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Mode-dependent and mode-independent representations of numerosity in the right intraparietal sulcus

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ABSTRACT

In humans, areas around the intraparietal sulcus (IPS) have been found to play a crucial role in coding nonsymbolic numerosities (i.e., number of elements in a collection). In the parietal cortex of monkeys, some populations of neurons were found to respond selectively to sequentially- or simultaneously-presented numerosities, whereas other populations showed similar activation in both modes of presentation. However, whether such mode-dependent and -independent representations of numerosity also exist in humans is still unknown. Here, we used fMRI to identify the areas involved in numerosity processing while participants classified linear arrays of dots (simultaneous stimuli) or flashed dot sequences (sequential stimuli). The processing of simultaneous numerosities induced activations bilaterally in several areas of the IPS, whereas activations during the processing of sequential numerosities were restricted to the right hemisphere. A conjunction analysis showed that only the right IPS and precentral gyrus showed overlapping activations during the judgement of sequential and simultaneous stimuli. Voxelwise correlations confirmed the highly similar pattern of activation found in these regions during both tasks. This pattern was weaker or absent in mode-dependent regions, like the right inferior frontal cortex and the lateral occipital complex. Finally, a close look at the right IPS revealed an anterior-to-posterior gradient of activation with selective activation for sequential and simultaneous stimuli in the anterior and posterior areas, respectively, and overlapping activations in-between. This study provides the first direct evidence that, in humans, the right IPS contains both mode-dependent and mode-independent representations of numerosity.

Introduction

Humans share with animals the early ability of estimating numerosity in a nonverbal nonsymbolic way (i.e., approximate quantification system), constituting the precursor of more elaborate numerical skills (Halberda et al., 2008; Nieder and Dehaene, 2009; Piazza and Izard, 2009). Moreover, simple arithmetical abilities involving a relatively sophisticated nonverbal representational system are observed both in children and in nonhuman primates (Hauser et al., 1996; Hodent et al., 2005; Houdé, 1997; Wynn, 1992; 1998). Involvement of the IPS in the processing of nonsymbolic numerical magnitudes (i.e., number of elements in a collection) is well established in humans. Indeed, activation of the left and right IPS was reported in response to deviant numerosities when participants were passively exposed to arrays of dots or squares in habituation paradigms (Cantlon et al., 2006; Piazza et al., 2004, 2007). Bilateral involvement of the IPS has also been demonstrated in dot comparison (Dormal and Pesenti, 2009; Leroux et al., 2009), dot enumeration (Fink et al., 2001; Piazza et al., 2002, 2003; Sathian et al., 1999), and nonsymbolic simple addition tasks (Venkatraman et al., 2005). Modulation of activation as a function of the distance of the to-be-compared numerosities, which has been observed in bilateral parietal areas during comparison tasks in electrophysiological (Libertus et al., 2007) and fMRI (Ansari and Dhital, 2006) studies, provides additional support to the critical role of these regions in nonsymbolic numerosity processing. Finally, two recent transcranial magnetic stimulation (TMS) studies showed that the comparison of dot collections was slowed down after left IPS stimulation when stimuli were presented sequentially (Dormal et al., 2008) or simultaneously (Cappelletti et al., 2007), but was not affected after right IPS or control stimulation.

The question of how numbers are represented and whether there is a unitary neuronal basis for all forms of numerical representation is at the center of recent debates. Several studies have shown that the same IPS area is involved in both nonsymbolic and symbolic numerical processing. For example, in the aforementioned TMS study (Cappelletti et al., 2007), the interference effect found when comparing patterns of dots after left IPS stimulation was also observed with Arabic digits. Recent fMRI adaptation studies showed an adaptation of the BOLD

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signal in the IPS in response to numerosity repetition, irrespective of notation (i.e., Arabic digits or sets of dots: Piazza et al., 2007; Arabic digits or number words: Cohen Kadosh et al., 2007), which confirms previous findings using other methods (e.g., ERP and fMRI: Pinel et al., 2001). Therefore, it is reasonable to assume that there are at least *notation-independent* numerical magnitude representations and processes in the IPS, as evidenced by common activation in response to numbers of elements, Arabic and verbal numerals (Ansari, 2007; Cantlon et al., 2009), and *modality-independent* ones, as visual and auditory numerosity processing were associated to similar neural codes in the IPS (Eger et al., 2003; Piazza et al., 2006). This, of course, does not exclude the presence of notation-dependent numerical representations in the parietal cortex, as suggested by some recent fMRI and TMS results (for a discussion, see Cohen Kadosh and Walsh, 2009; Cohen Kadosh et al., in press; Pesenti and Andres, 2009). The core representation of numerosity that is invariant with respect to the symbolic or nonsymbolic format of presentation is likely to be available in infants and shared with other species (Dehaene et al., 2003; Piazza and Izard, 2009). Whereas those characteristics are supported by a large amount of brain imaging data, the influence of the spatial or temporal structure of the stimuli on numerosity processing has received little interest in the human neuroimaging literature. Indeed, space and time are thought to be intrinsically involved in numerosity extraction models, although current proposals specify more clearly the contribution of space (e.g., numerosity extracted through *location maps*, Dehaene and Changeux, 1993; or *location fields*, Verguts and Fias, 2004). Yet, in terms of (neuro)cognitive models, it may be substantially different to make numerical judgements if space and/or time are critical cues than if they are not, or if their respective contribution to numerosity extraction differs; this may also lead to different associations and dissociations of deficits in case of brain damage. It is therefore crucial for current theorizing attempts to determine whether the numerical contribution of the IPS is rooted to spatial perception or whether it can extend to the processing of temporal series. Electrophysiological recordings in the monkey brain have demonstrated that number-sensitive neurons in the IPS can show different responses according to the presentation mode (Nieder et al., 2006). Some neurons were found to be tuned selectively by sequentially presented numerosities, whereas the same numerosities recruited other neurons when they were presented simultaneously, supporting the existence of distinct mechanisms for the parallel or sequential extraction of numerosity. A third class of neurons was found to discharge whether numerosity had been presented sequentially or simultaneously; these neurons were assumed to encode the final result of the quantification process irrespective of its mode of presentation. In humans, such a functional subdivision of the IPS areas involved in numerosity processing has never been reported. One previous fMRI study used both sequential and simultaneous presentations but, because the goal of the study was not to compare presentation modes, only common activations were reported (Castelli et al., 2006). Participants had to judge whether there was more blue or more green in discrete or continuous displays changing either in space (a single rectangle filled with blue and green hues, corresponding to simultaneous presentation) or in time (temporal sequences of blue and green squares, corresponding to sequential presentation). A greater bilateral activation of the IPS was reported during discrete compared to continuous quantity comparison, both in space (simultaneous) and in time (sequential). However, these data are inconclusive regarding the effect of the presentation mode since the overlap and/or dissociations between the IPS areas recruited during simultaneous and sequential presentations were not assessed. The functional segregation of the brain areas related to each presentation mode raises two additional challenges. First, it is necessary to design the stimuli very carefully in order to exclude any covariation between numerical and non-numerical variables, such as the surface covered by the stimuli or the duration of the display. Second, the range of numerosities and the presentation time need to be calibrated appropriately to prevent the use of counting strategies by the participant. Indeed, using of counting strategies may bias the study of the core numerical abilities, because counting abilities are effortful, culturally-defined and rely on additional brain networks relative to those involved in the estimation of numerosities (Demeyere and Humphreys, 2007; Gordon, 2004; Piazza et al., 2006; Pica et al., 2004).

The present fMRI study thus aimed at solving these issues to provide the first detailed investigation of the pattern of activations induced by simultaneous or sequential presentations of numerosities. Participants had to categorize as "few" or "many" the numerosity of linear arrays of dots (i.e., Simultaneous Numerosity categorization, hereafter SimN) or of flashed dot sequences (i.e., Sequential Numerosity categorization, hereafter SeqN). If the same numerosity representation underlies the processing of these two presentation modes, then common activations should be observed, most likely in the parietal areas usually involved in numerosity processing. Importantly, using simultaneous and sequential stimuli in the same experiment provides a direct test of the core numerosity representation by excluding the spatial and temporal components most often intrinsically involved in numerosity processing. In a first step, we performed a whole-brain analysis to see whether the distinct and common neuronal populations found in the monkey brain during similar tasks, could be observed at a macroscopic level in humans. In a second step, in order to specify the relationship between the parietal networks dedicated to simultaneous and sequential numerosity processing, we measured voxelwise correlations between the index of activation computed for each critical site. The rationale is that the overlapping activations revealed by fMRI may reflect spatial blurring or intermingled but functionally independent brain networks. In this case, the probability to observe similar variations of the fMRI signal across the voxels commonly activated by the two tasks is weak and a null or negative correlation is expected (Downing et al., 2007; Peelen et al., 2006, 2007; Peelen and Downing, 2007a,b). Alternatively, a positive correlation would suggest a functional dependency between the patterns of activation induced by simultaneous and sequential presentations. Indeed, if the overlap of the voxels activated by the two tasks follows functional lines, the peak voxels in one task should also exhibit the highest signal in the other task, and the less activated voxels in one task should be weakly activated in the other task as well. The quantitative assessment of task correlations across voxels should help us to address functional hypotheses while taking into account intrinsic biases in the processing of fMRI images. However, the spatial resolution of the fMRI is far from the one obtained with invasive electrophysiological recordings in monkeys. The multi-voxel pattern analysis should therefore be regarded as a way to specify the functional relationship between the patterns of activation observed in the two tasks at the level of 2-mm voxels, which was the highest spatial resolution available in the present study, but not as a tool to replicate the finding of common neuronal populations in neurophysiological studies. Finally, we performed an exploratory voxelwise analysis of the activations found along the right IPS in an attempt to specify the anatomical landmarks delineating the subdivision of the areas involved in sequential and simultaneous presentations. It is well known, for example, that the substrate of spatial processing extends in the posterior segments of the IPS, whereas the core numerosity representation has been located in the anterior horizontal segment of the IPS (Dehaene et al., 2003; Simon et al., 2002). These two complementary analyses allowed us to critically extend the classical basic approach of neural substrate identification.

Method

Participants

Fifteen healthy, French-speaking, male volunteers (mean age: 21 ± 2.3 years) participated in this study after giving their informed

written consent. All the participants were right-handed as attested by the Edinburgh inventory questionnaire (Oldfield, 1971), had no history of neurological or psychiatric disorders, had corrected-to-normal vision, and were unaware of the purpose of the study. The experiment was non-invasive and was performed in accordance with the ethical standards laid down in the 1964 Helsinki Declaration; the experimental protocol was approved by the Biomedical Ethical Committee of the Université catholique de Louvain.

Tasks and stimuli

Two categorization tasks were used: (1) a numerosity categorization of linear arrays of dots presented simultaneously (SimN) and (2) a numerosity categorization of sequences of dots (SeqN). In each task, the participants had to decide if the arrays/sequences contained "few" (i.e., 6) or "many" (i.e., 8) dots by pressing a left- or right-hand response button on a response box.

To prevent, as far as possible, potential explicit or implicit counting strategies, nonsubitizable numerosities were presented very briefly.[1] In the SimN task, the stimuli were composed of linear arrays of 6 or 8 black dots presented for 200 ms (Fig. 1A). Non-periodic signals were used so that spatial ratios were not confused with numerosity (for more details, see Dormal and Pesenti, 2007). The total length of the arrays remained constant (10 cm), while the diameter of each dot (Le_j) and the interdot spacing (Li_j) varied from 3.3 to 15 mm. To avoid pattern recognition, each series involved at least one Le_j and one Li_j of 3.3 mm and one of 15 mm. In the SeqN task, the stimuli were composed of a black dot (diameter: 3.5 cm) flashed rapidly in the center of the screen (Fig. 1C). The sequences contained 6 or 8 dots and were constructed using non-periodic signals so that temporal ratios did not constitute a potential confounding variable, and rhythm biases and pattern recognition were avoided (for more details, see Breukelaar and Dalrymple-Alford, 1998; Dormal et al., 2006). The total duration of the sequences was constant (1800 ms), while the duration of each dot presentation (De_j) and the duration of the interdot interval (Di_j) varied from 50 to 270 ms. To avoid pattern recognition, each series involved at least one De_j and one Di_j of 50 ms and one De_j and one Di_j longer than 200 ms; each sequence began and finished with a Di_j of 50 ms. The reference tasks were composed of the same stimuli as those in the corresponding experimental tasks except that the array of dots was presented in red in half of the SimN stimuli, and the last dot of each sequence was colored in red in half of the SeqN stimuli. Participants were required to indicate whether the array/last dot was colored or not. These reference tasks were equated with the experimental tasks in terms of visual complexity and manual forced-choice responses.

Experimental procedure

Before the fMRI experiment, each participant underwent, for each task separately, a preliminary training session outside the magnet room to learn the two numerical categories and to reach a stable performance level. This session included a learning block, a training block with feedbacks, and an example of an fMRI acquisition run. In the learning block, 20 examples of arrays/sequences with few and many dots were presented and the participants were instructed to observe carefully; the numerosity of the arrays/sequences was never mentioned. During the training block, randomized trials were presented and the participant had to categorize each of them as containing "few" or "many" dots by pressing one of two keys on the numerical pad (key 1 with the right index finger for arrays/sequences with few dots, key 3 with the right ring finger for arrays/sequences with many dots). After each answer, a visual feedback indicated whether the answer was correct or not. Several configurations of stimuli (i.e., same numerical properties but with different spatial or temporal characteristics) were used in order to avoid the possibility of pattern recognition. Along with the limited range of numerosities that were used, this ensures that the activations will not be related to various quantification procedures. Finally, four blocks (2 blocks of an experimental task alternating with 2 blocks of the corresponding reference task) without feedback were administered to familiarize the participants with the procedure used during the fMRI study.

In the magnet room, back-projected images were viewed through a tilted mirror mounted on the head coil, and the participants answered by pressing a 2-button response pad with the index of their left or right hand for "few" and "many" answers, respectively; the projector and the mirror (Silent Vision™ System, Avotec, Inc., <http://www.avotec.org>) and the response pad (Imagilys, <http://www.imagilys.com/>) were compatible with the MRI environment. Stimulus presentation and response recording were controlled with E-Prime (Schneider et al., 2002). Each participant underwent four acquisition runs in a counterbalanced order (i.e., ABBA or BAAB): two runs of 5 blocks of the SimN task alternating with 5 blocks of the corresponding reference task, and two runs of 5 blocks of the SeqN task alternating with 5 blocks of its reference task. These 10 blocks lasted 25 s and were interleaved with 12.5 s-fixation periods (black cross on white background) (Fig. 1B). Before each run, two blocks of examples of arrays/sequences with "few" and "many dots" respectively were presented as a reminder of the classes.

fMRI acquisition and analysis

Functional images were acquired with a 3.0 T magnetic resonance imager and an 8-channel phased array head coil (Achieva, Philips Medical Systems) as series of blood-oxygen-sensitive T2*-weighted echo-planar image volumes (GRE-EPI). Acquisition parameters were: TE = 32 ms, TR = 2500 ms, Flip angle = 90°, Field of view = 220 × 220 mm, slice thickness = 3.5 mm with no interslice gap, SENSE factor (parallel imaging) = 2.5. Each image volume comprised 36 axial slices acquired in an ascending interleaved sequence. High-resolution anatomical images were also acquired for each participant using a T1-weighted 3D turbo fast field echo sequence with an inversion recovery prepulse (150 contiguous axial slices of 1 mm, TE = 4.6 ms, TR = 9.1 ms, Flip angle = 8°, FOV = 220 × 197 mm, voxel size = 0.81 × 0.95 × 1 mm^3, SENSE factor = 1.4). Head movement was limited by foam padding within the head coil and a restraining band across the forehead.

Data were processed and analyzed using Statistical Parametric Mapping (SPM2, Welcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ac.uk/spm>). Functional images were (1) corrected for slice acquisition delays, (2) realigned to the first scan of the first run (closest to the anatomical scan) to correct for within- and between-run motion, (3) coregistered with the anatomical scan, (4) normalized to the MNI template using an affine fourth degree ß-spline interpolation transformation and a voxel size of 2 × 2 × 2 mm^3 after the skull and bones had been removed with a mask based on the individual anatomical images, and (5) spatially smoothed using a 10-mm FWHM Gaussian kernel.

Condition-related changes in regional brain activity were estimated for each participant by a general linear model in which the responses evoked by each condition of interest were modeled by a standard hemodynamic response function. The contrasts of interest were first computed at the individual level to identify the cerebral regions significantly activated by sequential and simultaneous numerosity, relative to the fixation periods used as a general baseline (respectively,

[1] This numerical range was used in previous experiments (e.g., Dormal and Pesenti, 2007) and allowed us (1) to avoid using numerosities that could be subitized (i.e., directly apprehend) and thus to focus on one single quantification procedure (namely, estimation since the presentation duration did not allow the participants to count), (2) to have two classes of numerosities that were neither to easy nor to difficult to discriminate in pilot studies, and (3) to create arrays that could be presented in a short amount of time and on a limited portion of space (i.e., 5° of visual angle).

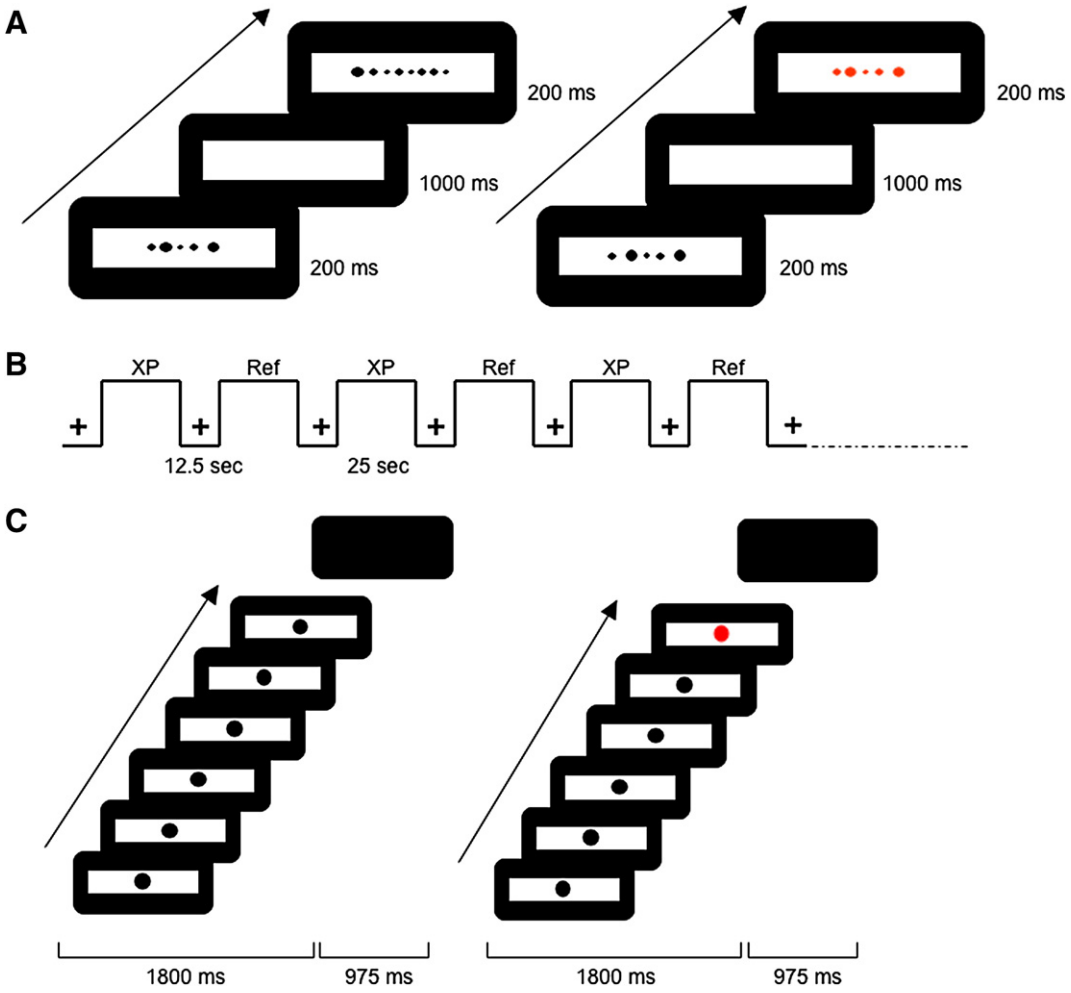

Fig. 1. Schematic representation of the temporal structure of the experiment. (A) Examples of simultaneous numerosity experimental (left) and reference (right) task: each trial was composed of a stimulus (a linear arrays of dots) displayed for 200 ms, and a blank response screen for 1000 ms. For the reference task, the array was either black or red. (B) fMRI design. Each run consisted of 10 alternations of a 12.5-s-fixation period (black cross on white background) and a 25-s-activation period. Each activation period corresponded to either an experimental condition or its reference condition. (C) Examples of sequential numerosity experimental (left) and reference (right) task: each trial was composed of a stimulus (a flashed dots series) displayed for 1800 ms, and a blank response screen for 975 ms. For the reference task, the last dot of the series was either black or red.

[*SeqN-fix*], and [*SimN-fix*]), and similarly for each reference task. Significant cerebral activations for the critical contrasts (experimental task *minus* reference task, each relative to the fixation periods) were then examined at the group level in random-effect analyses using one-sample *t*-tests and analyses of variance (ANOVAs) with the statistical threshold set at $p<0.05$ (FWE corrected at the voxel level) and extending to at least 60 contiguous voxels (k). Given the strong *a priori* hypotheses, activations in the parietal cortices were also screened at lower, uncorrected thresholds. The conjunction (using the Minimum Statistic compared to the Conjunction Null, MS/CN; Nichols et al., 2005) of the two experimental contrasts with their own reference contrast isolated the cerebral activations elicited in common by sequential and simultaneous numerosity categorization. Then, to assess the selectivity of activations observed in this conjunction, we performed a multi-voxel correlation analysis (Downing et al., 2007; Peelen et al., 2006). First, five functional regions of interest (ROIs) were defined based on the results of the conjunction analysis and the critical contrasts of each experimental task with its reference: the right IPS and the right precentral gyrus from the conjunction, the right frontal gyrus from the SeqN task, and the bilateral temporo-occipital junction from the SimN task. The frontal and occipital sites activated only in sequential and simultaneous numerosity respectively were chosen as control sites. These ROIs were then intersected with a 5-mm-radius sphere using the MarsBaR tool (<http://marsbar.sourceforge.net>; Brett et al., 2002), with the center of the sphere at the peak of the relevant contrast. Importantly, the intersection between the sphere and the cluster activated in the contrast used to define the ROI ensures that only active voxels were included in the ROI. This procedure guarantees that correlations were not contaminated by the inclusion of inactive white matter or CSF voxels. For a 5-mm sphere, the maximum number of voxels in each ROI was 81 voxels. The *t*-value for each voxel within a given ROI was then extracted from the unsmoothed normalized and resampled images of the two contrasts of interest ([*SeqN-RefSeqN*], and [*SimN-RefSimN*]). For each participant, the voxel-by-voxel correlation between *t*-values within the ROI defined by the group conjunction was calculated. The mean correlation across participants was then calculated, and its significance tested using a one-sample *t*-test against zero. Finally, in order to quantify the extent of the IPS activation corresponding to each task and to determine the sub-regions specifically implicated, we computed an anterior–posterior index over the right IPS region (Fig. 3C). This index was obtained by averaging the contrast-weighted *t*-values for the comparison of each experimental task versus its own reference task along the medial-to-lateral (x) and superior-to-inferior (z) dimensions. The anterior–posterior index was calculated for SimN and SeqN tasks.

Results

Behavioral data

An ANOVA was performed on the response latencies (RLs) of correct answers with condition (Experimental *vs.* Reference) and presentation (SimN *vs.* SeqN) as within-subject variables. Significant main effects of condition ($F(1,14)=39.461$, $p<.001$) and presentation ($F(1,14)=51.874$, $p<.001$) were observed. Participants responded faster overall in the reference (283 ± 53 ms) than in the experimental (346 ± 47 ms) conditions, and faster when the task used simultaneous (267 ± 51 ms) compared to sequential (362 ± 55 ms) presentation. Moreover, RLs showed a condition by presentation interaction ($F(2,13)=8.350$, $p<.02$): the difference between the experimental and reference tasks was larger for simultaneous (experimental: 311 ± 53 ms, reference: 223 ± 58 ms, difference: 88 ± 47 ms; $t(14)=7.378$, $p<.001$) than for sequential (experimental: 380 ± 67 ms, reference: 343 ± 57 ms, difference: 37 ± 57 ms; $t(14)=2.551$, $p<.03$) presentation (Fig. 2).

A similar ANOVA on error rates revealed a significant main effect of condition only ($F(1,14)=20.302$, $p<.001$), with participants making more errors in experimental ($10\pm5\%$) than in reference ($3\pm2\%$) conditions (Fig. 2). No other main effect or interaction was significant.

Functional data

Simultaneous numerosity processing

Contrasting the SimN task to its reference revealed a large focus of activation in the right inferior parietal lobule, in the depth of and around the IPS. Other activation foci were found bilaterally in the inferior temporal gyri and in the right precentral gyrus (Table 1a and Fig. 3A). At an uncorrected threshold ($p<.001$), activations were observed in the left inferior and superior parietal lobules along the posterior part of the IPS. Contrasted to SeqN, the SimN task revealed left-lateralized occipital and cingular activations. Foci of activation were also observed bilaterally in the precuneus (Table 1c).

Sequential numerosity processing

Contrasting the SeqN task to its reference revealed the cerebral areas involved in numerosity processing of sequentially presented nonsymbolic material. A right-lateralized hemispheric activation was identified in the inferior parietal lobule around the IPS. Areas of activation were also observed in the right inferior frontal gyrus, the right supplementary motor area, and the left insula (Table 1b and Fig. 3A). Only a small extra activation focus ($k=1$) appeared in the left superior parietal lobule at an uncorrected threshold ($p<.003$). Contrasted to SimN, the SeqN task activated a large focus in the right inferior frontal gyrus. Areas of activation were also observed in the right supplementary motor area (SMA) and in the left middle frontal gyrus (Table 1d).

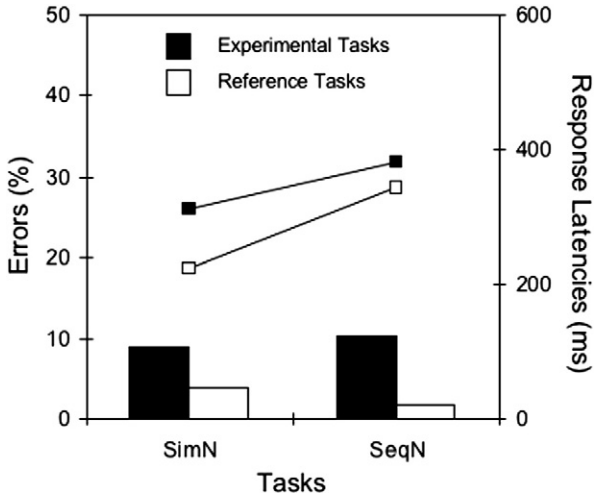

Fig. 2. Mean percentage of errors and response latencies in milliseconds for simultaneous and sequential numerosity categorization tasks (SimN *vs.* SeqN), as a function of the condition (experimental *vs.* reference).

Table 1
Brain areas showing significant activation for (a) Simultaneous numerosity (SimN), (b) Sequential numerosity (SeqN) categorization each compared to its own reference task (Ref), (c) SimN contrasted to SeqN and (d) inversely SeqN contrasted to SimN, and (e) conjunction of the two numerosity tasks (SeqN and SimN).

	Brain regions	L/R	*k*	*x*	*y*	*z*	*t*-statistic
a	[SimN-Fix]–[RefSimN-Fix]						
	IPS/inferior parietal lobule	R	693	30	−56	50	6.61****
	Inferior temporal gyrus	R	507	48	−58	−10	9.72****
	Inferior temporal gyrus	L	95	−46	−66	−10	6.33****
	Precentral gyrus	R	74	48	10	32	5.81****
	Superior parietal lobule	L	219	−28	−58	64	3.95***
	Inferior parietal lobule	L	93	−46	−38	50	3.71***
b	[SeqN-Fix]–[RefSeqN-Fix]						
	Inferior frontal operculum	R	2462	56	16	22	8.31****
	Supplementary motor area	R	672	8	20	54	8.43****
	ips/inferior parietal lobule	R	532	44	−46	50	7.75****
	Inferior frontal gyrus	R	448	42	22	4	7.61****
	Insula	L	136	−32	24	0	6.59****
	Superior parietal lobule	L	1	−40	−52	68	2.89**
c	[SimN-RefSimN]–[SeqN-RefSeqN]						
	Middle occipital gyrus	L	371	−50	−70	32	5.98****
	Cingular gyrus	L	234	−12	−40	38	5.99****
	Precuneus	L	100	−6	−64	72	5.68****
	Precuneus	R	82	6	−58	22	5.39****
d	[SeqN-RefSeqN]–[SimN-RefSimN]						
	Inferior frontal gyrus	R	1331	44	46	14	5.04****
	Supplementary motor area	R	326	8	20	58	4.97****
	Middle frontal gyrus	L	60	−42	46	16	3.64****
e	[[SeqN-Fix]–[RefSeqN-Fix]] and [[SimN-Fix]–[RefSim-Fix]]						
	IPS/inferior parietal lobule	R	134	42	−46	48	6.20****
	Precentral gyrus	R	74	48	10	32	5.81****
	Superior parietal lobule	L	2	−40	−52	68	2.72*

L = left hemisphere; R = right hemisphere; k = cluster size (number of voxels); *x*, *y*, *z* = stereotaxic coordinates of peak-height voxels.
**** = *p*-values < .05 FWE corrected for multiple comparisons.
*** = *p*-values < .001 uncorrected.
** = *p*-values < .003 uncorrected.
* = *p*-values < .004 uncorrected.

Mode-independent numerosity processing

The conjunction of SeqN and SimN, each contrasted to its own reference, revealed the areas involved in numerosity processing regardless of the mode of presentation. Only two right hemispheric foci were found to be activated in common, one in the IPS (with a local maximum at 42 −46 48; Fig. 3B) and one in the precentral gyrus (Table 1e and Fig. 3A). A small left superior parietal activation ($k=2$) also appeared at an uncorrected threshold ($p<.004$).

In the voxel-by-voxel correlation analysis, the two right foci activated in the conjunction (i.e., IPS and precentral gyrus), one frontal area activated only in SeqN and a bilateral temporal inferior focus activated in SimN task were chosen as ROIs. The pattern of activation for sequential and simultaneous numerosity processing was significantly correlated across voxels in the two conjunction ROIs (right IPS: $r=.5353$, $t_{14}=7.696$, $p<.001$; right precentral gyrus: $r=.4587$, $t_{14}=7.313$, $p<.001$) and slightly correlated in the frontal gyrus ($r=.174$, $t_{14}=2.188$, $p<.05$). Conversely, correlations in the left and right temporal gyri were not significant (left temporal: $r=.0533$, $t_{14}=0.7$, $p>.4$; right temporal: $r=.1827$, $t_{14}=2.028$, $p>.05$). Direct comparisons between ROI correlations using paired *t*-tests showed significant differences between the right IPS and the right temporal gyrus or the right frontal gyrus (respectively, $t_{14}=3.064$, $p<.01$;

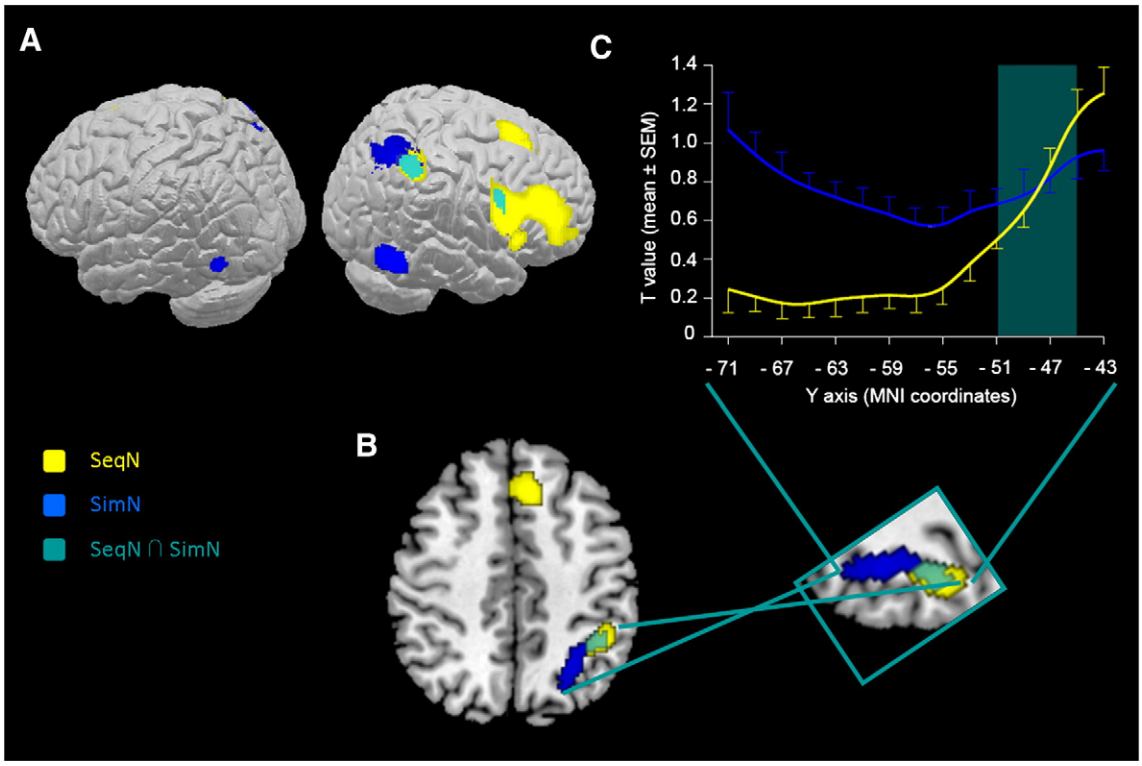

Fig. 3. (A) Brain regions activated specifically and jointly in the two experimental tasks (i.e., SimN and SeqN; at a corrected threshold : $p<.05$). (B) The overlay of colors shows the extent of the ROI in the right IPS (maximum $y=-43$; minimum $y=-71$). (C) Within this ROI, an anterior-to-posterior index was calculated by averaging the contrast-weighted *t*-values (experimental *minus* reference tasks) along the medial-to-lateral (*x* axis) and superior-to-inferior (*z* axis) dimensions, within the range of −43 to −71 on the *y* axis in stereotactic space. The results of this analysis are plotted in the panel for SeqN and SimN tasks respectively. Error bars represent the standard error of the mean for contrast-weighted *t*-values, averaged along the *x* and *z* axes.

$t_{14}=3.482$, $p<.005$), and also between the right precentral gyrus and the right temporal gyrus or the right frontal gyrus (respectively, $t_{14}=4.653$, $p<.001$; $t_{14}=2.872$, $p<.02$), indicating that the positive correlations observed in the right IPS and in the right precentral gyrus are not an artifact.

Finally, the averaged *t*-values along the anterior-to-posterior axis for sequential and simultaneous numerosity were not significantly different for coordinates between −45 and −49 on *y* axis (all *p*-values>.05).

Discussion

The parietal cortices have been shown to underlie a notation- and modality-independent representation of numerical quantity (Dehaene et al., 1998; Piazza et al., 2006, 2007; for a different view, see Cohen Kadosh and Walsh, 2009). Most studies investigating visual nonsymbolic numerosity processing used simultaneous material; few used sequential material. Therefore, although neurons that respond to numerosity irrespective of the presentation mode have been identified in monkeys (Nieder et al., 2006), whether or not the two modes of presenting numerosity dissociate or overlap totally or partially in humans has not yet been directly assessed. In the present fMRI study, participants were asked to categorize the numerosity of linear arrays of dots (simultaneous mode of presentation) or of sequences of flashed dots (sequential mode of presentation).

At the behavioral level, the results showed that the two experimental tasks were globally of similar complexity, with performance being equally accurate in the two presentation modes. This guarantees that the activations observed do not simply stem from differences in difficulty demand across tasks. Although their RLs had been equated in a pilot study, the SimN task was performed faster than the SeqN task during the fMRI session. This could reflect a greater recruitment of working memory and/or attentional tracking during the SeqN task. Moreover, the experimental tasks turned out to be more time consuming and more error prone overall than their reference tasks; again, this had not been observed in pilot studies with more participants and stimuli.

Mode-dependent numerosity processes

For simultaneously-presented numerosities, our results showed a bilateral involvement of parietal and frontal areas, predominantly in the right hemisphere. Bilateral activation of the IPS has been reported consistently in fMRI studies in numerosity comparison tasks (Ansari and Dhital, 2006; Leroux et al., 2009) and in adaptation paradigms (Cantlon et al., 2006; Piazza et al., 2004, 2007). We recently observed a similar fronto-parietal network of activation using the same material but in a different task (comparison of two linear arrays of dots; Dormal and Pesenti, 2009), which ensures that the IPS is involved in core aspects of numerosity processing, whatever the task. The parietal cluster activated specifically by simultaneous numerosity included the posterior part of the IPS and corresponded to the human homologue of lateral intraparietal (LIP) as previously reported (Koyama et al., 2004; Sereno et al., 2001; Simon et al., 2002). When contrasting directly the two experimental tasks, a set of left posterior parietal areas was activated during the SimN task, most probably reflecting visual complexity and visuo-spatial processing of stimuli extending in space (Corbetta, 1998; Grill-Spector et al., 1999).

Most interestingly, sequentially presented numerosity processing was found to activate the right IPS in the present study. A strictly right-lateralized activation of parietal regions including the IPS was reported previously when participants had to explicitly compare sequentially presented temporal stimuli, using visual (sequences of

squares) or auditory (sequences of tones) modalities (Piazza et al., 2006; Table SI). This right-lateralized activity in response to sequentially presented material may reflect involvement of a system that allows the serial position of each item in a sequence to be followed. Such a mechanism was shown to be recruited by the enumeration of sequentially in contrast to simultaneously-presented numerosities (Leroux et al., 2006; Nieder et al., 2006; Piazza et al., 2006), and might correspond to the accumulator stage postulated in computational models of number processing (Meck and Church, 1983; Nieder et al., 2006; Verguts and Fias, 2004). In line with this latter assumption, although the accumulation of relevant information preferentially involved LIP neurons in monkeys (Mazurek et al., 2003; Roitman and Shadlen, 2002; Roitman et al., 2007), it has been observed in the right IPS in humans (Belin et al., 2002; Coull and Frith, 1998; Coull et al., 2003). The right inferior frontal gyrus was found more activated with sequential than simultaneous presentation, a result often reported in time measurement tasks (for a review, see Lewis and Miall, 2003) and specifically when participants had to orient their attention to temporal features (Coull et al., 2000, 2003).

One may of course wonder to what extent these mode-dependent areas can be attributed to the coding of numerosity rather than to non-numerical processes. Although we cannot totally exclude the possibility that some activations reflect unspecific processes, we believe that they can be considered as numerosity-related quite confidently. The reason stems from the very concept of numerosity extraction. By essence, space processing (e.g., distinguishing stimuli from the background by moving the attentional focus over space or any other figure-background discrimination process) and duration processing (e.g., identifying the beginning and the end of an event over time) are necessary to the process of extracting numerosity from simultaneous and sequential stimuli, respectively. Although space and time can of course be processed to support non-numerical functions, they are intrinsically related to numerosity extraction in the present cases and should therefore be considered as reflecting critical steps of numerosity processing.

Mode-independent numerosity processes

The conjunction of the two categorization tasks showed that the central part of the right IPS was activated by both simultaneous and sequential stimuli, and it may thus correspond to the anatomical locus of a mode-independent numerosity representation. It is worth noting that using simultaneous and sequential material allowed us to isolate a core numerical representation independent of spatial or temporal processing. Comparable results were indirectly suggested in Castelli et al.'s (2006) study in which the IPS was activated more when comparing discrete numerosities than continuous quantities, both in time and in space. According to computational models of numerosity representations (Dehaene and Changeux, 1993; Verguts and Fias, 2004), these mode-independent activations could underlie the number-selective coding step localized in the VIP in monkeys (Nieder and Miller, 2004) and in the anterior part of the IPS in humans (Cantlon et al., 2006; Piazza et al., 2004, 2007). The neural code in VIP responding to auditory as well as to visual numerosity seemed to be implicated either for sequential or simultaneous presented numerosity. Indeed, the existence of a mode-independent numerosity representation is also supported by a neuronal recording study in which monkeys compared sequential and simultaneous numerosities (Nieder et al., 2006). Distinct populations of neurons inside the IPS were engaged in temporal and in spatial enumeration processes, and in a final convergence step, irrespective of whether stimuli were presented sequentially or simultaneously. In the present study, the right IPS activation observed in both categorization tasks may correspond to the human homologous area of this specific neuronal population in monkeys.

While the contribution of the right IPS to numerosity processing has been investigated extensively, the involvement of the right precentral gyrus has received little attention. Because both areas are also involved in the control of hand movements, we have argued that their contribution may actually reflect the use of hands and fingers to keep track of numerosity estimates (Andres et al., 2008a,b; Pesenti et al., 2000). This hypothesis is supported by the finding that numerosity processing increases corticospinal activity in the hand motor circuits, irrespective of the mode of presentation (Andres et al., 2007), and by various behavioral (Andres et al., 2008c; Badets et al., 2007; Badets and Pesenti, 2010; Lindemann et al., 2007), TMS and neuroimaging results (Pesenti et al., 2000; Sato et al., 2007), although increased activity was generally found in the left hemisphere presumably because the task involved counting rather than estimation (Piazza et al., 2006). It is worth noting that the involvement of hand motor circuits may be more important for processing sequential numerosities, as our results showed that activations in this condition extended anteriorly in the IPS, close to a motor-related area where number-selective neurons have been recorded while monkeys performed a given number of sequential arm movements (Sawamura et al., 2005). Due to the limited spatial resolution of fMRI compared to the invasive electrophysiological methods used in monkeys, and to the fact that coactivation of cerebral areas does not necessarily imply a common neural code but may simply stem from the activation of distinct intermingled neural populations (Cohen Kadosh et al., 2005; Pinel et al., 2004), these findings must however be interpreted with caution. The multi-voxel correlation analysis helped clarifying whether the overlapping activations were due to inter-individual averaging and smoothing or to a true functional relationship. A high correlation was observed at the best available resolution between sequential and simultaneous tasks in the right IPS and the right precentral gyrus. Only a weak correlation was observed for the frontal gyrus, whereas no correlation was observed in bilateral temporal areas, which were considered as mode-dependent regions based on direct contrasts in the whole-brain analysis. These results support the idea of a functionally relevant role of the right IPS and the right precentral gyrus in numerosity processing, independent of the presentation mode.

It has recently been proposed that the posterior part of the IPS could correspond to a number-sensitive coding system (i.e., tuned as a function of the number of elements) extracting an intermediate code from the stimulus and sending it to the anterior part of the IPS corresponding to a number-selective coding system (i.e., tuned to a preferred numerosity) in a hierarchical processing of numerosity information (Santens et al., 2010). We extend this proposal by showing in an exploratory analysis a different spatial distribution of the number-sensitive IPS activations as a function of the mode of presentation: whereas simultaneous numerosity processing involved a more extended dorsal and posterior part of the IPS (between −51 and −71 in the *y* coordinates axis), sequential presentation activated a more anterior part (between −43 and −45 in the *y* coordinates axis). Whether such a spatial organization of mode-dependent areas is also present in the monkey IPS is difficult to assess because, in previous studies, number-selective neurons were usually investigated randomly in recording areas centered on a limited portion of the IPS (e.g., Nieder et al, 2006). However, in one electrophysiological study where the recorded neurons were sampled over large territories of the superior and inferior parietal lobules (Sawamura et al., 2005), performing a given number of sequential arm movements was found to tune number-selective neurons in the anterior bank of the IPS, which is compatible with our finding that sequential numerosities activate the most anterior part of the IPS. Finally, electrophysiological studies in monkeys and fMRI studies in humans suggest that visuomotor functions are supported by the anterior part of the IPS, whereas the posterior part would be responsible for visuo-spatial processing (Grefkes and Fink, 2005; Simon et al., 2002). If confirmed, such a functional organization suggests that posterior IPS areas would contribute to processing simultaneous numerosities given their specialization for space processing, whereas motor-related areas in the

anterior IPS would contribute to keeping track of sequential events while processing numerosity in time.

It is worth noting that the proposal of Santens et al. (2010) concerned the left IPS, whereas the anterior-to-posterior gradient we describe was revealed by the post-hoc examination of the activations observed in the right IPS. Moreover, in contrast to previous studies suggesting that parietal regions of both hemispheres implement a nonsymbolic numerosity representation (Cantlon et al., 2006; Piazza et al., 2004, 2007), a predominantly right parietal activation was observed in the present study in both numerosity categorization tasks, only small left parietal foci being observed at an uncorrected threshold in the SimN task. All right parietal activations reported in previous studies were spatially close to the present peak (mean Euclidean distance = 12.7 ± 5.29 mm; Table SI) and were all situated along the IPS (Fig. S1). Interestingly, the left IPS activations were only observed with simultaneous numerosities, not with sequential numerosities. The present results support a right hemispheric dominance for nonsymbolic numerosity processing, as suggested in neuropsychological studies reporting deficits in dot estimation more frequently after right than after left parietal damage (Warrington and James, 1967), whereas preserved nonsymbolic numerosity abilities but impaired symbolic number processing were observed in a patient with a left parietal lesion (Polk et al., 2001). The superiority of the right hemisphere in nonsymbolic numerosity estimation was also demonstrated in healthy individuals in tachistoscopic dot enumeration tasks (Kimura, 1966; McGlone and Davidson, 1973; Young and Bion, 1979). Indeed, when children (from 3 years old) and adults were asked to quantify a collection of dots presented briefly in their left or right visual hemifield, an overall left visual hemifield superiority was observed both for accuracy and response latencies. However, TMS impaired dot comparison after left but not after right IPS stimulation (Cappelletti et al., 2007; Dormal et al., 2008). How can these TMS results be reconciled with the present findings? The reason for the apparent discrepancy may be the greater variability in right IPS activation foci. Fig. S1 shows the left and right IPS foci observed in studies that specifically investigated the estimation of nonsymbolic numerosity, displayed on a standard template. The left IPS foci appear much closer to each other than the right IPS foci (see also Table SI). Given this greater right-sided variability, the probability that TMS was actually applied to the critical area at an individual level may be smaller for the right than for the left IPS, hence little or no overall effect of TMS after right IPS stimulation.

General processes involved in numerosity extraction

Finally, although probably not specific to numerosity processing, the frontal activations observed bilaterally in both tasks likely reflect attentional control, as already suggested in previous studies on quantifying dots in the same range of numerosities (Sathian et al., 1999). They may also be linked to the fact that there was a greater demand on working memory in the experimental tasks compared to reference tasks. Indeed, participants may have encoded each simultaneous or sequential numerosity, maintained this information active in working memory, and then compared it with the stored "few" and "many" standard. It is plausible that the working memory load in the color reference tasks was lighter. This difference in cognitive recruitment was observed in the behavioral results: experimental tasks were more time consuming and more prone to error than their reference tasks. Moreover, direct contrast between the two experimental tasks revealed a stronger activation of the right frontal gyrus during SeqN task, possibly corresponding to a larger solicitation of working memory and a more important attentional demand, also reflected in the difference of latencies observed between the two tasks in the behavioral results. Assumption regarding which frontal focus of activation would be associated with stronger reliance on working memory is consistent with studies showing dorsolateral and ventrolateral frontal activation during the retention period in several visual memory tasks (for a review, Smith and Jonides, 1999). Both of these possibilities emphasize the role of the prefrontal cortex in temporal processing, whether attentional or mnemonic in nature (Coull et al., 2003).

In line with this, one may object that working memory demands or task complexity also contributed to the pattern of IPS activation we observed as this activation has previously shown some modulation as a function of task difficulty (Göbel et al., 2004). However, the fact that very similar IPS activations are observed in the absence of an explicit task during passive numerosity changes (Ansari et al., 2006) suggests that response-selection requirements and task difficulty cannot be the only sources of IPS activation. This, in turn, makes the possibility that task complexity contributed to the pattern of results we observed in the IPS little plausible. Moreover, it is worth noting that the two presentation modes did not differ as concerns error rate, which also speaks against a mere interpretation in terms of difficulty.

In conclusion, our results reveal, for the first time, that the right IPS and the right precentral gyrus are activated by the estimation of nonsymbolic numerosities whatever their mode of presentation. The functional relevance of the overlapping activation, demonstrated by the correlation analysis, thus supports the existence of a mode-independent nonsymbolic numerosity representation system in the human parietal cortex and in the precentral gyrus.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.04.254.

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