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A Supramodal Number Representation in Human Intraparietal Cortex

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Summary

The triple-code theory of numerical processing postulates an abstract-semantic “number sense.” Neuropsychology points to intraparietal cortex as a potential substrate, but previous functional neuroimaging studies did not dissociate the representation of numerical magnitude from task-driven effects on intraparietal activation. In an event-related fMRI study, we presented numbers, letters, and colors in the visual and auditory modality, asking subjects to respond to target items within each category. In the absence of explicit magnitude processing, numbers compared with letters and colors across modalities activated a bilateral region in the horizontal intraparietal sulcus. This stimulus-driven number-specific intraparietal response supports the idea of a supramodal number representation that is automatically accessed by presentation of numbers and may code magnitude information.

Introduction

If somebody showed us a “5” or said the word “five” we would have no problem copying that Arabic numeral on a piece of paper or repeating that number. A person not familiar with the numerical meaning of digits or number words could also perform these two tasks but would fail completely when asked whether these items are larger or smaller than “9”/“nine,” a question we barely have to think about. This obvious dissociation in levels of meaning that Arabic numerals or number words can have is reflected in cognitive models of number representation. The “triple-code theory” by Dehaene, for instance, assumes that there are modality-specific symbolic codes in the visual Arabic and auditory verbal domain but that there is also a supramodal abstract “number sense” that conveys semantic, i.e., magnitude, information and contributes to mathematical performance (Dehaene, 1992).

It is tempting to assume that these different codes are implemented in distinct neuroanatomical structures (Dehaene and Cohen, 1995) and that functional neuroimaging might reveal their anatomical substrate. However, there is a fundamental problem when addressing this issue experimentally: tapping with certainty into an abstract number representation requires that numbers be processed in a way that explicitly accesses magnitude information, as for instance, in size comparison or

approximation. Such paradigms inevitably activate both the stimulus-driven representation of numbers and task-driven cognitive processes recruited by the context (e.g., Chochon et al., 1999; Dehaene et al., 1999; Pinel et al., 1999; Pesenti et al., 2000; Rickard et al., 2000). These processes range from nonspecific instrumental components such as attention, working memory, language, and visuospatial processes to the specific operations mediating exact or approximate calculation. It is virtually impossible to construe control tasks that match the precise demands imposed on instrumental cognitive processes but do not rely on numbers or magnitude information. In terms of neural activity, these instrumental processes form a powerful confound, and accordingly, recent work has confirmed that the cortical networks activated by nonarithmetic operations performed on numbers or even letters are comparably strong as and barely distinguishable from those underlying true calculation (Gruber et al., 2001).

One way around this problem would be if, by virtue of overlearned associative coupling, the mere presentation of numbers were sufficient to implicitly activate the related supramodal abstract number representation even when this is not essential for the task actually performed with the numbers. Some behavioral evidence seems to support the notion of an automatic and thus task-independent activation of the magnitude code: the so-called SNARC effect (Dehaene et al., 1993), or the numerical distance effect that occurs even when numbers only have to be judged as same or different (Dehaene and Akhavein, 1995). If, as suggested by others (Dehaene and Cohen, 1995), a region of intraparietal cortex underlies this abstract “number sense,” then it should respond to numbers even when the task itself does not explicitly require processing of numerical magnitude. Since implicit activation of a representation will not be as strong as explicit recruitment by task demands, we based our experimental identification of an abstract number representation on the fact that it should be supramodal. In other words, we sought a putative neural substrate of this quantity code by eliciting number-related activations both in the visual and the auditory modality and then focused on determining the overlap of these modality-related responses.

We tested this theoretical approach in a rapid event-related functional neuroimaging experiment (see Experimental Procedures) in which we presented single digits in the visual modality (VN) and corresponding verbal numerals in the auditory modality (AN). We included additional conditions that we expected to provide a tight control within the modality-specific representations, ideally canceling out responses reflecting the visual Arabic and auditory verbal representations (Figure 1). Interleaved with numbers, we hence also showed size-matched single uppercase letters and color fields and presented spoken color words and letters. The reasoning was that visual letters (VL) provide a good match for the visual properties of Arabic digits, including familiarity with these visual items, and that color words (AC) are equivalent and highly familiar semantic items that also

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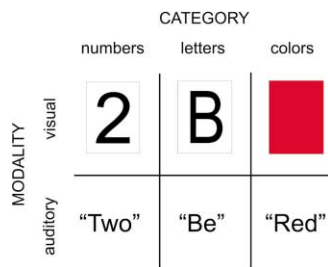


Figure 1. Schematic Overview of the Experimental Conditions Arranged in a Factorial Design

Arabic digits ("1," "2," "3," "4," "6," "8," "9"), single letters ("A," "B," "C," "D," "F," "G," "I"), and color fields (in red, yellow, green, blue, brown, white, or black) were presented in the visual, and the same items as spoken words or syllables, respectively, in the auditory modality.

refer to a scale, although only at the nominal level that does not imply magnitude. Visual colors (VC) and auditory letters (AL) were included in this factorial design as lower level control conditions within each modality, all items being presented in a randomized fashion across both modalities.

Results

During functional imaging, subjects looked at and listened to a sequence of stimulus items randomly interleaved across modalities and categories (see Experimental Procedures). They were instructed to report the occurrence of target items (one per category, i.e., numbers, letters, and colors) that were identical across both modalities (auditory and visual, e.g., as in Figure 1). This paradigm does not require the magnitude code and prevents attention or expectancy from being biased toward any given stimulus category or modality, thus removing effects of attentional set.

While the behavioral responses to target items served to obtain performance data from the experiment (see below), the neural responses were determined for the nontarget items, where no overt response occurred, and then tested for condition-related effects. Accordingly, in the analysis of the functional imaging data, we modeled separately both target and nontarget conditions but only

compared the cerebral activations related to nontargets. This avoided confounding neural responses to the different categories with activity related to oddballs (targets) and behavioral reporting.

In a first step, we determined modality-related neural responses to visual and auditory numbers. The corresponding statistical comparisons ($VN > AN$, $AN > VN$) revealed strong effects in auditory and visual associative areas, respectively, but, as expected, no specific response to numbers as opposed to the various control conditions, reflecting a good matching of low-level sensory processing (Table 1). This finding suggests that the visual Arabic and auditory verbal codes of number processing do not recruit neural structures that are macroscopically segregated from those that process other types of comparable visual or auditory input.

In a second step, we analyzed the responses to numbers compared to letters and colors across both modalities [$N > (L \text{ and } C)$] and found significant bilateral activations deep in the horizontal intraparietal sulcus ($p < 0.001$, uncorrected, Figure 2, Table 2). This finding was in accord with our central hypothesis and held when we applied a series of superimposed inclusive masks (each at $p < 0.05$, uncorrected) that let only those activations survive that were found in each of the four single contrasts related to numbers within the two modalities ($VN > VL$, $VN > VC$, $AN > AL$, $AN > AC$). Hence, the intraparietal activations in the test for supramodal number responses were neither driven by a single modality nor by the type of control condition against which they were contrasted (see also contrasts $N > L$ and $N > C$ in Table 2). This interpretation was further supported by the significant result of the conjunction between $VN > VL$ and $AN > AC$ ($p < 0.001$, uncorrected) that confirmed that the bilateral intraparietal activations were common to both modalities and specific to numbers. In a further step, we performed random-effect analyses over the nine subjects for the comparisons mentioned above and again found significant results in the same intraparietal region with similarly located response maxima as in the fixed-effect results (Tables 1 and 2). This confirms that our findings in the first-level group analysis were not driven by the activations of only a few individuals but were consistent across subjects.

The bilateral horizontal intraparietal sulcus was the only region reliably activated across the different afore-

Table 1. Modality-Specific Activations

Contrast	Region	Fixed-Effect				Random-Effect			
		Coordinates		t		Coordinates		t	
Modality-related effects									
AN > VN	right superior and middle temporal gyrus	56	−16	0	8.73*	44	−30	8	12.17
						64	−12	2	8.37
	left superior and middle temporal gyrus	−54	−24	−2	8.34*	−40	−36	12	9.51
						−54	−32	4	8.55
VN > AN	left fusiform gyrus	−42	−68	−14	7.86*	−40	−72	−14	8.19
	left inferior occipital gyrus	−32	−96	−2	4.30	−46	−74	−6	6.66
	right fusiform gyrus	44	−60	−18	7.20*	46	−76	−12	7.25
	right inferior occipital gyrus	44	−84	−6	5.30*	46	−82	−4	7.05
	superior parietal lobule	38	−62	56	4.54*				

Modality-specific brain responses to auditory and visual numbers in fixed-effect and random-effect group analyses ($n = 9$) at $p < 0.001$, uncorrected (* $p < 0.05$, corrected for multiple comparisons over the whole brain at voxel level).

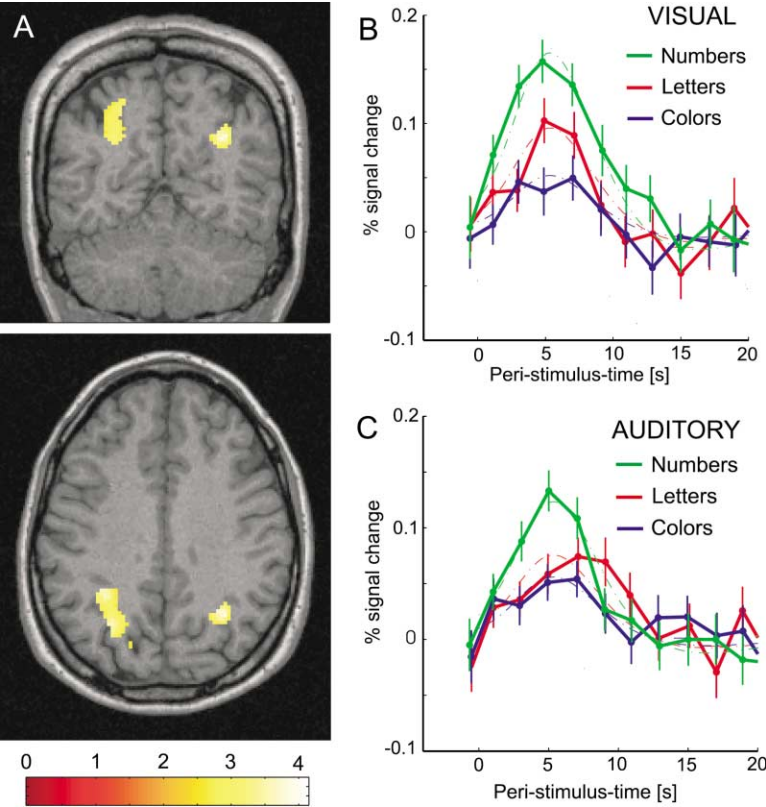


Figure 2. Cortical Localization of Supramodal Responses to Numbers

(A) Activation maps from a fixed-effect group analysis ($n = 9$) testing for greater event-related responses to visual and auditory numbers than to visual and auditory letters and colors. For visualization, the findings were color coded at $p < 0.005$ (masked inclusively with the simple main effects, i.e., responses to visual and auditory numbers compared to baseline at $p < 0.001$) and superimposed onto coronal (top) and horizontal anatomical images (bottom) from one of the participating subjects. Reader's left is subject's left. (B and C) Event-related responses to the different experimental conditions (solid line for peristimulus time histograms of the adjusted data; dotted line for the fitted responses). Data from intraparietal cortex are plotted as percent signal change for visual ([B], left focus) and auditory stimuli ([C], right focus).

mentioned contrasts and analysis types testing for supramodal responses to numbers. In some but not all of these tests, additional effects were observed in frontal cortical regions (premotor, operculum) at an uncorrected significance threshold of $p < 0.001$. As we had no prior hypothesis for activations in these regions and as these findings were inconsistent across tests and did not survive correction for multiple comparisons, we did not retain them as meaningful.

The question remained whether the responses to numbers in our experiment occurred in the same part of intraparietal cortex as in tasks where quantities are explicitly processed. Findings from several neuroimaging studies with mathematical tasks suggest that this is

the case, but the use of group averaging and spatially normalized stereotactical coordinates may blur fine spatial detail and thus compromise comparability. We therefore addressed this question within single subjects and performed additional experiments in three of the individuals studied previously. We used a covert subtraction task that was contrasted with covert naming of the next number in the number line (see Experimental Procedures for details). While subtraction is generally considered to strongly rely on access to the numerical magnitude code, the control task can be expected to activate this code to a far lesser degree. This is in line with examples from the literature of patients who, despite impaired understanding of abstract number meaning,

Table 2. Supramodal Activations

Contrast	Region	Fixed-Effect				Random-Effect			
		Coordinates		t		Coordinates		t	
Supramodal number-related effects									
N > L and C	left intraparietal cortex	-28	-68	30	4.12	-32	-48	32	5.51
		-32	-46	38	3.73				
		-24	-58	50	3.62				
N > L	right intraparietal cortex	34	-60	34	3.79	32	-58	30	6.49
	left intraparietal cortex	-24	-58	50	3.54	-32	-48	32	(4.11)
N > C	right intraparietal cortex	34	-60	34	3.10	32	-58	34	4.79
	left intraparietal cortex	-28	-68	30	4.28	-34	-50	28	5.80
		-32	-46	38	4.24	-34	-46	40	4.55
		-20	-76	30	3.78				
	right intraparietal cortex	34	-60	34	3.52	32	-58	28	5.32

Supramodal brain responses to numbers in fixed-effect and random-effect group analyses [$n = 9$, $p < 0.001$, uncorrected; () below significance threshold].

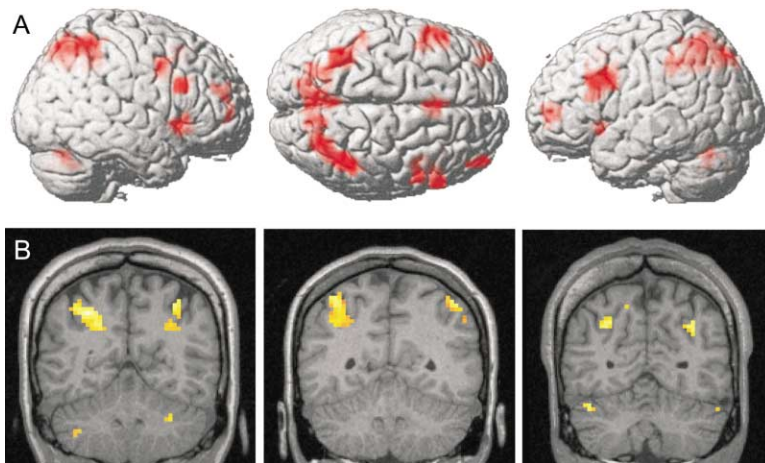


Figure 3. Parietal Responses during Calculation and Non-Mathematical Target Detection
(A) Activation maps during subtraction contrasted with naming of the next number. Pooled data from three subjects, thresholded at $p < 0.001$, uncorrected, and rendered onto a standard brain template. (B) Intraparietal overlap of responses to numbers from the main experiment and activations during the subtraction task, shown in three single subjects. Activation maps are derived from the conjunction of the contrasts (numbers > letters and colors) and (subtraction > naming next number) and were thresholded at $p < 0.001$ (subjects 1 and 2) or $p < 0.01$ (subject 3), uncorrected.

are able to name and write numbers and retrieve arithmetic facts from memory (Dehaene et al., 1998).

Results from the comparison of subtraction with the control task are shown in Figure 3A (pooled data from the three subjects). The distributed response pattern involving parietal, premotor, and prefrontal cortex is in good general agreement with what others have reported for these types of experimental conditions (e.g., Chochon et al., 1999; Menon et al., 2000; Gruber et al., 2001). Conjunction analyses showed that, in each of the three subjects tested, the responses from both paradigms overlapped bilaterally in a discrete region of intraparietal cortex (Figure 3B). This confirms that the number-related activations from our main experiment, which were obtained with a task that does not rely on explicit magnitude judgment, are colocalized with activations during explicit numerical magnitude processing, as in subtraction.

A remaining concern in the interpretation of our main imaging experiment might be that task difficulty was not matched across conditions. We obtained behavioral responses only for the target items but not the nontargets that served to define condition related neural responses. Analyzing the behavioral data (Figure 4A) in a multifactorial repeated measures ANOVA, we found a main effect of modality with about 150 ms longer reaction times for auditory than visual presentation [$F(1,8) = 61.6$, $p < 0.0001$] but no further significant main effects or interactions for reaction times or performance that might point to differences in neuronal cost for the critical comparisons (VN > VL, AN > AC). Nonetheless, the neural responses to nontargets could be influenced by task difficulty if rejecting nontargets was more difficult for numbers than the other conditions. As mentioned in the Introduction, a numerical distance effect occurs even when numbers are processed in nonnumerical contexts (Dehaene and Akhavein, 1995). In a same-different judgement, for instance, reaction times for the different-decision will be longer for numbers that are numerically close to the reference item than for those that are far. In other words, one finds it more difficult to state that “6” is different from “5” than to state that “9” is different.

To address this potential confound, we performed an independent behavioral experiment in ten further subjects with the same paradigm as in our main experiment.

The only difference was that we obtained responses for targets as well as for nontargets. In addition to the effects of category and modality, we assessed “distance” of the nontarget stimuli from the target as a further factor of interest (see Experimental Procedures for details). Figure 4B shows mean reaction times for the different conditions. A multifactorial ANOVA (category \times modality \times distance) on reaction times confirmed, as for target items in our imaging experiment, a main effect of modality [$F(1,9) = 156.3$, $p < 0.0001$] but also yielded a main effect of distance [$F(2,18) = 17.8$; $p < 0.0001$]. Interestingly, there were no further significant main effects and interactions. In other words, these data indicate no systematic difference between conditions in the difficulty of rejecting nontarget items. Furthermore, they demonstrate that, in our paradigm, the appearance of a distance effect is not restricted to numbers but also occurs with letters and colors, which underlines that our experimental conditions were well matched. Accordingly, the intraparietal activations we found in response to numbers cannot be accounted for by a distance effect, a common feature across all categories, but only by stimulus category. Since it is only in the case of numbers that distance between items corresponds to numerical magnitude, this underlines the specificity of our imaging results for numbers.

Discussion

The key finding of our study was a focal bilateral activation in the intraparietal sulcus when we compared nonarithmetic processing of numbers with that of letters and colors in a target-detection task across the visual and auditory modality. Further experiments confirmed that this region, but not this region alone, was also activated when mathematical operations were performed on numbers. In the absence of alternative interpretations, as for instance, category-related differences in task difficulty, we propose that these intraparietal responses to numbers reflect access to an abstract supramodal representation of numbers.

The location found here is in very good accordance with previous assumptions on the representation of the abstract “number sense” in the human brain (Dehaene et al., 1998). An essential implication of parietal areas

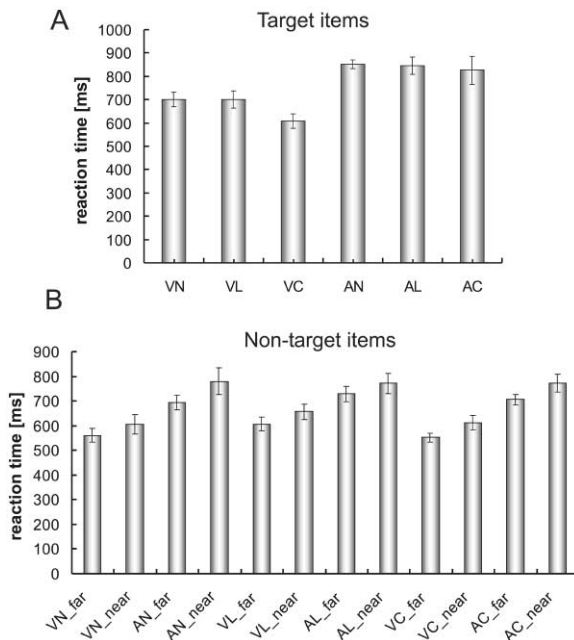


Figure 4. Behavioral Results

Reaction times (means and SEM) for the different experimental conditions for target detection during the imaging experiment ([A], data from nine subjects) and for rejection of nontarget stimuli in an independent behavioral control experiment ([B], data from ten subjects). These data illustrate highly matched task difficulty across categories (VN, visual numbers; AN, auditory numbers; VL, visual letters; AL, auditory letters; VC, visual colors; AC, auditory colors). The indices "near" and "far" refer to numerical, alphabetic, and chromatic proximity, respectively, of the test items to the target items. Note the occurrence of a distance effect across all categories (see text for statistical analysis and Experimental Procedures for details).

in representing numerical information can be derived from several lines of evidence. (1) The difficulties in processing numbers that patients with parietal lesions encounter range from magnitude comprehension to arithmetic tasks such as subtraction or number bisection (Dehaene et al., 1998). (2) Previous functional mapping studies have consistently found activations in the horizontal intraparietal sulcus over various number processing tasks, especially comparison and approximation, in which magnitude information is particularly necessary (Chochon et al., 1999; Dehaene et al., 1999; Pinel et al., 1999), but also in nonsymbolic processing of numerosity (Piazza et al., 2002).

In more detail, a recent study using a priming paradigm (Naccache and Dehaene, 2001) observed less intraparietal activation when numbers of identical versus different magnitude were repeated, irrespective of number notation (verbal versus Arabic). Another study found intraparietal activation during number comparison to be modulated by numeric distance, again independent of input notation (Pinel et al., 2001). While such response properties are compatible with a notation invariant and thus abstract coding of numbers, an alternative account of interparietal activations could rely on task-related instead of stimulus-related effects. In other words, the effects on parietal activity reported could equally well be due to systematic differences in task difficulty inher-

ent to the priming paradigm (shorter reaction times for repeated numbers) or the comparison task (shorter reaction times for numerically far numbers).

Here, we provide the necessary complementary evidence for a supramodal representation of numbers, by showing a merely implicit stimulus-driven intraparietal activation in the absence of a task recruiting numerical meaning. During control conditions, the identical task was performed on letters and colors. An independent behavioral study proved these controls to be very well matched in terms of task difficulty, as expressed by the behavioral responses, to the point that we observed distance effects in a similar way across categories and modalities. Nonnumerical distance effects have also been found by others (Taylor et al., 1984) and presumably reflect the fact that, just as numbers are embedded in the number line, letters hold positions in the alphabet and colors in the chromatic spectrum. This allows concluding that the intraparietal response does not generically reflect the representation of categories in which items can be arranged in an orderly way, as in the number line, but also the alphabet and the color spectrum. Instead, our finding must be specific for numbers, the category where this layout corresponds to numerical magnitude.

If the supramodal intraparietal focus contributes to magnitude representation, it should also be activated by mathematical processing. Reexamining some of our subjects in a subtraction task and finding responses at the same intraparietal locus confirmed this. In isolation, the finding from the calculation task is not conclusive, and activation of an abstract magnitude code is only one of its several alternative functional interpretations. However, this interpretation seems compelling when seen in conjunction with the colocalized response from our main experiment. The findings with calculation also underline the role of task-related processes that are performed on a given material. Subtraction activated a far more extensive distributed system than our main experiment with mere target detection, including closely neighboring other regions of parietal cortex. Moreover, in the intraparietal focus, explicit use of numerical information in subtraction yielded an activation level exceeding the one during implicit activation that was already to be expected for our control task, i.e., naming the next item in the number line. This observation supports a graded focal response in intraparietal cortex that reflects whether numerical information is only implicitly evoked by numbers as the appropriate stimulus or whether it is being actively processed in the context of a task. Together, the data presented reflect the top-down (explicit calculation) and bottom-up mechanisms (implicit recruitment during sensory target detection) for evoking the "magnitude code," and the overlap of these two approaches in a circumscribed cortical region provides strong evidence in favor of this theoretical concept.

But why should an abstract "number sense" be implemented so relatively remote from the temporal lobe structures dealing with symbolic visual and auditory number notations? Recently, growing evidence for an abstract understanding of numerical quantity in animals (Hauser et al., 1996; Orlov et al., 2000) and infants (see Dehaene et al., 1998) suggests that the processing of numerical information is a basic and innate cognitive

faculty. It does not presuppose proficiency in the cultural notations that represent it symbolically in the auditory or visual modality and that we learn during school education. This “number sense” seems to predate notation-dependent processing both phylogenetically and ontogenetically. Accordingly, recent single-cell recordings in monkeys have shown sensitivity to numerical aspects of self-action in response properties of a very circumscribed region of intraparietal cortex (Sawamura et al., 2002). However, another study in monkeys demonstrated effects of numerical magnitude in responses of prefrontal neurons, and less in parietal cortex (Nieder et al., 2002). Similar to functional neuroimaging experiments in humans, however, the relative contributions of categorical representation and cognitive process to neural responses can prove difficult to disentangle and may account for such apparent discrepancies. This could be of particular relevance for studies in monkeys that have been extensively trained in a specific task, thus emphasizing process-related response properties in subsequent recordings of neuronal activity. While several studies in humans and also, for instance, the findings presented here for single subjects show that the functional network underpinning numerical operations includes both parietal and prefrontal areas, the precise determinants of neural activity across all these sites still need to be determined in more detail.

Regarding the abstract representation of numerical magnitude, a teleological perspective would suggest intraparietal cortex to provide a strategically well-adapted localization. Given the proximity with cerebral resources that process spatial scene (and body) layouts and contribute to action sequences, an intraparietal locus of numerical representation seems ideally suited for close interactions with functional contexts in which numerosity in space and time is of importance. In this vein, a recent fMRI study has parcellated functional response properties of intraparietal cortex in relation to motor, visuomotor, attentional, linguistic, and mathematical operations (Simon et al., 2002). The findings of some overlap but also clear segregation of responses to these different functional demands support a distinct modular organization of intraparietal cortex rather than a diffuse pattern. This functional parcellation parallels the recently renewed neuroanatomical emphasis on architectonic differentiation of the cortex lining the intraparietal sulcus (Zilles and Palomero-Gallagher, 2001). On a larger spatial scale, it is becoming increasingly clear that separate regions in the parietal lobe support different aspects of number processing. Accordingly, a recent meta-analysis proposes three nodes of number processing in the parietal lobe that putatively underlie different cognitive operations (Dehaene et al., 2003). Important future issues are how the culturally determined and educationally acquired symbolic number notations link to the abstract “number sense,” and how the cortical site representing numerical meaning interacts with the other regions in the parietal lobe that support mathematical operations.

Experimental Procedures

Subjects and Imaging Procedure

Nine healthy young volunteers (four men and five women, mean age 27.9 ± 2.1 years) with normal or corrected vision participated in the

main functional imaging experiment after giving written informed consent. All subjects were right handed according to a modified version of the Edinburgh Inventory (Oldfield, 1971). Functional images were acquired on a 1.5 Tesla magnetic resonance imager with gradient booster and standard head coil (Siemens Vision, Erlangen, Germany) as series of blood-oxygenation-sensitive (T_2^* weighted) echo-planar image volumes every 2.7 s (echo time 60 ms, 24 parallel transverse slices, voxel size = $3.44 \times 3.44 \times 4$ mm³, 1 mm gaps). Additionally, high-resolution T1-weighted anatomical images were acquired for each subject (3D-MPRAGE-sequence, TR 9.7 ms, TE 4 ms, 170 contiguous slices, voxel size $1 \times 1 \times 1$ mm).

Stimulation and Behavioral Task

Single digit numbers (1, 2, 3, 4, 6, 8, 9), letters (A, B, C, D, F, G, I), and colors (red, blue, green, yellow, brown, white, black) served as stimulus items and were presented either visually as arabic numerals, capital letters, or colored surfaces, respectively, or auditorily as number words, spoken letters, or color words, respectively (see Figure 1). Visual stimuli appeared in the center of a background of a uniform intermediate gray level. Numbers and letters were presented in uppercase in black at the same font size (Arial for numbers, Arial Narrow for letters to produce approximately matched visual field coverage as numbers) and subtended about 1.6×1.2 deg of visual angle. To ease maintenance of central gaze, all stimuli were positioned in a rectangular field (height 2.2 deg of visual angle, width 1.7 deg of visual angle) that remained displayed throughout the interstimulus time. For colors, the stimulation consisted of uniformly filling this rectangular field with a certain color. Presentation duration was 150 ms for the visually presented items. Auditory stimuli were wav-files of one-syllable German words recorded from one speaker and lasting 400–800 ms.

Visual stimuli were projected onto a translucent screen and viewed by the subjects through a mirror attached to the head coil. Auditory stimulation used a custom-built headphone system. Stimulus delivery used ERTS (Experimental Run Time System, Version 3.18, 1996, J. Beringer, Germany) on a Pentium-based personal computer, as did the recording of behavioral responses (button presses). All six stimulus categories were equally grouped into five experimental sessions (length about 6 min each) in which their order of presentation was randomized. Interstimulus intervals were randomized between 2.5 and 5.5 s. Subjects were instructed to press a button as quickly as possible whenever one of three target items (one digit, one letter, one color) appeared in either modality. Target items differed between subjects (each letter, number, and color was used at least once and not more often than twice). Error rates and reaction times of the button presses served as a control for attention and performance of the subjects throughout the experiment.

In three of these subjects, we performed separate additional MR sessions with tasks that required the use of numerical meaning. The numbers 1, 2, 3, 4, 5, 6, 8, 9 were presented in blocks of ten stimuli each (one every 2 s) either visually or auditorily, separated by 20 s of baseline. Before each block of stimuli, a visual instruction either indicated to covertly subtract the number shown from “11,” or in the control condition, to covertly name the next number in the number line.

To rule out differences in task difficulty between categories for rejection of nontargets, we performed an independent behavioral control experiment. We tested ten further subjects (mean age 30.7 ± 4.3 years, normal or corrected vision, all right handed) in the same paradigm as for functional imaging but with a bimanual response (left key for target items, right key for nontarget items). The stimulus items used were 1, 2, 4, 5, 6, 8, 9 for numbers; A, B, D, E, F, G, I for letters; and white, red, yellow, green, blue, black, brown for colors. 5, E, and green served as targets for all subjects. 4 and 6, D and E, yellow and blue were defined as close items for numbers, letters, and colors, respectively, with the remaining stimuli defined as far items.

Image Processing and Data Analysis

Imaging data were analyzed using statistical parametric mapping software (SPM99, www.fil.ion.ucl.ac.uk/spm). The data set acquired for the main experiment consisted of 655 image volumes, and for the additional MR experiment, of 483 image volumes per subject.

To allow for steady-state magnetization, the first five scans of each session were discarded from analysis. Functional images were realigned to the first scan of each session, acquisition timing corrected with the medium slice as reference (in case of the event-related analysis), and normalized into standard stereotactical space. Spatial smoothing was performed on the normalized functional images using a Gaussian kernel of 10 mm FWHM in the group analysis and of 6 mm FWHM for the comparisons in single subjects.

We first assessed condition-specific event-related activations in the main experiment in a fixed-effect group analysis. Responses to targets as well as to the six conditions of interest (numbers, letters, and colors as categories, and visual and auditory as modalities) were modeled for each session as stick functions marking the stimulus onset convolved with the canonical hemodynamic response, and voxelwise regression coefficients were determined by least squares analysis. To remove low-frequency drifts and to control for serial autocorrelation, data were temporally bandpass filtered (high-pass 120 s, low-pass 4 s Gaussian), and global intensity normalization (linear scaling) was applied before model estimation. In addition, to test for consistency of the respective activation patterns across subjects, random-effect analyses (one-sample *t* test) were performed for all comparisons of interest. For visualization and comparison purposes, these were masked inclusively with the corresponding results of the fixed-effect analysis at $p < 0.05$, uncorrected. This should restrict further exploration of the data to voxels for which the first-level model provided a reasonable fit.

For statistical inference, we used appropriate *t* contrasts of the parameter estimates according to the 2×3 factorial design described above (with the factors corresponding to stimulus category and input modality). As targets (oddballs with a behavioral response) can be expected to cause differential activations compared to non-targets, they were not included in any *t* contrasts. We report significant activations at a threshold of $p < 0.001$, uncorrected, where we did have a prior neuroanatomical hypothesis (e.g., for intraparietal areas), otherwise at $p < 0.05$, corrected for multiple comparisons (applying Gaussian random fields theory as implemented in SPM99).

Single-subject analyses were performed in the three subjects that underwent the additional session with the subtraction task. Responses in this session were modeled according to a block design (boxcar function convolved with hemodynamic response). The overlap of responses in the two different paradigms was assessed as the conjunction (minimum *t* statistics) of the contrasts (numbers > letters and colors) and (subtraction > naming next number).

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