1999; Pinel et al.,
1999) and, less consistently, in IPL regions such as an-
gular gyri (Pesenti, Thioux, Samson, et al., 2000; Pesenti,
Thioux, Seron, et al., 2000; Rickard et al., 2000) or su-
pramarginal gyri (Le Clec'H et al., 2000). In contrast to
many activations reported during calculation, however,
intraparietal and inferior parietal activation during num-
ber comparison is not left lateralized but tends to be
bilateral (e.g., Rickard et al., 2000; Chochon et al., 1999)
or even right lateralized (Le Clec'H et al., 2000).

Whereas some studies have investigated magnitude
representation by simply comparing a number compar-
ison task with a nonnumber comparison task, other
studies have investigated how activation changes as
numerical distance between the presented and the refer-
ence number changes (Cohen-Kadosh et al., submit-
ted; Fias et al., 2003; Pinel et al., 1999; Pinel, Dehaene,
Riviere, & Le Bihan, 2001). In a double-digit number
comparison task Pinel et al. (2001), for example, found
the smaller the distance to the reference number, the
more activation in the right IPS (with an anterior focus),
in left and right precuneus, in the left middle temporal
gyrus, and the left posterior cingulate cortex. Numerical
distance, therefore, has been argued to have an effect on
which brain areas are active.

It can, however, be difficult to interpret activations
recorded in some number comparison tasks. Simply
selecting responses, such as a left- or right-hand key
press, regardless of whether a judgment is being made
about numerical magnitude, has been repeatedly shown
to activate similar bilateral IPS regions (Eliassen, Souza,
& Sanes, 2003; Jiang & Kanwisher, 2003; Bunge, Hazel-
tine, Scanlon, Rosen, & Gabrieli, 2002, 2003; Schluter,
Krams, Rushworth, & Passingham, 2001; Richter et al.,
2000; Carpenter, Just, Keller, Eddy, & Thulborn, 1999).
This may be particularly problematic if the control task
does not contain a clear response-selection element.
For example, the letter-naming task used by Chochon
et al. (1999) as a control task is unlikely to have strong
response-selection elements.

Similarly the interpretation of numerical distance
effects can be problematic; reaction time (RT) is not
only an index of numerical distance, but it is also an
index of many other factors that may affect the difficulty
of response selection. IPS activation is known to covary
with several other factors influencing RT (Rushworth,
Ellison, & Walsh, 2001; Rushworth, Krams, & Passing-
ham, 2001; Winstein, Grafton, & Pohl, 1997; Deiber,
Ibanez, Sadato, & Hallett, 1996). Furthermore, the evi-
dence that the IPS is concerned with some aspect of re-
sponse selection or intention is not restricted to human
brain imaging experiments (Rushworth, Johansen-Berg,
Göbel, & Devlin, 2003; Snyder, Batista, & Andersen, 1997;

Wise, Boussaoud, Johnson, & Caminiti, 1997). There is
also evidence that parietal single-neuron activity is mod-
ulated during selection between spatially defined re-
sponses to graded visual information (Gold & Shadlen,
2001). Therefore, the IPS activation for number compar-
ison or numerical distance could be because of a com-
mon mechanism for quantitative processing of numerical
and nonnumerical visuospatial stimuli, or it might be
related to a general task component such as response
selection or task difficulty. Most studies investigating
the effect of numerical distance on brain activations
have not been able to exclude these alternative explana-
tions. The interpretation of impaired performance in
similar number comparison tasks after parietal lesions
or TMS may also be affected by the same problem (Lemer
et al., 2003; Göbel, Rushworth, & Walsh, 2001; Göbel,
Walsh, & Rushworth, 2001).

Although we have contrasted explanations based on
response selection and number magnitude, a strict
dichotomy may not be appropriate. It is possible that
neural mechanisms of magnitude representation are
inextricably tied to response-selection mechanisms
(Walsh, 2003). Walsh argues that spatial and temporal
magnitude representations in the parietal cortex are
closely linked to response selection and that the same
is true in the case of numerical magnitude. Similarly,
Butterworth (1999) draws on neuropsychological, devel-
opmental, and linguistic evidence to argue that numeri-
cal representation in the parietal cortex may be related
to hand and finger response processes in the same area.
Evidence to support this hypothesis stems from recent
imaging studies on comparison processes. For example,
both Fias et al. (2003) and Cohen-Kadosh et al. (submit-
ted) have reported parietal activation when subjects
compare angles, lines, physical size, or stimulus bright-
ness. However, any areas specific to number comparison
found in these studies might also be accounted for by
the greater difficulty, as indexed by RT, of the number
task. There is also evidence for a tight link between the
representation of number magnitude and response se-
lection in nonhuman animals. For example, single neu-
rons in the macaque monkey IPS region may code some
aspects of numerical magnitude (Sawamura, Shima, &
Tanji, 2002). In this study, neurons with number-related
responses on the medial bank of the IPS were clearly
identified as being interspersed within the representa-
tion of the proximal forelimb that the animals used for
making the responses.

The first aim of the present study of number compar-
ison was therefore to disentangle activations specific to
number comparison or activations, which changed with
numerical distance from activations related to response
selection as indexed by RT. Our analysis allowed the
effect of both variables to be measured independently.
The explanatory variable or regressor representing RT
was orthogonalized with respect to all other number-
related regressors in the analysis. In this way, the RT

variable was only able to account for variance left unaccounted for by the other regressors.

Furthermore, it is also often unclear whether the brain regions activated by number comparison are also activated by number recognition in the absence of any numerosity judgment. Chochon et al. (1999) reported that only one brain region, the right postcentral sulcus, a region quite anterior to those normally implicated in number processing, was more active during number comparison than during digit naming. In contrast Eger, Sterzer, Russ, Giraud, and Kleinschmidt (2003), using a region-of-interest-based approach, claimed that a quite distinct region of the IPS was more active when number, as opposed to other stimuli, was used. Our second aim was therefore to examine whether magnitude representation is mandatory when Arabic digits are presented by testing the degree to which the IPS is activated by numerical or nonnumerical stimuli.

Finally, our third question concerned the possibility of separate subsets of neurons coding for different number sizes. Naccache and Dehaene (2001) suggested that distinct populations of IPS neurons encode different numbers. In their study, a left parietal region showed greater activation for number 9 than number 4. Stanescu-Cosson et al. (2000) reported greater blood oxygenation level-dependent (BOLD) activations in the left IPS for numerical problems involving large numbers (from 5 to 9) than for those using small numbers (1–5). Across studies there is a tendency for smaller and large number tasks to be impaired by more anterior and more posterior parietal TMS, respectively (Göbel, Rushworth, et al., 2001; Göbel, Walsh, et al., 2001). Single digits can be represented by the fingers (Butterworth, 1999), but there is no clear and intuitive way to represent double digits with 10 fingers. Thus, their association with more anterior IPS may be because of this region's greater involvement in representing finger movements (Grefkes, Weiss, Zilles, & Fink, 2002; Rushworth, Ellison, et al., 2001; Rushworth, Krams, et al., 2001; Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Binkofski, Dohle, et al., 1998).

During number comparison (NC) blocks subjects had to indicate whether digits were greater or smaller than a reference number (5 or 65) (Figure 1A). NC blocks consisted mainly of numbers that were either close to the reference number (*distance close*) or further away from the reference number (*distance far*). Blocks also differed in *number size* (single-digit or double-digit numbers). In control blocks, participants were asked to perform a perceptual task (vertical line judgment [VLJ]) on numerical or nonnumerical stimuli (N-VLJ and X-VLJ, respectively). In total, there were three *judgment types* (Figure 1B). In addition to behavioral and whole-brain analyses, we performed an analysis based on signal change in regions of interest (ROIs). Four ROIs were defined: left and right anterior IPS (aIPS) and left and right posterior IPS (pIPS).

RESULTS

Behavioral Results

Subjects failed to respond on average on 0.4% of all trials. It took subjects on average the same time to respond on NC blocks as on N-VLJ and X-VLJ blocks (Figure 2), suggesting that overall the three judgment types were of equal difficulty ($p > .1$). For each task, however, the reaction times (RTs) were longer for double-digit than for single-digit stimuli, $F(1,11) = 114.74$, $p < .001$. Irrespective of judgment type, on average subjects responded 66 msec faster to single-digit than to double-digit stimuli.

The effect of distance varied between judgment types: Interaction Judgment Type \times Distance, $F(2,22) = 10.812$, $p = .001$ (see Figure 2). Only for stimuli during NC blocks were RTs longer for stimuli that were closer to the reference number than for those that were further away ($t = 3.64$, $df = 11$, $p = .004$). Hence, subjects showed a behavioral distance effect during NC inside the scanner. The opposite pattern was observed in N-VLJ blocks. Here, it took subjects 21 msec longer to respond to stimuli that were far from the reference number than to those that were closer ($t = -2.40$, $df = 11$, $p = .04$; see Figure 1). Distance showed no effect in X-VLJ blocks.

Whole-Brain Analysis

Comparing Number Comparison with Rest

When NC judgment was compared with rest there were significant clusters of activation (Table 1). As can be seen in Figure 3A, a large bilateral parietal network was active during NC. This network includes the posterior part of IPS, the medial bank of the IPS extending into the superior parietal lobule and the postcentral sulcus. We failed, however, to find any significant activation in IPL areas further from the IPS.

Several motor regions were active: bilateral motor cortex, left premotor area, right supplementary motor area (SMA), bilateral PreSMA, bilateral cingulate motor areas and bilateral superior precentral sulcus/superior frontal sulcus (probably FEF). In the right hemisphere, a region in the middle temporal gyrus/inferior temporal sulcus also showed significant activation. The right fusiform gyrus was activated. Other regions of activation were bilateral insula and putamen, left caudate nucleus, and bilateral cerebellum.

Judgment-Type Specific Results

No significant clusters of activation were found when NC blocks were contrasted with either N-VLJ or X-VLJ blocks. Neither did we find any significant clusters of activation when we contrasted N-VLJ and X-VLJ blocks. These findings are followed up in the ROI analysis (see below).

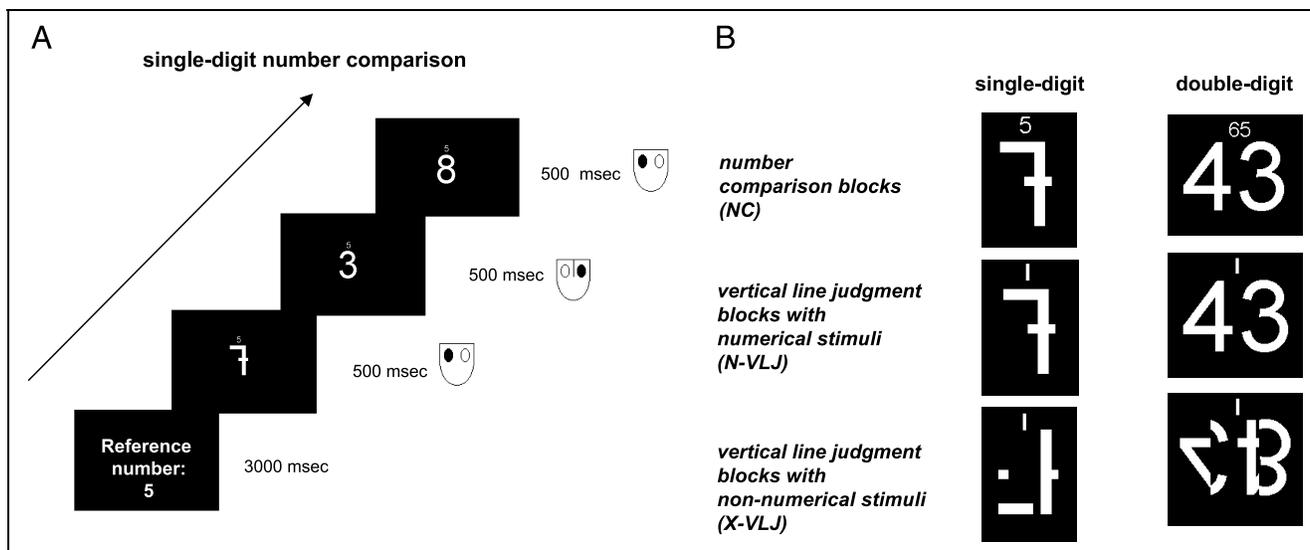


Figure 1. (A) example of the first three trials of a number comparison block with single-digit stimuli. Subjects had to indicate with one of two possible key presses whether the displayed number was larger or smaller than a reference number. The intertrial interval varied between 1.4 and 1.6 sec. Timings were the same for each block. (B) overview of stimuli used. There were three judgment types (NC, N-VLJ, and X-VLJ) and two number sizes (single-digit and double-digit).

Effect of Number Size

There were no brain areas significantly more active for single-digit NC than for double-digit comparison. For the opposite contrast (double-digit NC vs. single-digit NC) there were significant clusters of activation only within the extrastriate visual areas in bilateral, lateral occipital/lunate sulci, the fusiform gyri, and in the left hemisphere around the inferior occipital sulcus and the calcarine fissure (see Figure 3B).

Effect of Distance

We failed to find any significant clusters of activation for the contrast of NC blocks with stimuli that were close to the reference number (distance close) versus those that were far from the reference number (distance far). Neither were there any areas more active during NC of stimuli with greater distance than during NC of stimuli that were on average closer to the reference number. This finding is followed up in the ROI analysis (see below).

RT Effects

Figure 3C and Table 2 show brain areas that vary with RT irrespective of judgment type. Several parietal activations were found in the left hemisphere. The activation found in the left supramarginal gyrus (SMG) extends into the lateral bank of the IPS. There is a second cluster of activation in the lateral bank of the IPS, but it is located more posteriorly. We also found activation in the left superior parietal lobule that extends into the medial bank of the IPS and a cluster around the left postcentral sulcus.

Several motor regions were also active: left motor cortex, right premotor area, bilateral SMA, right PreSMA and bilateral cingulate motor areas. Other regions of activation were in the right hemisphere around the inferior frontal sulcus and in the left frontal operculum.

ROI Analysis

When overall mean percentage signal change was compared between the four ROIs in and around the IPS, left and right aIPS, and left and right pIPS, there were significant differences in mean percentage signal change, $F(1,11) = 17.92, p = .001$ (see Figure 4). In the left hemisphere, the mean percentage signal change in the aIPS

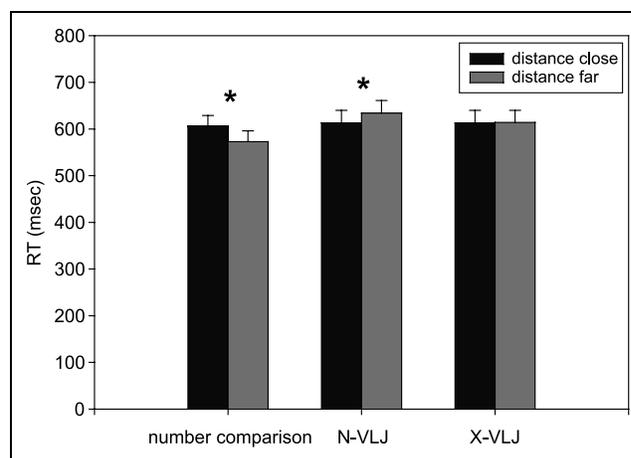


Figure 2. Reaction times (msec) in number comparison N-VLJ, and X-VLJ blocks when stimuli were close to or far from the reference number.

Table 1. Talairach Coordinates of Activation Peaks for Number Comparison versus Rest

Brain Area	Left Hemisphere				Right Hemisphere			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>
Medial bank of IPS/SPL	-42	-36	44	4.03	32	-50	36	3.94
	-30	-46	48	3.91	40	-42	46	3.65
	-44	-26	42	3.75				
Posterior IPS					28	-54	36	3.65
					34	-60	48	3.51
Postcentral sulcus/SPL	-48	-20	44	3.58	40	-30	38	3.80
Central sulcus/motor cortex	-42	-4	40	4.36	46	-12	52	3.56
Premotor area	-46	-2	32	4.16				
SMA					8	-4	58	3.89
PreSMA	-8	4	62	4.25	2	2	54	4.33
Cingulate motor area	-14	12	40	4.46	12	16	46	3.78
	-10	8	46	4.30	12	14	34	3.77
Superior precentral sulcus/ superior frontal sulcus (probably FEF)	-26	-8	50	4.62	28	-6	42	4.11
	-24	-10	40	4.47				
Middle temporal gyrus/ inferior temporal sulcus					50	-34	-8	3.47
Inferior occipital gyrus/ fusiform gyrus					46	-60	-24	3.23
Frontal operculum of the insula	-56	10	4	3.44	58	20	-2	3.95
Anterior insula					40	14	-2	4.10
Putamen	-30	8	8	4.85	26	18	0	4.34
	-20	8	14	4.58	26	0	16	4.07
Tail of caudate/thalamus					22	-24	20	4.23
Caudate					8	-22	20	4.83
Cerebellum	-6	-62	-26	4.19	22	-56	-30	4.75
					2	-56	-16	4.44
					24	-64	-28	3.95

Activation peaks were determined by using cluster analysis ($Z > 2.7$, cluster significance threshold of $p = .01$). Only activation peaks with $Z > 3.0$ are reported in this table.

was higher than in the left pIPS, but the pattern was reversed for the right hemisphere. Overall, the mean percentage signal change is highest in the right pIPS region.

Judgment-Type Specific Results

None of the four ROIs showed higher mean percentage signal change during NC than during the control tasks (see Figure 4). There was no significant difference in signal change between the three types of judgment nor

did judgment type interact with site or hemisphere in any fashion ($p > .1$).

Effect of Number Size

Signal change was higher for double-digit than for single-digit stimuli, $F(1,11) = 8.47$, $p = .02$ (see Figure 5A, B), but the effect interacted with site and hemisphere, $F(1,11) = 5.05$, $p = .05$. Separate analyses of each ROI confirmed that signal change was only significantly higher

for double-digit stimuli in the right and left pIPS: left, $F(1,11) = 10.32, p = .008$; right, $F(1,11) = 18.08, p = .001$.

The effect of number size also interacted with judgment type, $F(2,22) = 3.53, p = .05$. The interaction was partly due to changes in the right aIPS where number size and judgment type interacted significantly, $F(2,22) = 5.11, p = .02$. From Figure 5B it is apparent that the interaction is due to the signal being higher when single-digit stimuli were presented for NC but higher when double-digit stimuli were presented for N-VIJ and X-VIJ. Therefore, in summary, double-digit

stimuli were associated with greater activation in the posterior parietal cortices, but in the right aIPS, there was some suggestion of the converse specialization for smaller, single-digit stimuli.

Effect of Distance

Distance interacted significantly with hemisphere, $F(1,11) = 6.81, p = .03$, and with site, judgment type, and number size, $F(2,22) = 4.05, p = .03$. We followed up these interactions by analyzing each ROI separately. For

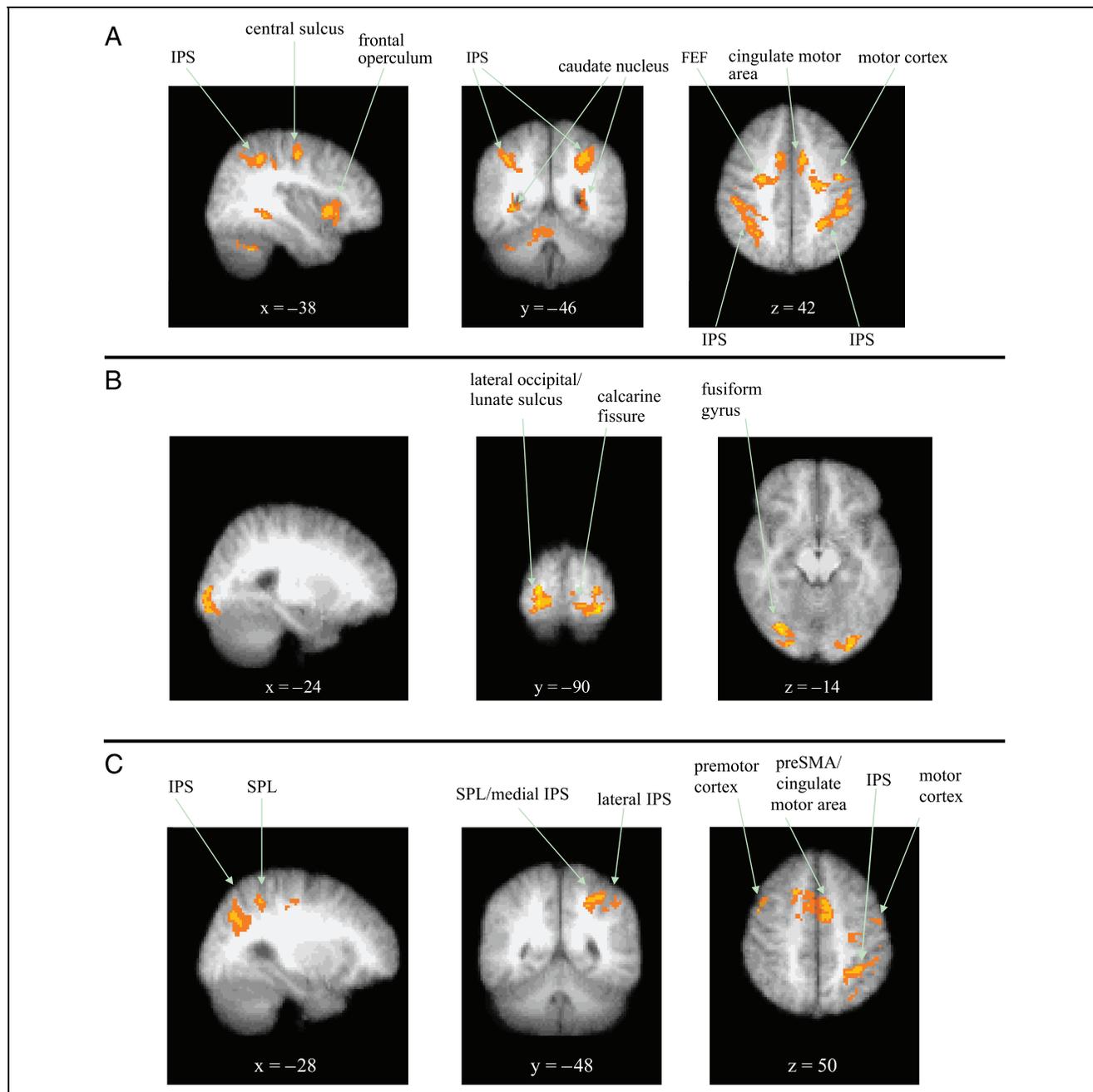


Figure 3. Regions of significant BOLD signal change on the mean average structural image of all 12 subjects registered in standard space (sagittal, coronal, and axial view from left to right). (A) Number comparison versus rest, (B) double-digit versus single-digit stimuli during number comparison, (C) correlated with RT.

Table 2. Talairach Coordinates of Activation Peaks for Reaction Time Effects versus Rest

Brain Area	Left Hemisphere				Right Hemisphere			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>
SMG/lateral bank of IPS	-56	-42	44	3.92				
	-52	-24	54	3.41				
Lateral bank of pIPS	-28	-70	36	4.05				
	-26	-64	30	3.81				
	-32	-58	32	3.72				
SPL/medial bank of IPS	-34	-46	52	3.90				
	-22	-46	48	3.73				
Postcentral sulcus	-46	-18	56	3.25				
Motor cortex/central sulcus	-48	-4	50	3.22				
	-34	-22	54	3.12				
	-42	-12	52	3.10				
Premotor cortex					52	10	36	5.03
					52	10	44	4.30
					48	10	48	4.03
					54	18	18	3.93
					44	10	14	3.76
SMA	-2	-8	58	4.22	6	-10	64	4.27
	-4	-10	66	4.05	4	-6	54	4.04
PreSMA					10	4	56	4.05
Cingulate sulcus/motor area	-6	10	48	3.98	8	22	46	3.31
	-8	0	48	3.98				
	-8	6	40	3.72				
Inferior frontal sulcus					52	30	20	3.05
Frontal operculum of the insula					38	22	16	3.64

Activation peaks were determined by using cluster analysis ($Z > 2.7$, cluster significance threshold of $p = .01$). Only activation peaks with $Z > 3.0$ are reported in this table.

the left and right aIPS, there were no effects of distance on signal change. In the left pIPS there was an increase in signal change with an increase in distance, $F(1,11) = 9.66$, $p = .01$ (see Figure 5C). In the right pIPS region the effect of distance was also modulated by judgment type and number size, $F(2,22) = 3.5$, $p = .05$ (see Figure 6). On NC blocks, there was a tendency for signal to increase with increasing distance but only for single-digit stimuli.

DISCUSSION

NC versus rest yielded a large bilateral parietal-posterior frontal network. However, no areas showed more activation during NC than during the control tasks, which were matched for response selection and task difficulty,

nor for numerical as opposed to nonnumerical stimuli. This result is consistent with a number of other studies that have found it difficult to identify activation changes in the IPS when numerical and nonnumerical tasks matched for difficulty and response selection are directly compared (Molko et al., 2003; Gruber et al., 2001; Cohen-Kadosh et al., submitted). A left-lateralized parietal-posterior frontal network varied significantly with RT. Numerical distance-related IPS activations may be difficult to dissociate from IPS activations associated with fundamental stimulus and response-selection processes associated with RT changes. This result is consistent with numerous studies that have identified response-selection-related or intention-related activations in the same IPS regions (Elliasen et al., 2003; Jiang & Kanwisher,

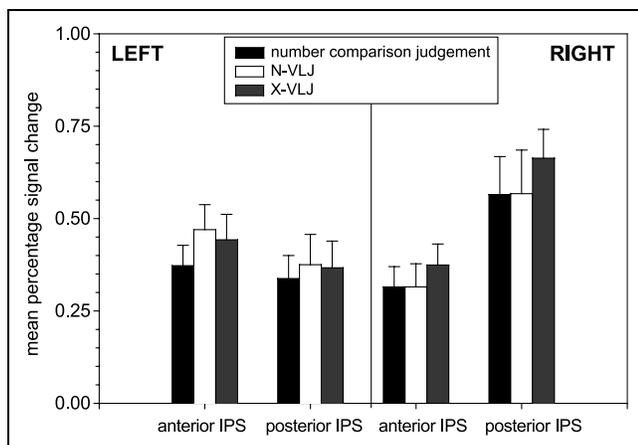


Figure 4. Mean percentage of signal change in the four ROIs (left and right aIPS and pIPS) during the three types of judgment (NC, N-VLJ, and X-VLJ).

2003; Bunge et al., 2002, 2003; Rushworth et al., 2003; Thoenissen, Zilles, & Toni, 2002; Rushworth, Ellison, et al., 2001; Rushworth, Krams, et al. 2001; Schluter et al., 2001; Deiber et al., 1997) and with the suggestion that numerical representation in the human IPS is inextricably linked with the representation of hand movement responses and intentions, as is the case in nonhuman primates (Walsh, 2003; Sawamura et al., 2002; Butterworth, 1999). An ROI analysis suggested that the representation of small numbers countable on the hand may be particularly closely associated with the aIPS regions concerned with finger movements. A link between finger movements and number representations has been postulated on the basis of developmental, neuropsychological, and linguistic studies (Butterworth, 1999; Fayol, Barrouillet, & Marinthe, 1998). The ROI analyses also provided some grounds for thinking that activation in more posterior IPS regions, which might be expected to be more visuospatial in nature, was associated with traveling a greater distance along the mental number line. Each of these findings is discussed in detail below.

Behavioral Distance Effect

Subjects showed a behavioral distance effect during NC inside the scanner, with longer RTs the closer the displayed number was to the reference number. Interestingly, in the second condition, when making vertical line judgments on numerical stimuli (N-VLJ), distance still had an effect, but an opposite one, with longer RTs the farther away the displayed number was from the reference number. The reversed distance effect during vertical line judgment of numerical stimuli in our experiment could be due to an automatic activation of a magnitude representation that then interferes with vertical line judgment, perhaps in a Stroop-effect-like man-

ner (Stroop, 1935). In NC blocks subjects always made comparisons against reference numbers (5 and 65 in the small and large number conditions, respectively), and so comparisons may have been made automatically against these reference numbers even when subjects were performing the N-VLJ task. This is in line with findings from Besner and Coltheart (1979) showing that numerical stimuli often automatically activate a magnitude representation, even if subjects are asked to perform a nonnumerical task with these stimuli. It is also important to notice that distance had no effect on RT when subjects made line judgments on nonnumerical stimuli in the third condition (X-VLJ). The presence and absence of distance effects on RT in the conditions in which subjects made line judgments on numerical and nonnumerical stimuli, respectively, confirm that the stimuli in each condition were treated differently by subjects. There was a mandatory appreciation of magnitude when numerical stimuli were used in the N-VLJ condition even though it was irrelevant to the task in hand. The manipulation of the stimuli used in the nonnumerical X-VLJ task was sufficient to prevent subjects from having any similar sense of magnitude.

Brain Activation during Number Comparison

In line with other neuroimaging studies a large bilateral parietal network was active during NC. The network includes the posterior part of IPS, the medial bank of the IPS extending into the superior parietal lobule, and the postcentral sulcus. Other activations during NC were found in the bilateral motor cortex, left premotor area, right SMA, bilateral PreSMA, bilateral cingulate motor areas and bilateral superior precentral sulcus/superior frontal sulcus (probably FEF), right middle temporal gyrus/inferior temporal sulcus, right fusiform gyrus, bilateral insula and putamen, left caudate nucleus, and bilateral cerebellum. Similar activations have been reported before in NC and number processing tasks (Eger et al. 2003; Fias et al., 2003; Dehaene et al., 2003; Le Clec'h et al., 2000; Pesenti, Thioux, Seron, et al., 2000; Rickard et al., 2000; Chochon et al., 1999; Pinel et al., 1999, 2001; Dehaene, Tzourio, Frak, Raynaud, Cohen, Mehler, & Mazoyer, 1996). These results seem to point toward an important role for the parietal lobe, and the IPS in particular, in number representation.

No brain areas, however, were *overall* more active during NC than during control tasks, either in the whole-brain analysis or when we analyzed ROIs around the IPS. These results indicate that the activations seen for NC versus rest may not be easily interpreted as specific to NC.

It is perhaps not that surprising that in our study no areas were found to be more active during NC than during N-VLJ, because, as explained above, the numerical stimuli automatically activated magnitude representation. Few imaging studies on number comparison have

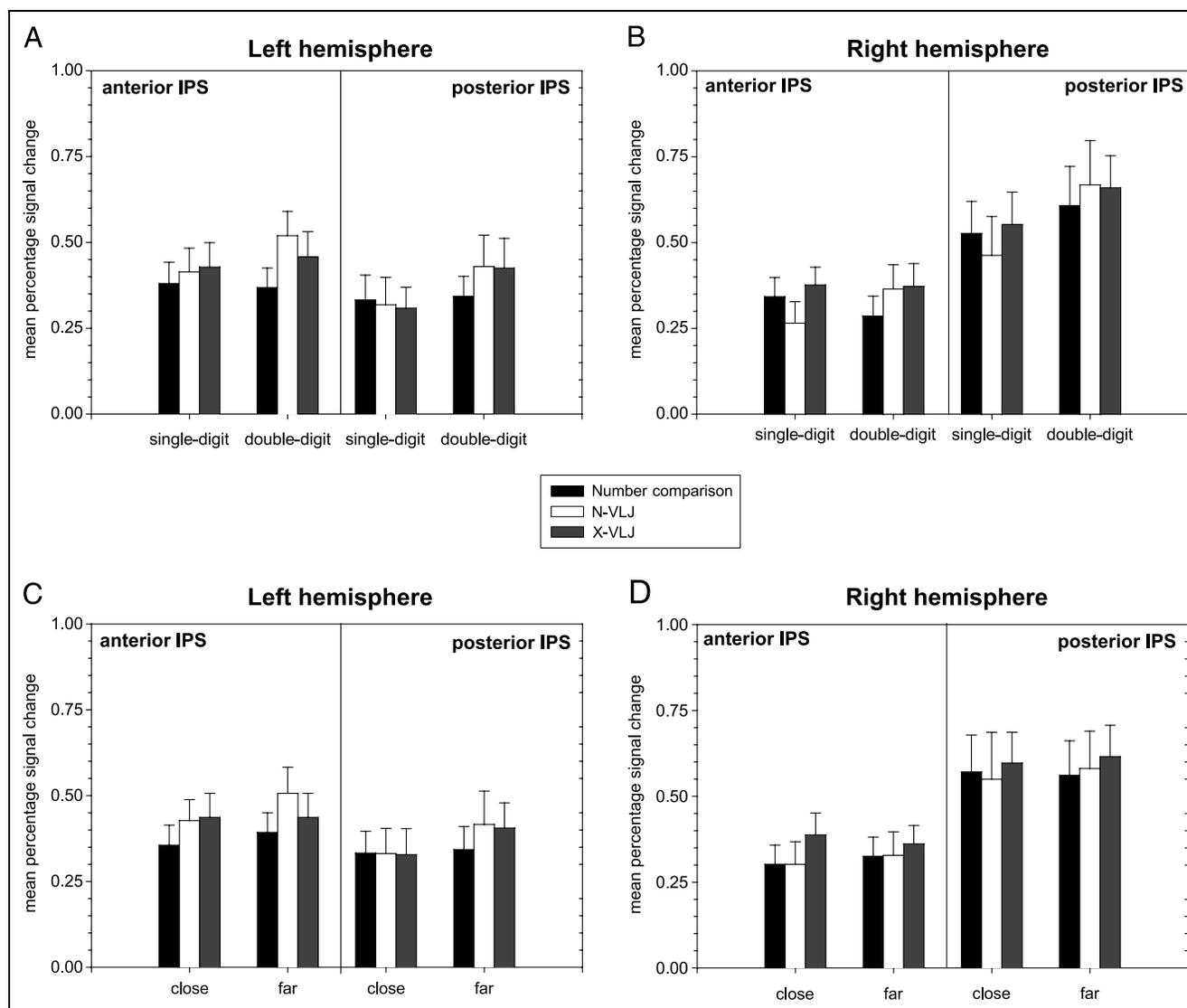


Figure 5. Mean percentage signal change in aIPS and pIPS in the left (A, C) and the right hemisphere (B, D). Results are shown for single-digit versus double-digit stimuli blocks (A, B) and for blocks in which the distance of the stimuli to the reference number was either close or far (C, D) during three types of judgment (NC, N-VLJ, X-VLJ).

compared activation during number comparison explicitly with activation during numerical stimulus presentation (e.g., Chochon et al., 1999). The only significant area of difference in the study by Chochon et al. (1999) was in the postcentral sulcus, anterior to the IPS proper and the parietal regions that are normally linked to number processing. Even when number comparison was compared with the second line judgment task involving nonnumerical stimuli (X-VLJ) there was still no significant difference in IPS activity, thus suggesting that simply presenting meaningful numbers to subjects was not sufficient to differentially activate the IPS.

Despite the interest in the parietal contribution to number representation and the possibility of an area specific to calculation near the IPS (Simon et al., 2002; Gruber et al., 2001) it is important to recognize that the present results are similar to those of previous studies.

Activations during non-arithmetic operations performed on numbers are nearly indistinguishable from those performed on letters (Gruber et al., 2001). Molko et al. (2003), for example, found the classical frontoparietal network during number processing tasks versus rest. However, in their study, all these areas were also activated for a letter-matching task.

Similar regions of the IPS in both neurophysiology and neuroimaging have also been related to the selection of motor responses and intention (Eliassen et al., 2003; Jiang & Kanwisher, 2003; Rushworth et al., 2003; Bunge et al., 2002, 2003; Thoenissen et al., 2002; Schluter et al., 2001; Deiber et al., 1997; Snyder et al., 1997; Wise et al., 1997), sometimes in ways that are related to RT (Rushworth, Ellison, et al., 2001; Rushworth, Krams, et al., 2001; Winstein et al., 1997; Deiber et al., 1996). As the parametric whole-brain analysis of our data showed, RTs

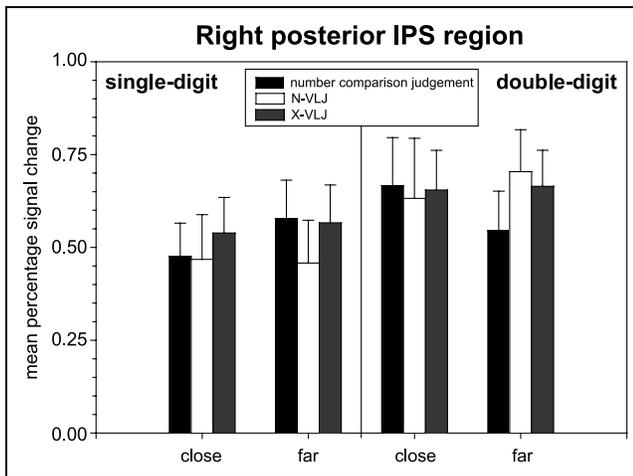


Figure 6. Mean percentage signal change in the right pIPS for single-digit stimuli (on the left) versus double-digit stimuli (on the right). Results are subdivided into blocks in which the distance of the stimuli to the reference number was either close or far during three types of judgment.

were associated with a large left-lateralized parietal network of activations, which is not correlated with any of the three task manipulations. In fact, the parietal network found to be significantly associated with RTs (left SMG, left lateral and medial banks of the IPS, left superior parietal lobule, medial bank of the IPS, and the left postcentral sulcus) is very similar to networks previously described for either number comparison or distance effects (e.g., Pesenti, Thioux, Seron, et al., 2000; Pinel et al., 1999). It is unlikely that this left-lateralized IPS activation is related to increased visuospatial attention during higher task demands because sustained visual attention is typically associated with right rather than left IPS activations (Cabeza & Nyberg, 2000; Nobre et al., 1997; Pardo, Fox, & Raichle, 1991).

In the past, number comparison has sometimes been compared with tasks with just one prespecified response in which no response selection is necessary (e.g., Chochon et al., 1999). Differences in response-selection demands and RT could partially account for parietal activations found during number comparison. Eger et al. (2003) used an ingenious task in which subjects were presented with number stimuli on several trials but only responded to detect instances of one particular number. Eger et al. reported greater activation within an IPS ROI when subjects were making judgments about numbers as opposed to letters even on those trials in which no response was made. Such a result would seem to rule out any possible confounding effect of response selection. Cell recording, lesion, TMS, and neuroimaging studies of the IPS in both monkeys and human subjects have, however, all highlighted that this region, unlike the premotor cortex, is not concerned with selection per se but with the representation of the different possible response alternatives that might be selected

(Rushworth et al., 2003; Bunge et al., 2002; Thoenissen et al., 2002; Rushworth, Ellison, et al., 2001; Rushworth, Krams, et al., 2001; Rushworth, Nixon, & Passingham, 1997; Rushworth, Nixon, Renowden, Wade, & Passingham, 1997; Kalaska & Crammond, 1995). Even if ultimately the response is withheld, IPS neurons are active (Thoenissen et al., 2002; Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998; Kalaska & Crammond, 1995).

Eger et al. (2003) compared activation in an IPS ROI when subjects were making judgments about number or letter stimuli and found that there was more activation when numbers were presented. They argued that the similarity of RTs in those trials of each task when responses were made indicated that the tasks were matched for difficulty. It might therefore be argued that the failure of the present experiment to find IPS activation specific to number stimuli or numerical comparison is a consequence of the control condition that used number stimuli that had been cut, rotated, and reversed. It could be argued that such stimuli inadvertently engendered a sense of magnitude in subjects. This cannot, however, be the full explanation. First, the lack of any reversed distance effect, when line judgments were made with the nonnumerical stimuli (X-VLJ) as opposed to the numerical stimuli (N-VLJ) suggested that the stimuli did not impart any sense of magnitude as was the case with the normal number stimuli. Second, other studies have not been able to identify IPS activation even when number processing is compared to control tasks involving letter processing (Molko et al., 2003; Gruber et al., 2001). Perhaps this is not surprising, even if one assumes that it is the distance between a stimulus and a reference, as opposed to any response-selection process, that accesses spatial processing functions in the parietal cortex, because the distance between an exemplar letter and a reference letter also influences RT (Eger et al., 2003). There is evidence that parietal single-neuron activity in the monkey is also modulated during selection between spatially defined responses to other types of graded visual stimuli (Gold & Shadlen, 2001). Fias et al. (2003) found an area in the left IPS that was commonly activated during angle, line, and number comparison, thus showing that comparison of visuospatial stimuli in general rather than number comparison activates this intraparietal area. Parietal activations consistently reported during number comparison could be due to a more general process that may also be recruited by other sensorimotor and comparison tasks.

Effects of Number Size

The current fMRI experiment was also designed to compare number comparison with small and large stimuli. There was more activation in extrastriate areas and the posterior parietal ROIs during double-digit stimulus presentation than during single-digit stimulus presenta-

tion, which may reflect the greater amount of visual information on the screen. However, in the right aIPS region there was an indication of higher mean signal change for single-digit than for double-digit stimuli. Although only suggestive, this result is particularly interesting, because it was specific to NC blocks and cannot be explained by differences in RT; single-digit stimuli were associated with a shorter RT.

In line with Naccache and Dehaene (2001) and Stanesco-Cosson et al. (2000), the present results suggest that distinct populations of IPS neurons encode different numbers. It might mirror a between-experiment tendency for small numbers to be represented more anteriorly within the IPS than larger numbers (Göbel, Rushworth, et al., 2001; Göbel, Walsh, et al., 2001). It is now well established that such aIPS regions code hand and finger movements (Grefkes et al., 2002; Rushworth, Ellison et al., 2001; Rushworth, Krams, et al., 2001; Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Binkofski et al., 1998). Developmental, neuropsychological, and linguistic studies have suggested that the mental representation of small numerical digits may be related to the mental coding of hand digits (Butterworth, 1999; Fayol et al., 1998). It has also been argued that, as is the case with spatial and temporal magnitude representation, numerical magnitude representation in the IPS might occur in the context of response representation (Walsh, 2003). This suggestion is also consistent with single-unit recording studies in nonhuman primates. Sawamura et al. (2002) reported number-encoding neurons intermingled within the part of the monkey IPS containing the representation of the forelimb used to make responses. That magnitude representation might be encoded in a similar way in both human and nonprimate IPS is consistent with the similarity in the organization of much of this region in different primate species (Astafiev et al., 2003; Grefkes et al., 2002; Simon et al., 2002; Rushworth, Krams, et al., 2001). The human IPS may contain a region specialized for calculation (Simon et al., 2002), but human numerical magnitude representation may be distributed throughout parts of the IPS also concerned with forelimb movement. Such a hypothesis might also account for Eger et al.'s (2003) finding. In their study, like in our study, number-specific IPS activation was only detected when using a mask based on the activation recorded during number presentation versus rest. The activation they recorded was within areas known to encode limb and hand movements.

The suggestion that even though there may be no single macroscopic area within the IPS that is concerned with number-related response selection is consistent with evidence that the IPS is always activated during response selection (Jiang & Kanwisher, 2003), but that hemispheric biases and subtle changes in activation strength may occur depending on the type of cues used to select the movements (Hazeltine, Bunge, Scanlon, &

Gabrieli, 2003; Schumacher & Jiang, 2003). Such a hypothesis could account for the low incidence of complete impairment of magnitude appreciation in human patient studies. Patients may only lose a sense of magnitude if parietal and perhaps other (frontal) movement representations are damaged extensively and bilaterally. There is also evidence that prefrontal neurons in the monkey encode aspects of stimulus quantity (Nieder & Miller, 2003; Nieder, Freedman, & Miller, 2002).

Brain Activation Related to the Distance Effect

In recent brain imaging studies on number comparison, numerical distance to the reference number has been investigated as a variable of interest. Pinel et al. (1999, 2001) found activation changes in the left and right IPS that were related to numerical distance. Whether the brain regions underlying this distance effect are specific to number comparison, however, is still open to debate. Distance effects are not only found in number comparison, but also in various tasks that require mental manipulation of visuospatial information (e.g., mental rotation; Shepard & Metzler, 1971), and IPS activation has been found during various nonnumerical visuospatial tasks (Richter et al., 2000; Carpenter et al., 1999). Similar RT curves have also been reported with changes in the alphabetic distance between comparison and reference letters or with graded changes in the physical appearance of a stimulus (Eger et al., 2003; Gold & Shadlen, 2001). Therefore, the IPS activation found during number comparison tasks could be due to common mechanisms for quantitative processing of numerical and nonnumerical visuospatial stimuli.

When we analyzed the effect of distance on brain activation in the whole-brain analysis we failed to find any area that was more active during distance close than during distance far blocks and vice versa. In the ROI analysis, however, we found that distance had an influence on signal change in the pIPS regions. In both the left and right pIPS regions there were conditions in which there was more signal change during blocks with distance far than blocks with distance close. The results offer some tentative support that there may have been greater pIPS activation when subjects traveled further along the mental number line. It should be noted that the effect, however, was most prominent in the control tasks. It is possible that pIPS activations showing some correlation with numerical distance are also concerned with a process common to both numerical and nonnumerical visuospatial stimuli.

Choice of Control Tasks

Most imaging studies on number comparison have compared either numerical stimuli with very different stimuli (such as letters or body parts; e.g., Le Clec'H et al., 2000; Rickard et al., 2000; Chochon et al., 1999) or

they compared trials with numerical stimuli processed with different RTs (Fias et al., 2003; Pinel et al., 1999, 2001). Stimuli and motor responses in both our control tasks were closely matched to the number comparison task. In both control tasks, subjects had to judge the orientation of a line. One could argue that during the control tasks subjects searched through a visual array for a yellow vertical line and therefore engaged in visual search. Walsh and Pascual-Leone (2003) showed that a region in the posterior part of the IPL/IPS is important during visual search, but only when the target was a conjunction of more than one visual feature, whereas in the present experiment it was defined by a simple, single visual feature. The parietal cortex has also been implicated in visual search by imaging studies (Corbetta & Shulman, 1999; Nobre et al., 1997; Corbetta, Miezin, Shulman, & Petersen, 1993). Nobre, Coull, Walsh, and Frith (2003), however, showed that the region was only activated in difficult inefficient search tasks as indexed by very slow responses. It seems unlikely that parietal activation was the consequence of any covert visual search process. Furthermore, even if one assumes that the activation in the control tasks in the posterior part of the IPS can be accounted for by a visual search explanation, this does not explain why also the activations in the anterior part of the IPS were higher during control tasks than during number comparison. There is no evidence for a role of the aIPS region in visual search.

Conclusion

This fMRI experiment on number comparison successfully replicated activations in a large bilateral parietal-motor network during number comparison versus rest. However, it failed to find any activations specific to NC blocks that were not seen during control tasks. The IPS activation common to all the tasks may be related to a parietal role in maintaining a representation of possible motor responses. Although there may be specialized calculation areas within the IPS, there might be no human brain areas in which most neurons are specifically and solely dedicated to abstract quantity representation. As in the nonhuman primate and as predicted by some theories of number and magnitude processing (Walsh, 2003; Butterworth, 1999), magnitude may be represented within response-related areas of the human IPS. Small, single-digit numbers may have a particularly close relationship to IPS regions that also represent hand digits.

METHODS

Participants

Twelve right-handed subjects (6 women, 6 men, aged 20–34 years, mean age 26.7 years) participated. Subjects gave informed consent in accordance with ethical ap-

proval from the Central Oxford Regional Ethics Committee (OxREC C02.092). After the experiment all subjects filled out a short questionnaire concerning their number representations (an English translation of Seron et al.'s questionnaire of number representation; see Seron, Pesenti, Noel, Deloche, & Cornet, 1992). None of the subjects reported a subjective visuospatial number form that was automatically activated when confronted with numbers. In this respect the experimental subjects are representative of the majority in the population who do not report a subjective number form (Seron et al., 1992).

Image Acquisition

A 3T Varian INOVA MRI system with a multislice gradient-echo EPI sequence (TR = 3000 msec, TE = 30 msec, flip angle = 90°, FOV = 256 × 256, matrix = 64², twenty-four 5-mm axial slices) was used. For each subject, a high-resolution T1-weighted anatomical scan was acquired (1.5-mm-thick axial slices with 1 × 1-mm in-plane resolution).

Paradigm Design

Subjects were given full verbal and written instructions for the experiment before entering the scanner. Once the instructions were understood, subjects were given a practice run of all block types. The paradigm consisted of alternating 30-sec blocks of three judgment types (NC, N-VLJ, and X-VLJ) and rest (see Figure 1). Each task required the subject to press one of two buttons with their right or left index finger as quickly and accurately as possible. Within each block, except during rest periods, yellow stimuli were presented centrally for 500 msec on a black background using the font Arial (type size = 96 points). When viewed from the distance of 3 m, single-digit stimuli subtended 1.2° of visual angle and double-digit stimuli subtended 1.9° of visual angle. The interstimulus interval was varied randomly between 1.4 and 1.6 sec (mean 1.5 sec) to minimize anticipatory responses. At the beginning of each block, a visual instruction cue in red was on the screen for 3 sec. The instruction cue was either “rest,” “reference number: 5,” “reference number: 65,” or “vertical line ?” Except during rest periods, each stimulus display contained a small symbolic repetition of the instruction cue (either 5 for “reference number 5,” 65 for “reference number 65,” or | for “vertical line ?” in white font, Arial, font size = 24 points) directly above the stimulus (see Figure 1B). In blocks with the instruction “rest” a white cross appeared in the screen center and subjects were asked to fixate that cross for the duration of the block.

When the instruction was “reference number: 5,” subjects saw single digits (1, 2, 3, 4, 6, 7, 8, 9) on the screen and had to judge whether the number on the screen was smaller or larger than the reference number 5

by pressing the left button with the left index finger or the right button with the right index finger, respectively (see Figure 1A). In blocks with instruction cue “reference number: 65,” subjects saw double-digit numbers ranging from 31 to 99 on the screen. Again, they had to use similar responses to indicate whether the number on the screen was larger or smaller than the reference number.

Numbers within each of these NC blocks were chosen with respect to their distance from the reference number, thus generating two subtypes of blocks (distance close and distance far). For double-digit blocks, the mean distance to 65 in blocks with distance close was 7.6, whereas the mean distance from the reference number in blocks with distance far was 26.5. In single-digit blocks, the mean distance to reference number 5 was either 2.0 (distance close) or 3.1 (distance far). Subjects were not informed of these two block subtypes.

When the visual instruction cue was “vertical line ?,” subjects were asked to press the right button with their right index finger if the stimulus on the screen contained a vertical line (numbers 1, 4, 7, and 9; numbers 7 and 9 were slightly manipulated to contain a vertical line) and the left button with their left index finger, when the stimulus on the screen did not contain a vertical line (numbers 2, 3, 5, 6, and 8). For these blocks, subjects were instructed to completely ignore the fact that the stimuli were numbers. For double-digit numbers, each stimulus could contain none, one, or two vertical lines.

There were two subtypes of blocks with vertical line detection. In N-VLJ, the stimuli were exactly the same as displayed in the NC blocks (see Figure 1B). In X-VLJ, the same numbers as in the NC blocks were used to generate the stimuli. The numbers, however, were rotated, flipped, and cut in a way to make them as different from numbers as possible while still keeping the vertical line intact and the height and width of the stimuli constant across conditions (see Figure 1B). All block types were balanced for button response side.

In total there were 16 NC blocks (4 double-digit blocks with distance close, 4 double-digit blocks with distance far, 4 single-digit blocks with distance close, and 4 single-digit blocks with distance far), 16 N-VLJ blocks, and 16 X-VLJ blocks and eight rest periods. The order of the 56 blocks was generated pseudorandomly once and then held constant for each subject because the ordering of the 56 blocks was counterbalanced within subjects. The paradigm took roughly 30 min. Exact timings of stimulus presentations and button responses were measured with Spike 2, version 4.00 (Cambridge Electronic Design).

Behavioral Data Analysis

RTs from erroneous responses (3.7% of all responses) were not included in the behavioral analysis. A repeated-measures three-way analysis of variance (ANOVA) on

median RTs with judgment type (NC, N-VLJ, X-VLJ), number size (single-digit stimulus, double-digit stimulus), and distance to reference number (close, far) was carried out. Distance to the reference number for the N-VLJ and X-VLJ blocks was defined by distance of the corresponding numerical stimulus from the corresponding reference number in the NC block (i.e., for the examples in Figure 1B, distance was 2 for the single-digit stimuli and 22 for the double-digit stimuli). In some cases ANOVA results were followed up with paired sample *t* tests.

Image Analysis

Image analysis was performed using tools from the FMRIB Software Library, FSL 1.4 (FMRIB, Oxford, UK, www.fmrib.ox.ac.uk/fsl). First, a slice dropout detection procedure was carried out. In three subjects slice dropouts were detected and corrected. The following pre-statistic processing was applied: motion correction using MCFLIRT (Jenkinson & Smith, 2001), spatial smoothing using a Gaussian kernel of full width half maximum 5 mm; mean-based intensity normalization of all volumes by the same factor; nonlinear high-pass filtering (Gaussian-weighted least squares straight line fitting with $\sigma = 350$ sec). Statistical analysis was then carried out for each subject within FEAT 4.10, the FMRI Expert Analysis Tool (FMRIB, Oxford, UK) using FILM (FMRIB’s Improved Linear Model) with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001).

Regressors or explanatory variables (EVs) were binary except for RT. For this EV median RTs for each paradigm block were computed and normalized for each subject, so that the maximum RT was 1. The normalized RTs were then entered into the design matrix and orthogonalized with respect to other EVs. This means that any overall effects of task versus rest will be fit by the main task EVs. The RT contrast can only fit variance in the residuals that remain after fitting main task effects, that is, variations between task blocks that correlate with RT. One EV corresponded to whether small or large numbers were presented in each of the three tasks, NC, N-VLJ, and X-VLJ. To ensure sufficient power when comparing tasks, however, contrasts were used that combined both small and large number blocks. In other words, to look at overall effects of number (regardless of size, distance, etc.), we ran a contrast with a value of 1 for all number-related blocks and 0 for all non-number-related blocks. This is exactly equivalent to combining all number blocks into a single EV and running a contrast of 1 for that EV and 0 for other EVs.

Z values were calculated for contrasts of experimental conditions versus rest and between experimental conditions. Registration of EPI images to high-resolution images and into standard space (Talairach & Tournoux, 1988) was carried out using FLIRT (FMRIB’s Linear Image Registration Tool; Jenkinson & Smith, 2001).

Group Analysis

Group analysis was performed by using a random effects analysis. Cluster detection was applied to the group Z (Gaussianized T) statistic images determined by $Z > 2.7$ and a corrected cluster extent significance threshold of $p = .01$ (Forman et al., 1995; Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994; Worsley, Evans, Marrett, & Neelin, 1992).

ROI Analysis

We were particularly interested in the possibility of brain activation differences in IPS areas. The random effects group analysis, however, did not yield any of these differences. The random effects analysis is a strict test as it requires not only that a large number of subjects show an effect, but also that after registration of activation images from the individual subjects, the loci of that effect from the different subjects overlap in the same standard brain space (Johansen-Berg, Christensen, Woolrich, & Matthews, 2000). To allow for individual variation in the location and magnitude of response in IPS areas, we performed an additional analysis based on signal change in ROIs. To define the ROIs we used the random effect brain activations found for the contrast number comparison judgment versus rest. Only those activations were used that were in and/or around the lateral or medial bank of the IPS.

These activations were further divided into anterior and posterior activations. Anatomically, the IPL is divided by the sulcus intermedius primus of Jensen, a descending ramus of the IPS (Duvernoy, Bourgouin, Cabanis, & Cattin, 1999) into the SMG and the angular gyrus (ANG). Therefore, we first identified Jensen's sulcus on sagittal sections of subjects' high-resolution, T1-weighted anatomical scans in standard space. In each subject and for each hemisphere separately, we then measured the minimum and maximum y coordinates of this sulcus. The mean y coordinate of all subjects (left hemisphere: $y = -48$, right hemisphere: $y = -45$) was subsequently used to split the parietal activation mask into two masks, an aIPS mask and a pIPS mask. Thus, four ROIs were defined: left aIPS, left pIPS, right aIPS, and right pIPS.

These ROIs were then applied to each subject's signal change images comparing activation conditions to rest. A five-way ANOVA on mean percentage signal changes with hemisphere (left, right), site (aIPS, pIPS), judgment type (NC, N-VLJ, X-VLJ), number size (single-digit stimuli, double-digit stimuli) and distance (distance close, distance far) was carried out. This was followed by more detailed analyses of differences in mean percentage signal change for each separate ROI. Four independent three-way ANOVAs with judgment type (NC, N-VLJ, X-VLJ), number size (single-digit stimulus, double-digit stimulus), and distance to reference number (close, far)

were performed. In some cases, ANOVA results were followed up with two-tailed paired sample t tests.

Acknowledgments

This study was supported by the Medical Research Council (MRC). SG is a Junior Research Fellow at Jesus College, University of Oxford, and was supported by the German Exchange Service (DAAD: HSPIII) and the German Scholarship Foundation. HJB was supported by the Wellcome Trust, TB by the Engineering and Physical Sciences Research Council (EPSRC), and MFSR by the Royal Society. We thank Dr. Pesenti for providing us with a copy of his questionnaire used for assessing subjective, explicit number forms, and Peter Hobden for his assistance with the MRI scans.

Reprint requests should be sent to Silke M. Göbel, Department of Experimental Psychology, University of Oxford, OX1 3UD, UK, or via e-mail: silke.gobel@psy.ox.ac.uk.

The data reported in this experiment have been deposited in the fMRI Data Center (<http://www.fmridc.org>). The accession number is 2-2004-116EE.

REFERENCES

- Astafiev, S. V., Shulman, G. L., Stanley C. M., Snyder, A. Z., Van Essen, D. C., & Corbetta, M. (2003). Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *Journal of Neuroscience*, *23*, 4689–4699.
- Besner, D., & Coltheart, M. (1979). Ideographic and alphabetic processing in skilled reading of English. *Neuropsychologia*, *17*, 467–472.
- Binkofski, F., Buccino, G., Posse, S., Seitz, R. J., Rizzolatti, G., & Freund, H. J. (1999). A fronto-parietal circuit for object manipulation in man: Evidence from an fMRI-study. *European Journal of Neuroscience*, *11*, 3276–3286.
- Binkofski, F., Buccino, G., Stephan, K. M., Rizzolatti, G., Seitz, R. J., & Freund, H. J. (1999). A parieto-premotor network for object manipulation: Evidence from neuroimaging. *Experimental Brain Research*, *128*, 210–213.
- Binkofski, F., Dohle, C., Posse, S., Stephan, K. M., Hefter, H., Seitz, R. J., & Freund, H. J. (1998). Human anterior intraparietal area subserves prehension: A combined lesion and functional MRI activation study. *Neurology*, *50*, 1253–1259.
- Bunge, S. A., Hazeltine, E., Scanlon, M. D., Rosen, A. C., & Gabrieli, J. D. E. (2002). Dissociable contributions of prefrontal and parietal cortices to response selection. *Neuroimage*, *17*, 1562–1571.
- Burbaud, P., Camus, O., Guehl, D., Bioulac, B., Caille, J., & Allard, M. (2000). Influence of cognitive strategies on the pattern of cortical activation during mental subtraction. A functional imaging study in human subjects. *Neuroscience Letters*, *287*, 76–80.
- Butterworth, B. (1999). *The mathematical brain*. London: Macmillan.
- Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, *12*, 1–47.
- Carpenter, P. A., Just, M. A., Keller, T. A., Eddy, W., & Thulborn, K. (1999). Graded functional activation in the visuospatial system with the amount of task demand. *Journal of Cognitive Neuroscience*, *11*, 9–24.
- Chochon, F., Cohen, L., van de Moortele, P. F., & Dehaene, S. (1999). Differential contributions of the left and right

- inferior parietal lobules to number processing. *Journal of Cognitive Neuroscience*, *11*, 617–630.
- Cipolotti, L., & van Harskamp, N. (2001). Disturbances of number processing and calculation. In R. S. Berndt (Ed.), *Language and aphasia* (Vol. 3, pp. 305–331). Amsterdam: Elsevier.
- Cohen, L., & Dehaene, S. (1996). Cerebral networks for number processing: Evidence from a case of posterior callosal lesion. *NeuroCase*, *2*, 155–174.
- Cohen-Kadosh, R., Henik, A., Rubinstein, O., Mohr, H., Dori, H., van de Ven, V., Zorzi, M., Hendlar, T., Goebel, R., & Linden, D. E. J. Are numbers special? The comparison of the human brain investigated by fMRI. Manuscript submitted for publication.
- Corbetta, M., Miezin, F. M., Shulman, G. L., & Petersen, S. E. (1993). A PET study of visuospatial attention. *Journal of Neuroscience*, *13*, 1202–1226.
- Corbetta, M., & Shulman, G. L. (1999). Human cortical mechanisms of visual attention during orienting and search. In G. W. Humphreys, J. Duncan, & A. Triesman (Eds.), *Attention, space and action: Studies in cognitive neuroscience* (pp. 183–198). Oxford: Oxford University Press.
- Cowell, S. F., Egan, G. F., Code, C., Harasty, J., & Watson, J. D. G. (2000). The functional neuroanatomy of simple calculation and number repetition: A parametric PET activation study. *Neuroimage*, *12*, 565–573.
- Dehaene, S. (2000). Cerebral bases of number processing and calculation. In M. S. Gazzaniga (Ed.), *The new cognitive neurosciences* (pp. 987–998). Cambridge: MIT Press.
- Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cognitive Neuropsychology*, *20*, 487–506.
- Dehaene, S., Spelke, E., Pinel, P., Stanescu, R., & Tsivkin, S. (1999). Sources of mathematical thinking: Behavioral and brain-imaging evidence. *Science*, *284*, 970–974.
- Dehaene, S., Tzourio, N., Frak, V., Raynaud, L., Cohen, L., Mehler, J., & Mazoyer, B. (1996). Cerebral activations during number multiplication and comparison: A PET study. *Neuropsychologia*, *34*, 1097–1106.
- Deiber, M. P., Ibáñez, V., Sadato, N., & Hallett, M. (1996). Cerebral structures participating in motor preparation in humans: A positron emission tomography study. *Journal of Neurophysiology*, *75*, 233–247.
- Deiber, M. P., Wise, S. P., Honda, M., Catalan, M. J., Grafman, J., & Hallett, M. (1997). Frontal and parietal networks for conditional motor learning: A positron emission tomography study. *Journal of Neurophysiology*, *78*, 977–991.
- Delazer, M., & Butterworth, B. (1997). A dissociation of number meanings. *Cognitive Neuropsychology*, *14*, 613–636.
- Duvernoy, H. M., Bourgouin, P., Cabanis, E. A., & Cattin, F. (1999). *The human brain: Surface, three-dimensional sectional anatomy with MRI, and blood supply*. New York: Springer.
- Eger, E., Sterzer, P., Russ, M. O., Giraud, A. L., & Kleinschmidt, A. (2003). A supramodal number representation in human intraparietal cortex. *Neuron*, *37*, 719–725.
- Eliassen, J. C., Souza, T., & Sanes, J. N. (2003). Experience-dependent activation patterns in human brain during visual-motor associative learning. *Journal of Neuroscience*, *23*, 10540–10547.
- Fayol, M., Barrouillet, P., & Marinthe, C. (1998). Predicting arithmetical achievement from neuro-psychological performance: A longitudinal study. *Cognition*, *68*, B63–B70.
- Fias, W., Lammertyn, J., Reynvoet, B., Dupont, P., & Orban, G. A. (2003). Parietal representation of symbolic and non-symbolic magnitude. *Journal of Cognitive Neuroscience*, *15*, 47–56.
- Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine*, *33*, 636–647.
- Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping*, *1*, 214–220.
- Göbel, S. M., Rushworth, M. F. S., & Walsh, V. (2001). rTMS disrupts the representation of small numbers in supramarginal gyrus. *Neuroimage*, *13*, S409.
- Göbel, S. M., Walsh, V., & Rushworth, M. F. S. (2001). The mental number line and the human angular gyrus. *Neuroimage*, *14*, 1278–1289.
- Gold, J. I., & Shadlen, M. N. (2001). Neural computations that underlie decisions about sensory stimuli. *Trends in Cognitive Sciences*, *5*, 10–16.
- Grefkes, C., Weiss, P. H., Zilles, K., & Fink, G. R. (2002). Crossmodal processing of object features in human anterior intraparietal cortex: An fMRI study implies equivalencies between humans and monkeys. *Neuron*, *35*, 173–184.
- Gruber, O., Indefrey, P., Steinmetz, H., & Kleinschmidt, A. (2001). Dissociating neural correlates of cognitive components in mental calculation. *Cerebral Cortex*, *11*, 350–359.
- Hazeltine, E., Bunge, S. A., Scanlon, M. D., & Gabrieli, J. D. (2003). Material-dependent and material independent selection processes in the frontal and parietal lobes: An event-related fMRI investigation of response competition. *Neuropsychologia*, *41*, 1208–1217.
- Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*, 143–156.
- Jiang, H., & Kanwisher, N. (2003). Common neural substrates for response selection across modalities and mapping paradigms. *Journal of Cognitive Neuroscience*, *15*, 1080–1094.
- Johansen-Berg, H., Christensen, V., Woolrich, M., & Matthews, P. M. (2000). Attention to touch modulates activity in both primary and secondary somatosensory areas. *NeuroReport*, *11*, 1237–1241.
- Kalaska, J. F., & Crammond, D. J. (1995). Deciding not to GO: Neuronal correlates of response selection in a GO/NOGO task in primate premotor and parietal cortex. *Cerebral Cortex*, *5*, 410–428.
- Krams, M., Rushworth, M. F. S., Deiber, M. P., Frackowiak, R. S., & Passingham, R. E. (1998). The preparation, execution and suppression of copied movements in the human brain. *Experimental Brain Research*, *120*, 386–398.
- Le Clec'h, G., Dehaene, S., Cohen, L., Mehler, J., Dupoux, E., Poline, J. B., Lehericy, S., van de Moortele, P. F., & Le Bihan, D. (2000). Distinct cortical areas for names of numbers and body parts independent of language and input modality. *Neuroimage*, *12*, 381–391.
- Molko, N., Cachia, A., Riviere, D., Mangin, J. F., Bruandet, M., Le Bihan, D., Cohen, L., & Dehaene, S. (2003). Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. *Neuron*, *40*, 847–858.
- Naccache, L., & Dehaene, S. (2001). The priming method: Imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. *Cerebral Cortex*, *11*, 966–974.
- Nieder, A., Freedman, D. J., & Miller, E. K. (2002). Abstract representation of the quantity of visual items in the primate prefrontal cortex. *Science*, *297*, 1708–1711.

- Nieder, A., & Miller, E. K. (2003). Coding of cognitive magnitude: Compressed scaling of numerical information in the primate prefrontal cortex. *Neuron*, *37*, 149–157.
- Nobre, A. C., Coull, J. T., Walsh, V., & Frith, C. D. (2003). Brain activations during visual search: Contributions of search efficiency versus feature binding. *Neuroimage*, *18*, 91–103.
- Nobre, A. C., Sebestyen, G. N., Gitelman, D. R., Mesulam, M. M., Frackowiak, R. S., & Frith, C. D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. *Brain*, *120*, 515–533.
- Noël, M. P., & Seron, X. (1993). Arabic number reading deficit: A single case study. *Cognitive Neuropsychology*, *10*, 317–339.
- Pardo, J. V., Fox, P. T., & Raichle, M. E. (1991). Localization of a human system for sustained attention by positron emission tomography. *Nature*, *349*, 61–64.
- Pesenti, M., Thioux, M., Samson, D., Bruyer, R., & Seron, X. (2000). Number processing and calculation in a case of visual agnosia. *Cortex*, *36*, 377–400.
- Pesenti, M., Thioux, M., Seron, X., & De Volder, A. (2000). Neuroanatomical substrates of Arabic number processing, numerical comparison, and simple addition: A PET study. *Journal of Cognitive Neuroscience*, *12*, 461–479.
- Pinel, P., Dehaene, S., Riviere, D., & Le Bihan, D. (2001). Modulation of parietal activation by semantic distance in a number comparison task. *Neuroimage*, *14*, 1013–1026.
- Pinel, P., Le Clec'H, G., van de Moortele, P. F., Naccache, L., Le Bihan, D., & Dehaene, S. (1999). Event-related fMRI analysis of the cerebral circuit for number comparison. *NeuroReport*, *10*, 1473–1479.
- Richter, W., Somorjai, R., Summers, R., Jarmasz, M., Menon, R. S., Gati, J. S., Georgopoulos, A. P., Tegeler, C., Ugurbil, K., & Kim, S. G. (2000). Motor area activity during mental rotation studied by time-resolved single-trial fMRI. *Journal of Cognitive Neuroscience*, *12*, 310–320.
- Rickard, T. C., Romero, S. G., Basso, G., Wharton, C., Flitman, S., & Grafman, J. (2000). The calculating brain: An fMRI study. *Neuropsychologia*, *38*, 325–335.
- Rueckert, L., Lange, N., Partiot, A., Appollonio, I., Litvan, I., Le Bihan, D., & Grafman, J. (1996). Visualizing cortical activation during mental calculation with functional MRI. *Neuroimage*, *3*, 97–103.
- Rushworth, M. F. S., Ellison, A., & Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nature Neuroscience*, *4*, 656–661.
- Rushworth, M. F. S., Johansen-Berg, H., Göbel, S. M., & Devlin, J. T. (2003). The left parietal and premotor cortices: Motor attention and selection. *Neuroimage*, *20*, S89–S100.
- Rushworth, M. F. S., Krams, M., & Passingham, R. E. (2001). The attentional role of the left parietal cortex: The distinct lateralization and localization of motor attention in the human brain. *Journal of Cognitive Neuroscience*, *13*, 698–710.
- Rushworth, M. F. S., Nixon, P. D., & Passingham, R. E. (1997). Parietal cortex and movement. I. Movement selection and reaching. *Experimental Brain Research*, *117*, 292–310.
- Rushworth, M. F. S., Nixon, P. D., Renowden, S., Wade, D. T., & Passingham, R. E. (1997). The left parietal cortex and attention to action. *Neuropsychologia*, *35*, 1261–1273.
- Sawamura, H., Shima, K., & Tanji, J. (2002). Numerical representation for action in the parietal cortex of the monkey. *Nature*, *415*, 918–922.
- Schluter, N. D., Krams, M., Rushworth, M. F. S., & Passingham, R. E. (2001). Cerebral dominance for action in the human brain: The selection of actions. *Neuropsychologia*, *39*, 105–113.
- Schumacher, E. H., & Jiang, Y. (2003). Neural mechanisms for response selection: Representation specific or modality independent? *Journal of Cognitive Neuroscience*, *15*, 1077–1079.
- Seron, X., Pesenti, M., Noël, M. P., Deloche, G., & Cornet, J. A. (1992). Images of numbers, or “When 98 is upper left and 6 sky blue.” *Cognition*, *44*, 159–196.
- Shepard, R. N., & Metzler, J. (1971). Mental rotation of three-dimensional objects. *Science*, *171*, 701–703.
- Simon, O., Mangin, J. F., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron*, *33*, 475–487.
- Snyder, L. H., Batista, A. P., & Andersen, R. A. (1997). Coding of intention in the posterior parietal cortex. *Nature*, *386*, 167–170.
- Stanescu-Cosson, R., Pinel, P., van de Moortele, P. F., Le Bihan, 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*, 2240–2255.
- Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *28*, 643–662.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain: 3-Dimensional proportional system: An approach to cerebral imaging* (M. Rayport, Trans.). New York: Thieme.
- Thoenissen, D., Zilles, K., & Toni, I. (2002). Differential involvement of parietal and precentral regions in movement preparation and motor intention. *Journal of Neuroscience*, *22*, 9024–9034.
- van Harskamp, N. J., & Cipolotti, L. (2001). Selective impairments for addition, subtraction and multiplication. Implications for the organisation of arithmetical facts. *Cortex*, *37*, 363–388.
- Walsh V. (2003). A theory of magnitude: Common cortical metrics of time, space and quantity. *Trends in Cognitive Sciences*, *7*, 483–488.
- Walsh, V., & Pascual-Leone, A. (2003). *Transcranial magnetic stimulation—A neurochronometrics of mind*. Cambridge: MIT Press.
- Winstein, C. J., Grafton, S. T., & Pohl, P. S. (1997). Motor task difficulty and brain activity: Investigation of goal-directed reciprocal aiming using positron emission tomography. *Journal of Neurophysiology*, *77*, 1581–1594.
- Wise, S. P., Boussaoud, D., Johnson, P. B., & Caminiti, R. (1997). Premotor and parietal cortex: Corticocortical connectivity and combinatorial computations. *Annual Review of Neuroscience*, *20*, 25–42.
- Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of fMRI data. *Neuroimage*, *14*, 1370–1386.
- Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism*, *12*, 900–918.
- Zago, L., Pesenti, M., Mellet, E., Crivello, F., Mazoyer, B., & Tzourio-Mazoyer, N. (2001). Neural correlates of simple and complex mental calculation. *Neuroimage*, *13*, 314–327.