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Mapping subcomponents of numerical cognition in relation to functional and anatomical landmarks of human parietal cortex

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ABSTRACT

Human functional imaging has identified the middle part of the intraparietal sulcus (IPS) as an important brain substrate for different types of numerical tasks. This area is often equated with the macaque ventral intraparietal area (VIP) where neuronal selectivity for non-symbolic numerical stimuli (sets of items) is found. However, the low spatial resolution and whole-brain averaging analysis performed in most fMRI studies limit the extent to which an exact correspondence of activations in different numerical tasks with specific sub-regions of the IPS can be established. Here we acquired high-resolution 7T fMRI data in a group of human adults and related the activations in several numerical contrasts (implying different numerical stimuli and tasks) to anatomical and functional landmarks on the cortical surface. Our results reveal a functional heterogeneity within human intraparietal cortex where the retinotopic visual field maps in superior/medial parts of the IPS and superior parietal gyrus respond preferentially to the visual processing of concrete sets of items (over single Arabic numerals), whereas lateral/inferior parts of the IPS are predominantly recruited during numerical operations such as calculation and quantitative comparison. Since calculation and comparison-related activity fell mainly outside the retinotopic visual field maps considered the human functional equivalent of the monkey VIP/LIP complex, the areas most activated during such numerical operations in humans are likely different from VIP.

1. Introduction

The human posterior parietal cortex, especially within and around the horizontal intraparietal sulcus (HIPS), is known to play a key role in numerical cognition, being recruited by a variety of diverse tasks involving numerical processing (Dehaene et al., 2003; Hubbard et al., 2005; Piazza and Eger, 2016; Eger, 2016; Knops, 2017).

FMRI studies provided evidence for a rough co-localization of activity during calculation and more basic number related tasks: areas within and around HIPS were found to be overall activated during approximate and exact calculation (Dehaene, 1999; Knops et al., 2009; Pinel and Dehaene, 2010; Pinel et al., 2007; Simon et al., 2002), as well as during numerical comparisons, where their BOLD signal was moreover modulated by the numerical distance of the compared numbers (Pinel et al., 2001, 2004; Ansari et al., 2006). A common set of IPS regions were found activated when solving both non-symbolic and symbolic additions compared to visually and difficulty matched control tasks (Bugden et al., 2019). Independent of the execution of such numerical operations, enhanced activity for numbers as opposed to letters or colors was also to a lesser extent measured in HIPS during an orthogonal target detection task (Eger et al., 2003). Moreover, parietal regions were reported to habituate to repeated presentation of the same numerical quantity and show numerical distance-dependent recovery of activity for deviant numbers (Piazza et al., 2004; Cantlon et al., 2006) to some extent even across formats (Piazza et al., 2007; Vogel et al., 2017), to encode numerical quantity in multi-voxel patterns of evoked activity (Borghesani et al., 2019; Bulthé et al., 2014; Castaldi et al., 2016, Castaldi et al., 2019; Cavdaroglu and Knops, 2018; Damarla and Just, 2013; Eger et al., 2009, 2015; Lasne et al., 2019) and to contain topographically organized numerosity maps (Harvey et al., 2013; Harvey and Dumoulin, 2017a,b).

Recently, two meta-analyses quantified the degree of overlap of the parietal activations elicited by a large range of numerical tasks and concluded that the same regions are recruited, namely the inferior and superior parietal lobules (IPL and SPL) which delimit the intraparietal sulcus (IPS), during calculation and numerical tasks that were unrelated to arithmetics, both in adults (Arsalidou and Taylor, 2011) and in children (Arsalidou et al., 2018).

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FMRI studies in developmental dyscalculia showed abnormal activations of, among others, the mid-posterior parietal cortex during symbolic (Mussolin et al., 2010) and non-symbolic (Bulthé et al., 2019; Kaufmann et al., 2009a; Price et al., 2007) numerical comparisons, ordinality judgements (Kaufmann et al., 2009b), approximate calculation (Kucian et al., 2006) or simple arithmetical verification (Iuculano et al., 2015; Rosenberg-Lee et al., 2015) in dyscalculic children with respect to controls. While some studies found hypoactivation of the IPS in DD children (e.g. Price et al., 2007), others found hyperactivation of this region which normalized after short term math tutoring (Iuculano et al., 2015). Moreover, a meta-analysis identified the IPS as one of the areas consistently differing between individuals with and without dyscalculia during diverse number processing tasks (Kaufmann et al., 2011).

Thus, overall, at least when considered at a coarse spatial scale, a large body of imaging work in humans suggests the existence of a neuronal substrate supporting a wide range of numerical functions (including different tasks and numerical formats) within the same general areas, which is altered in subjects with impaired numerical skills. Nevertheless, there are also reports of format-specific responses (see Sokolowski et al., 2017 for a recent metanalysis), which may suggest a subregional specialization within parietal cortex. For example, during number comparison tasks, activity in the IPS was higher for non-symbolic with respect to symbolic numbers, while the reverse contrast elicited activation in the angular gyrus (Holloway et al., 2010) or the temporal parietal junction (He et al., 2014). Moreover, topographically organized maps were found only for non-symbolic, but not for symbolic numbers (Harvey et al., 2013).

However, what are the more precise neuroanatomical substrates or functional subregions of intraparietal cortex responsive to the heterogeneity of tasks and stimuli used to investigate numerical cognition, remains insufficiently understood. One influential review article made an effort in this direction, and described the location of numerical functions within the context of the more general functional organization of intraparietal cortex by comparing human and non-human primate findings (Hubbard et al., 2005). Electrophysiological studies in macaque monkeys have recorded numerical responses of single neurons, which distinguish between different numbers of items presented, from ventral (VIP) and lateral (LIP) intraparietal areas in macaques (Nieder et al., 2006; Roitman et al., 2007). Hubbard et al. noted that in humans numerical processing-related activation foci (for estimation, comparison and simple arithmetic) were found in close spatial proximity to activations elicited by visuo-tactile multisensory, grasping and saccadic eye movement tasks, tasks that in monkeys activate areas VIP, AIP and LIP (Bremmer et al., 2001; Sereno et al., 2001; Simon et al., 2002). Based on these colocalizations and overall similarities of the spatial arrangement of the intraparietal sub-regions, the brain regions activated for numerical tasks in humans have come to be considered the equivalent of macaque VIP (and to a lesser extent, LIP). However, it is important to note that the numerical responses considered here in humans (mostly including the execution of numerical operations) were quite different from the ones investigated by macaque neurophysiology (preferential responsiveness to non-symbolic sample numbers during a delayed comparison/match-to-sample task). It still remains to be confirmed whether at a more fine-grained level of anatomical localization of activations, these different aspects of numerical processing recruit identical sub-regions in humans, and what is their precise substrate in terms of known functionally defined areas.

One important set of functional markers underlying the organization of intraparietal cortex is a series of retinotopic visuals field maps (Arcaro et al., 2011; Kastner et al., 2017; Konen and Kastner, 2008; Sereno et al., 2001; Silver et al., 2005; Swisher et al., 2007) which can be identified by means of phase-encoded or population receptive field mapping. In human IPS, six such field maps have been identified from its most posterior to most anterior subparts, labelled IPS0 to IPS5 (Konen and Kastner, 2008; Silver et al., 2005; Swisher et al., 2007). Activity in the retinotopic visual field maps was shown to increase during visual (Sheremata et al., 2018) and auditory (Michalka et al., 2016) working memory tasks, with activity being modulated by memory load (Sheremata et al., 2010). Activation patterns in these areas can represent specific features (e.g. orientation, Ester et al., 2015) and location (Sprague et al., 2014) of a remembered target. Transiently disrupting activity in these field maps, in particular in IPS2, was shown to affect accuracy of memory-guided saccades (Mackey and Curtis, 2017), similarly to what was observed in monkeys when selectively inactivating LIP (Li et al., 1999), where neurons discharging during the delay period of memory-guided saccades were found (Gnadt and Andersen, 1988). In humans the responses across intraparietal visual field map sub-regions change from IPS1/2, located in the posterior/medial parietal cortex, preferring saccadic eye movements, to IPS 3/4/5 preferring smooth pursuit eye movements (Konen and Kastner, 2008), located more anteriorly and laterally and roughly overlapping with areas responsive to visuo-tactile stimulation (Bremmer et al., 2001; Sereno and Huang, 2006). These functional properties mirror those observed in monkeys: neurons in macaque LIP respond to saccadic eye movements (Andersen et al., 1990), whereas the majority of the neurons in VIP prefer smooth pursuit eye-movements (Schlack et al., 2003) and multisensory motion (Avillac et al., 2005). Based on these similarities in the relative anatomical localization and functional response properties of individual areas, the visuals field maps in human cortex have been proposed to constitute a plausible human equivalent of the macaque LIP/VIP complex (Kastner et al., 2017; Konen and Kastner, 2008).

Topographic numerosity maps in human cortex, where individual voxels respond preferentially to different numbers of visual items but not symbolic numbers (Harvey et al., 2013), were found to roughly overlap with the area containing retinotopic field maps. In a recent review article, Harvey et al. (2017) noted that the numerosity maps in humans were located superior/medially in the superior parietal lobule, rather than in the fundus of the IPS where activations for numerical comparison and calculation tasks usually appear to be centered. Based on these observations, they proposed that the neuronal circuits supporting basic physical quantity processing and numerical tasks, as for example comparison, may be distinct, and questioned the often-assumed correspondence between number processing related activations in human HIPS and macaque VIP. However, this proposal was based on a review of the local maxima reported across multiple studies in different groups of subjects, where data were in addition acquired at different spatial resolutions and field strengths. Group analyses in whole brain space are likely to insufficiently represent the precise cortical location of activation foci. They depend on the inter-subject variability of every given sample of subjects from which they are derived, and projections of such maxima from different studies onto an average surface could reflect the different samples used, rather than true differences in activated anatomical location.

In the work reported here, we explicitly tested for the first time within the same group of human subjects the idea that there exists a regional specialization within human intraparietal cortex with separate subregions recruited during different aspects of numerical processing, such as the visual processing of concrete sets of items or digits on the one hand, and different numerical operations (comparison and mental calculation), on the other hand. For a more precise anatomical localization of activations, we exploited the enhanced resolution of ultra-high field (7T) fMRI in combination with extraction of the cortical surface in each subject. We further related the observed activations on the cortical surface to anatomical and functional markers derived from two atlases: one based on identifying the major sulci and gyri (Destrieux et al., 2010), and the other based on visual topography, corresponding to the visual field maps IPS0–5 mentioned above (Wang et al., 2015). Given the evidence in the literature for a functional correspondence between the series of topographic maps and regions LIP and VIP, we used these field maps here as a means to identifying the likely human equivalent of the macaque LIP/VIP complex independently of a numerical task. This independent definition then allows us to test whether a preferential recruitment of the human equivalent of the LIP/VIP complex holds for all or just some of the number-related functions investigated here, thereby advancing the understanding of how numerical processing fits into the more general functional architecture of human parietal cortex.

2. Methods

2.1. Subjects, data acquisition procedure and fMRI paradigms

Sixteen healthy adult volunteers (seven males and nine females, mean age 25±2 years) with normal or corrected vision participated in the study. The experiment was approved by the regional ethical committee (Hôpital de Bicêtre, France) and undertaken with the understanding and written consent of each subject.

A SIEMENS MAGNETOM 7T scanner with head gradient insert (Gmax 80mT/m and slew rate 333T/m/s) and adapted 32-channel head coil (Nova Medical, Wilmington, MA, USA) was used to collect functional images as T2*-weighted Fat-Saturation echo-planar image (EPI) volumes with 1.3 mm isotropic voxels using a multi-band sequence (Moeller et al., 2010) (https://www.cmrr.umn.edu/multiband/, multiband [MB] = 2, GRAPPA acceleration with [IPAT] = 2, partial Fourier [PF] = 6/8, matrix = 150 × 150, repetition time [TR] = 1.75 s, echo time [TE] = 21 ms, echo spacing [ES] = 0.74 ms, flip angle [FA] = 65°, bandwidth [BW] = 1516 Hz/px, phase-encode direction anterior to posterior). Calibration preparation was done using Gradient Recalled Echo (GRE) data. Fifty transversal slices covering the parietal and frontal cortex were obtained in ascending interleaved order. At the beginning of the scanning session, two single volumes were acquired with the parameters listed above but with opposite phase encode directions. The single-band reference images of these two initial volumes were used for distortion correction (see Data Analysis).

Anatomical images (T1-weighted) were acquired at 1 mm isotropic resolution using an MP2RAGE sequence (GRAPPA acceleration with [IPAT] = 3, partial Fourier [PF] = 6/8, matrix = 256 × 256, repetition time [TR] = 5 s, echo time [TE] = 2.82 ms, time of inversion [TI] 1/2 = 800/2700 ms, flip angle [FA] 1/2 = 4°/5°, bandwidth [BW] = 240 Hz/px). A radiofrequency absorbent jacket (Accusorb MRI, MWT Materials Inc., Passaic, NJ, USA) was used to minimize the so-called "third-arm" or "shoulder" artifacts due to regions where the head gradient is unable to unambiguously spatially encode the image (Wald et al., 2005). The participants' head was stabilized by padding and tape to prevent excessive movements. They saw the visual stimuli back-projected onto a translucent screen through a mirror attached to the head coil, and responses were recorded via two buttons held in their left and right hands.

In different runs participants performed either a delayed number comparison task, or a mental arithmetic task. In the delayed number comparison task (Fig. 1A), different numbers presented either in symbolic or non-symbolic formats were presented in random positions inside a white circular region subtending ~7° of visual angle at the center of the screen. Black Arabic digits and numbers of items were shown with two different fonts (Arial Rounded MT versus Times New Roman for symbolic numbers) and shapes (circles versus triangles for non-symbolic numbers). The total surface area covered (number of black pixels) was approximately equated between all non-symbolic numbers (resulting in smaller items for larger numerosities) and symbols. The image RMS contrast was equivalent between formats (RMS contrast: non-symbolic = 0.24, symbolic = 0.24). Other visual features were not explicitly controlled. A post-hoc analysis of the visual features revealed that convex hull was larger for non-symbolic compared to symbolic stimuli (t(14)=155.9, $p<10^{-5}$), while the center of mass did not differ across formats (X-coordinates: non-symbolic = 200 ± 2, symbolic = 199 ± 3, t(14)=0.7, p = 0.5; Y-coordinates: non-symbolic = 200 ± 3, symbolic = 199 ± 3, t(14)=0.7, p = 0.5). Examples of all conditions are shown in Fig. 1B.

The delayed comparison task started with brief (200 ms) presentation of a sample stimulus. Participants had to attend to the numerical content of each stimulus and to hold this information in memory until the following stimulus was presented (after an SOA of 10.5 s). One second before the onset of the following trial the fixation cross color changed from gray to either red or green. When red, this marked a match trial: in that case participants had to compare the current stimulus with the previously seen one, and respond by pressing one of the two buttons held by their left or right hand depending on whether they judged the current stimulus as numerically larger or smaller than the previous one. On the contrary, if the fixation cross turned green, participants only had to update their memory with the new sample stimulus. Three different sample numbers (digits 3, 5 or 8 or the corresponding sets of items, see Fig. 1B for examples) were used and two possible match stimuli could appear in each case (2 and 5 for sample 3, 3 and 8 for sample 5, 5 and 13 for sample 8). The presentation format (non-symbolic vs symbolic) always differed between a given sample and match. Analyses of the behavioral data collected during scanning are reported in the supplementary material (Fig. S1). Each participant performed six 8.5 min long runs for the delayed number comparison paradigm. Each run contained six sample trials and two match trials (one smaller and one larger) per number and format.

In addition, all but one participant also performed a 4.9 min run with a mental arithmetic task (Fig. 1C and D) adapted from a previously published functional localizer study (Pinel and Dehaene, 2010; Pinel et al., 2007). One participant was not tested with this paradigm, due to a longer than usual preparation procedure at the beginning of the session and subsequent lack of time. In different blocks, participants either solved mental subtraction problems according to verbal instruction (as for example: "Calculez quinze moins sept" [Calculate fifteen minus seven], see Fig. 1C), with the first operand ranging from 10 to 19 and the second from 2 to 9, or read mathematics-unrelated sentences (as for example: "Il y a beaucoup de ponts à Paris" [There are many bridges in Paris], see Fig. 1D). Each one of six blocks for each condition contained ten sentences, which were written in white on a black background, and centrally presented on four successive screens (each shown for 250 ms) separated by a 100 ms interval within sentence and a 2700 ms interval at the end of each sentence). Each screen presented a maximum of three words. Calculation and reading blocks were interleaved with baseline periods consisting of an additional 4 s of blank screen.

Stimuli were presented under Matlab 9.0 using Cogent (http://www.vislab.ucl.ac.uk/cogent.php) or using E-Prime software.

(A) In a delayed number comparison task, sample and comparison stimuli were briefly shown (200 ms) in either non-symbolic (sets of items) or symbolic (Arabic digit) format. Participants were instructed to keep in memory the number seen in a given trial until the following trial appeared (after 10.5 s), and to perform a numerical comparison on occasional match trials, marked by a change in the fixation color. Participants were asked to judge whether the number displayed in the match trial was smaller or larger than the one seen in the previous sample trial. (B) Examples of sample stimuli. (C-D) During the mental arithmetic task, participants performed mental calculation (subtractions) according to written verbal instructions (C) or read math unrelated sentences (D).

3. Data analysis

Statistical parametric mapping software (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used to motion-correct the EPI images and to co-register them to the first single-band reference image. EPI images were corrected for distortions in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) in two steps: first we estimated a set of field coefficients with the topup function from the single-band reference images of the two initial volumes acquired with opposite phase encoding directions, and then we applied these to all the EPI images with the apply_topup function. Freesurfer 6.0 (https://surfer.nmr.mgh.harvard.edu/) was used to perform cortical

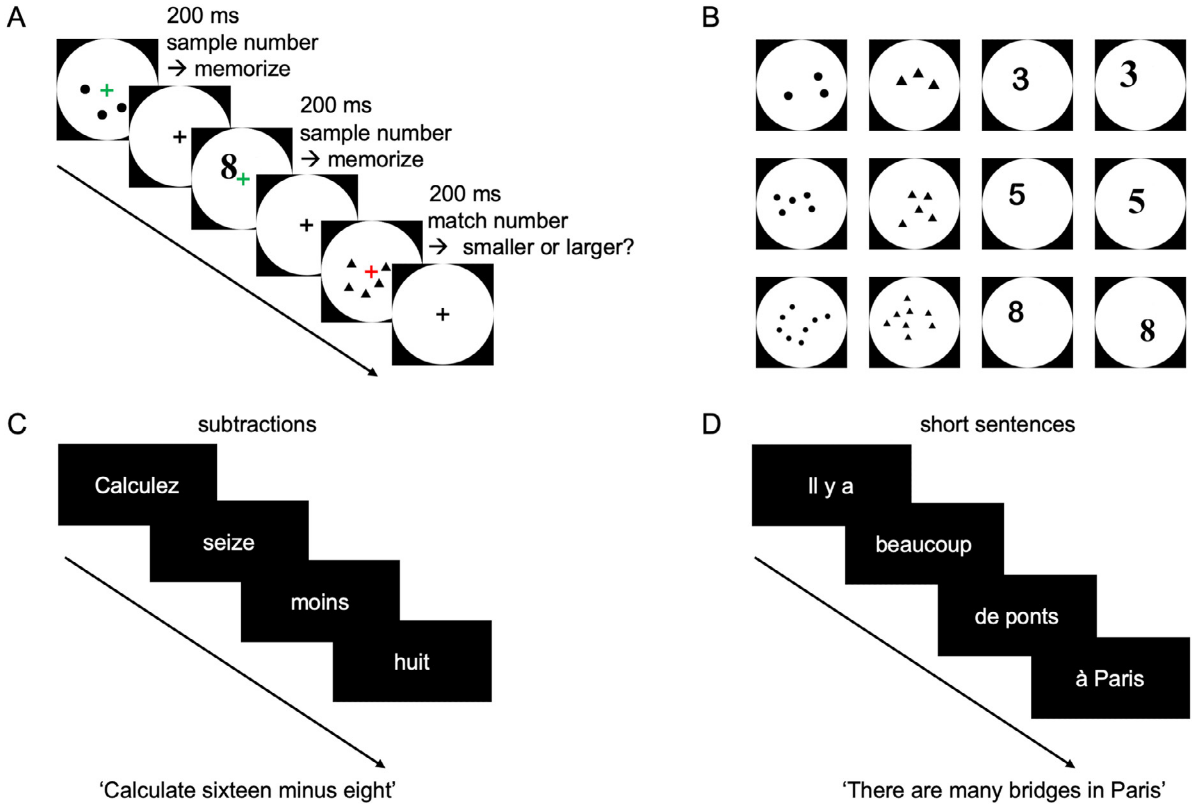

Fig. 1. Experimental paradigms.

surface reconstruction of the anatomical image and boundary based registration of the mean single-band reference image to each subject's anatomy.

The preprocessed EPI images (in subjects' native space) were entered into GLMs using SPM, for the delayed comparison task modeling separately 12 sample stimulus conditions (3 numbers x 2 formats x 2 stimulus sets [shapes/fonts in case of non-symbolic/symbolic format]) within each run and 4 match stimulus conditions (2 formats x 2 magnitudes [smaller vs larger than sample]) as stick functions (using the default of 0 duration for events) convolved with the standard hemodynamic response function. Only two regressors (calculation and reading) modeling the onset of each sentence with a duration of 3.5 s were included in the GLM for the mental arithmetic task. To account for serial auto-correlation, an AR(1) model was used and low-frequency signal drifts were removed by high-pass filtering the data with a cutoff of 128 s.

To identify the cortical areas preferentially involved in visual processing of concrete sets of items (over Arabic numerals), we contrasted the activation elicited by non-symbolic against symbolic sample stimulus conditions during the delayed number comparison task (contrast name: 'Non-symbolic > Symbolic'). To isolate the correlates of two different numerical operations (comparison and calculation), we contrasted (A) the activation elicited by all match stimulus conditions against all sample stimulus conditions (contrast name: 'Comparing > Viewing'), and (B) the activation elicited while participants performed mental subtractions against the activation elicited while reading mathematical unrelated sentences (contrast name: 'Calculation > Reading'). These three contrasts were first created in each single subject's volume space and then projected onto the surface with Freesurfer 6.0. Single subject's contrast maps were aligned to fsaverage and smoothed with a 3-mm (FWHM) Gaussian kernel. Finally, a random-effects group analysis was performed in the surface space. The resulting statistical maps were thresholded at $p<0.05$, corrected, using correction for multiple comparisons at cluster level (method based on Hagler et al., 2006) with cluster forming threshold $p<0.001$.

Individual subjects' statistical results were also projected onto their respective cortical surfaces to qualitatively appreciate the localization of activations elicited by the different contrasts with respect to the atlases-based region-of-interest. To quantify the degree of activation overlap between different pairs of contrasts at the individual subject level, and to test whether some contrasts overlapped more than others within the intraparietal cortex, we then performed receiver operating characteristics (ROC) analyses (Green and Swets, 1996), using a similar approach as Pinel et al. (2007). These analyses focused on the intraparietal and transverse parietal sulci as defined by the Destrieux et al. (2010) atlas as region of interest. Within this ROI, for each subject and each possible pairwise comparison between the three contrasts, the first contrast was thresholded (at $p<0.0001$, uncorrected), and considered the reference (or "ground-truth") against which the second contrast was compared. The threshold of the second contrast was varied between its lowest and highest t-values. Comparison of the second contrast against the first at each of these thresholds yielded hit rates (corresponding to the proportion of voxels above threshold in contrast 2 within the active voxels of contrast 1) and false alarm rates (corresponding to the proportion of voxels above threshold in contrast 2 within the non-active voxels of contrast 1), subsequently used to draw ROC curves. From the ROC curve based on the relation between hit and false alarm rates, the area under the curve (AUC) for each subject and contrast pair was computed. AUC can be considered a measure of activation overlap that is as far as possible independent of threshold. The difference in AUC across contrast pairs was then tested for significance across subjects with repeated measures ANOVAs.

As a complementary approach to single subject analysis, we compared the individual activation strength (as quantified by t-values) across different subregions of the intraparietal cortex. For each subject, we defined regions of interest from two surface based parcellation

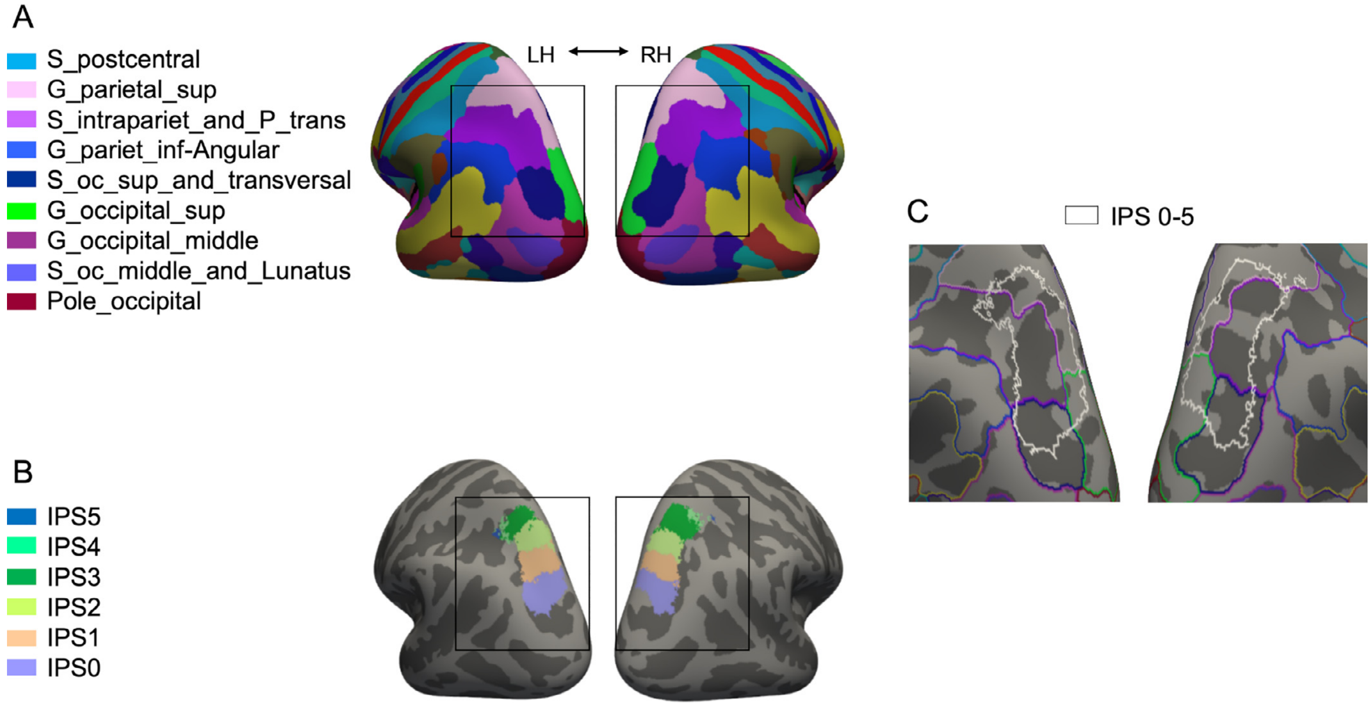

Fig. 2. Visualization of regions of interest.

schemes: one based on the Destrieux et al. (2010) atlas, which identifies the major sulci and gyri based on curvature estimates (Fig. 2A), and the other based on the Wang et al. (2015) atlas, which provides probabilistic maps of the retinotopic visual field maps, including those from IPS0 to IPS5 (Fig. 2B). All ROIs were created on the Freesurfer surface and projected back into each subject's volume space, where the left and right hemispheres were merged.

The parietal field maps IPS0 to IPS5 derived from the Wang et al. (2015) atlas were merged into one large ROI (we refer to this most comprehensive region of interest as either 'field map ROI' or 'IPS 0–5 complex'). As highlighted in Fig. 2C, the field map ROI (IPS 0–5 complex, white outline) partly overlaps with several gyri and sulci of the parietal cortex, including the Destrieux Atlas intraparietal and transverse parietal sulci (IPS) and the superior parietal gyrus (SPG), without fully matching any of them. We subdivided the region surrounding the fundus of the IPS into four ROIs roughly extending from lateral to medial, or inferior to superior parietal lobule: 1) Destrieux Atlas intraparietal sulcus exclusive of IPS0–5, 2) Destrieux Atlas intraparietal sulcus inclusive of IPS0–5, 3) Destrieux Atlas Superior Parietal Gyrus inclusive of IPS0–5, and 4) Destrieux Atlas Superior Parietal Gyrus exclusive of IPS0–5. For each subject, mean t-scores for the different contrasts were extracted from these four ROIs, as well as from the entire IPS0–5 complex, and more specific ROIs corresponding to its separate subparts: IPS0, IPS12 (merging IPS 1 and 2) and IPS345 (merging IPS 3, 4 and 5). As a measure of regionally specific contributions more independent of differences in overall activation strength across different contrasts, for each ROI and contrast, we also computed the difference between the mean t-scores measured inside and outside each ROI (i.e. in the rest of the parietal lobe, here defined by the union of the following Destrieux Atlas regions: Superior Parietal Gyrus, Angular Part of Inferior Parietal Gyrus, Supramarginal Part of Inferior Parietal Gyrus, Postcentral Sulcus, and Intraparietal Sulcus). Differences in signal strength across ROIs and contrasts were tested for significance with repeated measures ANOVAs.

(A) Freesurfer anatomical parcellation according to Destrieux et al. (2010) atlas and (B) field maps (IPS0 to IPS5) derived from the Wang et al. (2015) atlas are shown color-coded on the inflated template brain. The brain regions enclosed within the black rectangle are shown in more detail in (C) where regions defined by the two atlases in (A) and (B) are superimposed. The field map ROI (IPS0–5 complex, white outline) overlaps with the superior parietal gyrus ROI (SPG, pink outline), the intraparietal sulcus and transverse parietal sulci ROI (IPS, purple outline), the superior occipital sulcus and transverse occipital sulcus ROI (blue outline) and the superior occipital gyrus ROI (green outline).

4. Results

To identify brain regions preferentially recruited during different types of numerical processing, such as viewing and maintenance of either non-symbolic or symbolic numerical stimuli on the one hand, and operation as numerical comparison and calculation on the other hand, as a first step, we performed surface-based group analyses. Fig. 3 shows the main three different contrast maps displayed on the surface of a template brain in relation to the parcellations derived from the two atlases used.

Visual processing of sets of items compared to viewing Arabic digits preferentially activated both occipital-parietal and frontal regions (red activations for the 'Non-symbolic > Symbolic' map in Fig. 3A). More specifically, activations covered the superior occipital sulcus and transverse occipital sulcus, intraparietal sulcus and transverse parietal sulci (IPS), superior parietal gyrus (SPG), postcentral sulcus and precentral sulcus in the frontal cortex. Importantly, the parietal activations were mainly localized within the field map ROI (delimited by the white outlines in Fig. 3), covering the superior/medial portion of IPS and the inferior part of SPG. The reverse contrast showed that symbolic numbers elicited stronger activations than non-symbolic stimuli (blue activations in Fig. 3A) in the angular gyrus and superior temporal sulcus.

Explicitly performing a numerical comparison over mere viewing of sample stimuli most strongly activated regions in the inferior/lateral bank of IPS, outside the field map ROI ('Comparing > Viewing', Fig. 3B). Activations for this contrast spread also more anteriorly into the postcentral sulcus and gyrus, and the central and precentral sulci. Mental calculation over reading also activated inferior/lateral regions of IPS

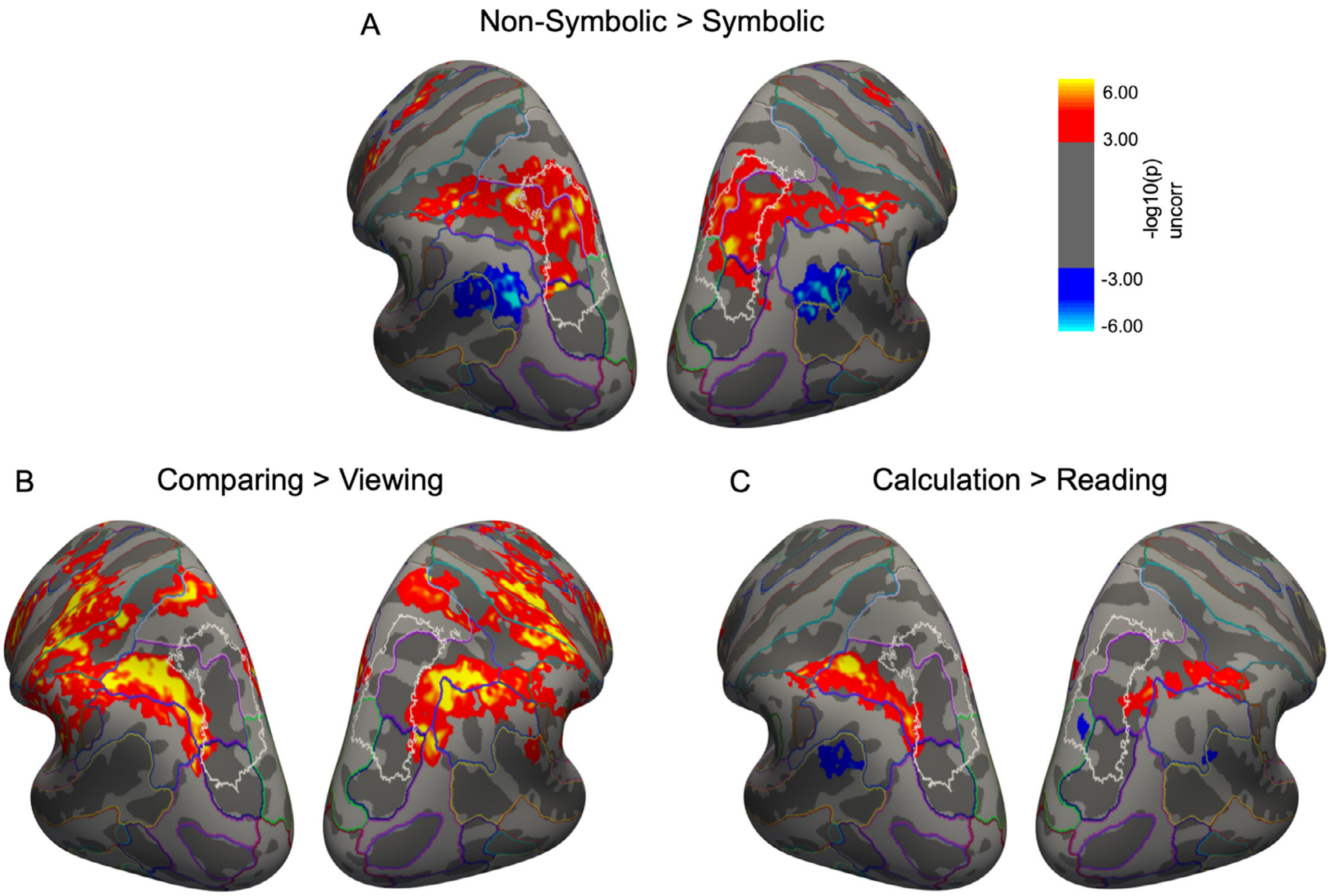

Fig. 3. Regions within the intraparietal cortex recruited for visual processing of concrete sets of items over Arabic numerals, numerical comparison and calculation – group maps.

(red activations for the ‘Calculation > Reading’ map in Fig. 3C), while the reverse contrast led to some minor activations in the superior temporal sulcus (blue activations in Fig. 3C).

Overall, the surface-based group analyses revealed that while all the different contrasts targeting different components of numerical processing activated areas within and around the IPS, different sub-regions within this larger area were activated predominantly as a function of the contrast: the medial/superior portion of the sulcus were most strongly recruited for mere viewing of non-symbolic over symbolic stimuli, whereas the most lateral/inferior regions of the sulcus were most strongly activated for numerical operations, i.e. during numerical comparison or calculation.

Activation maps from the surface-based random effects group analyses ($n = 15$), thresholded at $p<0.05$ corrected for multiple comparisons at cluster level with cluster forming threshold $p<0.001$. The color code is corresponding to voxel-level significance (i.e. each voxel included in the clusters surviving correction is displayed with its uncorrected significance value). (A) Activations for mere viewing of “Non-symbolic > Symbolic” stimuli occurred predominantly within the field map ROI, while the reverse contrast showed activations in angular gyrus and superior temporal sulcus. (B) Activations for “Comparing > Viewing” of numbers were more pronounced in the areas outside the field map ROI (in the intraparietal sulcus, inferiorly/laterally to the IPS0–5 complex). (C) Activations for “Calculation > Reading” were mainly found in regions outside the field map ROI, while activations for the reverse contrast occurred in superior temporal sulcus. The cluster summary table for each contrast is provided in Supplementary Table 1.

To further investigate in how far the organization of regional activations observed in the group analyses within sub-regions of intraparietal cortex was also evident at the level of individual subjects, we conducted further analyses at the individual subject level. Fig. 4A visualizes activations of three representative subjects on their corresponding cortical surfaces (for the other subjects see Figs. S2 and S3). The topological organization of activations in the parietal cortex observed in the group analysis is visible here also in individual subjects: the medial/superior sub-regions of IPS and the inferior portion of SPG, comprising the field map ROI, were activated during simple viewing of non-symbolic over symbolic stimuli while comparing numbers or performing mental calculation both elicited activations within more lateral/inferior sub-regions.

(A) For each subject, t-maps for each contrast are shown on the participants’ inflated surface, thresholded at $p<0.0001$, uncorrected. These individual subject maps indicate a similar localization of activations elicited by different contrasts as the one observed in the group analyses. The white outline represents the field map ROI (IPS 0–5 complex borders). Maps of the other subjects are shown in Figs. S2 and S3. (B) Activation overlap as quantified by receiver operating characteristics (ROC) analysis. ROC curves for all possible contrast pairs are shown for the exemplar subject 2 (S2, top panel, ROC curves for all subjects are shown in Fig. S4). Within each given contrast pair, the first contrast specifies the reference, and the second the test condition for the ROC analysis. The bar graph (bottom panel) shows the area under the ROC curve (AUC) averaged across subjects for all contrast pairs. Error bars represent the standard error of the mean.

To quantify the degree of activation overlap between different contrasts within the intraparietal region of interest, we performed receiver

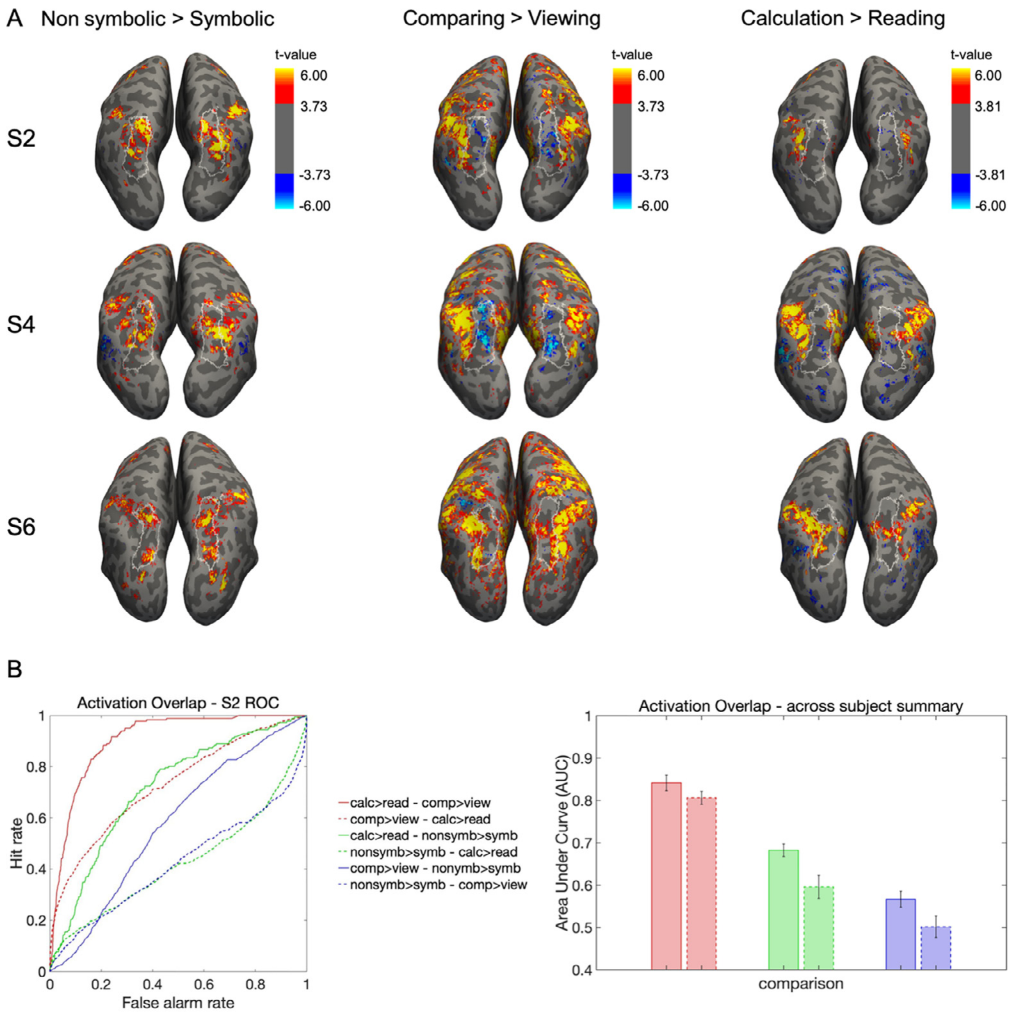

Fig. 4. Regions within the intraparietal cortex recruited for visual processing of concrete sets of items over Arabic numerals, numerical comparison and calculation - individual subjects' maps and activation overlap analysis.

operating characteristics (ROC) analyses for all possible contrast pairs and subjects (see Methods section for details). An example of the resulting ROC curves plotting hit rate against false alarm rate for one subject for all the different pairwise comparisons (where each given contrast could serve either as reference or test condition) as well as the resulting area under the ROC curve (AUC) averaged across subjects, are displayed in Fig. 4B. The AUC, which corresponds to a threshold independent measure of the overlap in activated voxels in the IPS, was most pronounced when the two contrasts in a pair corresponded both to numerical operations ("Calculation > Reading" and "Comparing > Viewing", plotted in red in Fig. 4B). It was lower when comparing each type of numerical operation contrast against the Non-symbolic > Symbolic contrast (plotted in green and blue in Fig. 4B).

AUC scores obtained for the different contrast pairs were entered into a two-way repeated measures ANOVA with comparison type (3 levels, corresponding to the three possible unique pairs between two of the three contrasts of interest) and direction (2 levels, reflecting the direction of the comparison, where each given contrast could serve either as reference or test condition, for example 'Calculation > Reading – Non-Symbolic > Symbolic' vs 'Non-Symbolic > Symbolic - Reading > Calculation') as factors. The ANOVA confirmed a highly significant main effect of comparison type (F(1.7,23.5)=60.7, $p<10^{-5}$). The AUC (and thus degree of activation overlap) was significantly higher when both contrasts in the pair corresponded to numerical operations (red conditions in Fig. 4B), compared to the situations where one contrast in the pair was 'Nonsymbolic > Symbolic' and the other either 'Calculation > Reading' (green conditions in Fig. 4B, F(1.0,14.0)=33.1, $p = 0.00005$) or 'Comparing > Viewing' (blue conditions in Fig. 4B, F(1.0,14.0)=192.3, $p<10^{-5}$). Although not expected, the ANOVA also revealed a significant interaction between comparison type and direction (F(1.9,26.5)=8.1, $p = 0.002$) on top of a main effect of direction (F(1.0,14.0)=37.1, $p = 0.00003$). As shown in Fig. 4B, the effect of direction is most pronounced for the second and third levels (green and blue conditions) of the comparison type factor, with AUC being higher when the reference condition is one of the two numerical operation contrasts and the test condition is 'Non-symbolic > Symbolic', compared to the reverse. This difference suggests that the voxels most activated for numerical operations are also recruited to some extent by the 'Non-symbolic > Symbolic' contrast, whereas the voxels most activated for the 'Non-symbolic > Symbolic' contrast are more specifically recruited only for that particular contrast.

The individual subject analyses reported so far quantified the relative degree of activation overlap between different contrast without explicitly considering in which sub-regions these activations occurred. Therefore, to provide some complementary information, we performed additional analyses comparing activations strength across several subparts of the intraparietal cortex. First, we focused these ROI analyses specifically on parts of anatomically defined IPS and SPG that either did or did not overlap with the entire field map ROI (IPS0–5 complex) (Fig. 5A). The IPS0–5 complex centrally overlapped with parts of both IPS and SPG which further extended laterally/inferiorly and medially/superiorly from the IPS0–5 complex, respectively. We therefore extracted the signal for the different contrasts (mean t-values across voxels for each individual subject) from four ROIs defined along a lateral-

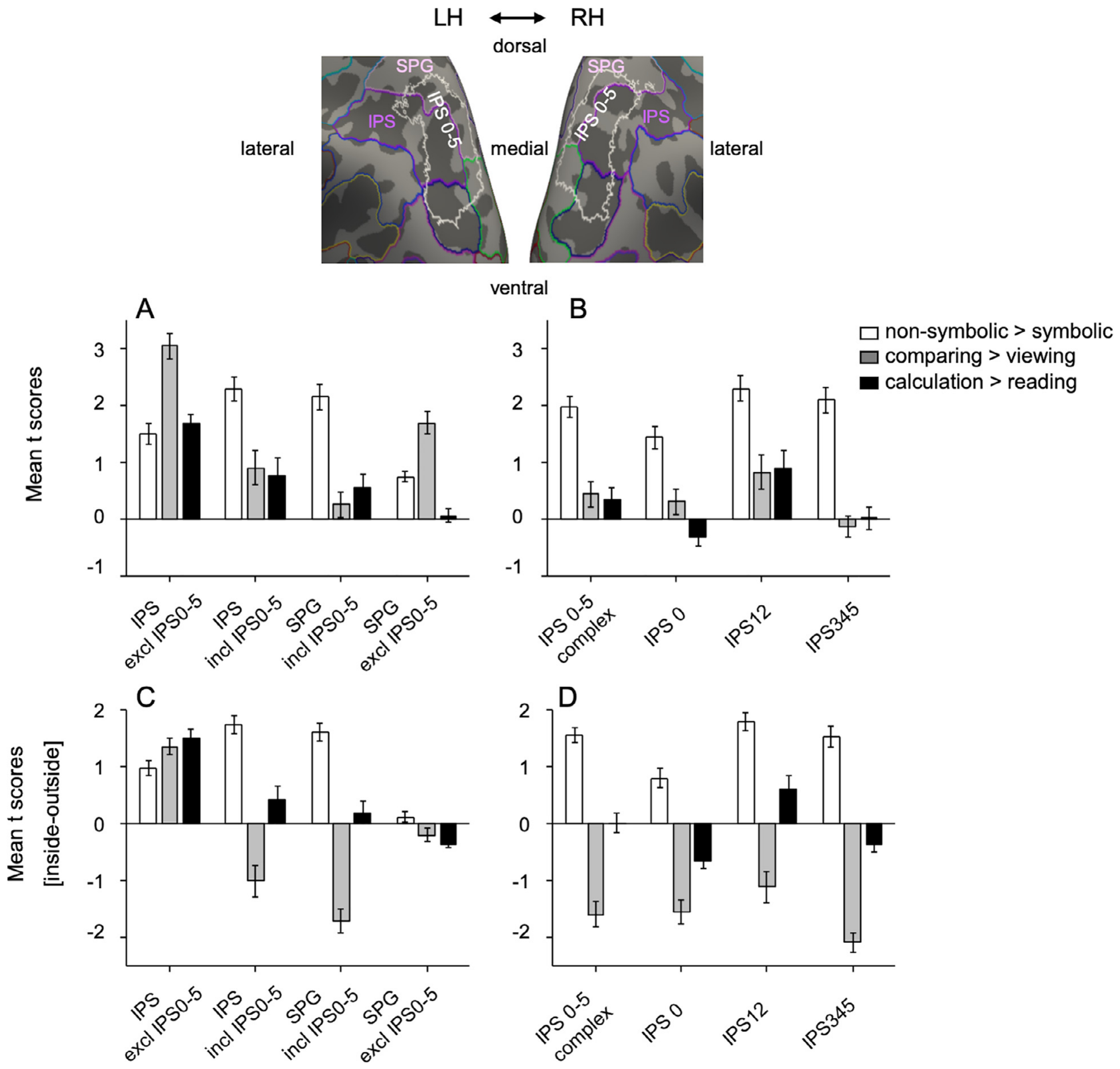

Fig. 5. Results of ROI analyses.

medial gradient. Specifically, moving from the most inferior/lateral to the most medial/superior part of the intraparietal region, we defined the first and second ROIs along IPS, excluding or including the IPS0–5 complex, respectively, then in the third and fourth ROIs the IPS 0–5 complex was included or excluded, respectively, from the ROIs defined along SPG.

Mean t-scores varied across the four ROIs depending on the contrast (Fig. 5A), as confirmed by the significant interaction between ROI and contrast (F(3.6,50.6)=45.6,$p<10^{-5}$). The mean t-scores for the contrast 'Non-symbolic > Symbolic' were significantly above zero in all four ROIs (all $p<10^{-5}$), however the signal intensity varied between regions (Fig. 5A, white bars): mean t-values became significantly higher when proceeding from the most lateral ROI in IPS, which did not include the IPS 0–5 complex, towards the more medial ROIs, which included the IPS 0–5 complex along IPS and SPG, respectively, and then significantly decreased again for the most medial ROI in SPG, in which the IPS 0–5 complex was excluded (post-hoc tests across ROIs: all significant at $p<0.0005$ at least, except for the difference between the two ROIs including the IPS 0–5 complex that was not statistically significant). On the contrary, the mean t-scores measured for the contrast 'Comparing > Viewing' followed an opposite trend, being highest whenever the IPS 0–5 complex was excluded from the ROI, i.e. for the most lateral ROI along IPS and the most medial ROI along SPG, and lowest for the IPS and SPG ROIs inclusive of the IPS0–5 complex (the latter not even being significantly different from zero, Fig. 5A, black bars, post-hoc tests across ROIs were all significant with $p = 0.01$ at least). Finally the mean t-scores for the contrast 'Calculation > Reading' were highest in the most lateral ROI defined along IPS, excluding the IPS 0–5 complex, and progressively and significantly lower in the more medial ROIs, reaching a value not significantly different from zero for the most medial ROI in SPG, excluding IPS 0–5 complex (Fig. 5A, gray bars, post-hoc tests for the most lateral vs the progressively more medial ROIs: $p = 0.003$, $p = 0.0002$, $p < 10^{-5}$).

To detect any potential additional specializations within the entire field map ROI, we also compared mean t-scores for smaller subparts of it (in particular IPS0, IPS12, and IPS 345) (Fig. 5B). The ANOVA showed a significant interaction between ROI and contrast (F(2.3,32.7)=5.5 $p = 0.007$). The values measured for the contrast 'Non-symbolic > Symbolic' were significantly above zero in all ROIs (all $p < 10^{-5}$), and significantly higher in IPS12 and IPS345 with respect to IPS0 (post-hoc tests across ROIs: significant at $p = 0.002$ at least). The mean t-scores measured for the contrasts 'Comparing > Viewing' and 'Calculation > Reading' were not significantly different from zero, except for IPS12 where nevertheless the t-scores for these contrasts were much lower than the ones measured for the contrast 'Non-symbolic > Symbolic' (post-hoc tests across tasks in IPS12: $p = 0.002$ and $p = 0.003$).

As an alternative measure of relative regional preference more independent of the overall activation strength of each contrast, we further computed for each contrast the difference between the mean t-scores measured inside each ROI and outside it in the rest of parietal cortex (Fig. 5C and D). Positive values indicate stronger activations inside a given ROI with respect to the rest of the parietal cortex, whereas negative values point at the opposite pattern. A significant interaction between ROI and contrast ($F(3.7,51.9)=43.7, p<10^{-5}$) was confirmed also for these measures for the four main regions of interest. For the contrast 'Non-symbolic > Symbolic', mean t-score differences were positive inside IPS, especially when the IPS 0–5 complex was included in the ROI (Fig. 5C). As for the SPG ROIs, the mean t-score differences were positive only when including the IPS 0–5 complex, whereas excluding it resulted in values not significantly different from zero. Regional differences were confirmed by significant post-hoc tests across ROIs inclusive versus exclusive of the IPS 0–5 complex (all significant at $p = 0.001$ at least). For the contrast 'Comparing > Viewing', mean t-scores differences were positive in the most lateral ROI defined along IPS excluding IPS 0–5 complex, whereas more medial ROIs along IPS and SPG showed progressively more negative values (post-hoc test across ROIs all significant at $p = 0.02$ at least). In the most medial ROI along the SPG, excluding the IPS0–5 complex, values were nearly zero. The mean t-score differences for the contrast 'Calculation > Reading' were positive for the most lateral ROI defined along IPS excluding the IPS 0–5 complex (post-hoc tests for the most lateral vs the progressively more medial ROIs: $p = 0.002$, $p<0.0001$, $p<10^{-7}$), and they were not significantly different from zero for the other more medial ROIs, except for the most medial one where the value was negative.

Mean t-scores for the selected ROIs corresponding to (A) anatomically defined intraparietal sulcus and superior parietal gyrus according to Destrieux et al. (2010) masked inclusively or exclusively with IPS0–5 complex (field map ROI) according to Wang et al. (2015) (see ROI display on top) and (B) field map ROI overall and its smaller subdivisions. (C and D) Differences in mean t-scores for the same ROIs with respect to the rest of parietal cortex (inside ROI-outside ROI). The ROI analyses confirmed a cross-over pattern: higher t-scores for "Non-symbolic > Symbolic" numbers (white bars) within the field map ROI with respect to more lateral IPS areas, and higher t-scores for contrasts "Comparing > Viewing" (gray bars) and "Calculation > Reading" (black bars) in lateral IPS regions outside with respect to inside the field map ROI. Plots show mean t-scores (or difference of mean t-scores) across subjects ($n = 15$) ± standard error of the mean (SEM).

Overall, the individual subject analyses confirmed a similar pattern of regional activation preferences as the one described previously in the group data. They showed that at the level of individual brains, contrasts "Comparing > Viewing" and "Calculation > Reading" showed a larger degree of activation overlap (as quantified by ROC analyses) between each other than with the "Non-symbolic > Symbolic" contrast within the intraparietal region. Further analyses focusing on activation strength within a set of intraparietal subregions confirmed a significant cross-over pattern: higher overall activations for the contrast "Non-symbolic > Symbolic" within the field map ROI compared to most lateral IPS or most medial SPG areas, as well as compared to all the rest of parietal cortex, and higher overall activations for the contrasts "Comparing > Viewing" and "Calculation > Reading" in lateral IPS parts outside compared to inside the field map ROI, and compared to all the rest of the parietal cortex. Between the smaller field map ROI subdivisions a weak, but significant, sub-regional specialization emerged in addition: activations in IPS0 were lower than those in IPS12 and IPS345 for the contrast "Non-symbolic > Symbolic" and IPS12 showed low but significant activations also for the contrasts "Comparing > Viewing" and "Calculation > Reading".

5. Discussion

While previous coarse-scale quantitative meta-analyses (Arsalidou and Taylor, 2011; Arsalidou et al., 2018) suggested an implication of human intraparietal cortex in a wide range of cognitive processes related to numerical processing, the present study investigated whether a finer-scale pattern of sub-regional specialization for different kinds of numerical stimuli and tasks can be revealed in these regions when using the enhanced spatial resolution provided by ultra-high field fMRI combined with cortical surface-based analysis in individual subjects. To more precisely localize the observed activation foci and shed new light on the way in which these are related to the more general functional organization of human (and more generally primate) intraparietal cortex, we further related activations to anatomical and functional markers on the cortical surface, with the help of two atlases based on curvature and visual topography.

Our results showed that mere viewing of sets of items as opposed to digits and numerical operations (explicit comparison and calculation), all led to activations within and around the IPS, however with clear differences across conditions and sub-regions. Viewing non-symbolic numerical stimuli activated the superior/medial parts of IPS and SPG more strongly than symbolic numbers which in turn activated more the angular gyrus and superior temporal sulcus. On the other hand, operating on the numerical information either to perform a comparison task or to compute the result of simple subtraction problems maximally recruited different and more inferior/lateral areas of IPS with respect to those involved in visual processing of non-symbolic sample stimuli.

Using population receptive field (pRF) mapping, Harvey et al. (2013) and Harvey and Dumoulin (2017b) described a topographically organized map of preferential responses to non-symbolic numerosities that overlapped with the areas containing retinotopic visual field maps, even though not coinciding with the borders of any particular one of those maps. The specific paradigm with extensive amount of stimulation and long scanning time required to perform pRF mapping reliably made it unfeasible for us to use the same approach here. Rather, we used a more classical activation contrast for non-symbolic number stimuli (compared to symbolic numbers) overall. This contrast is similar to the ones used by some previous studies which also reported preferential activation for non-symbolic over symbolic numerical stimuli in intraparietal regions, either during explicit comparison (Holloway et al., 2010) or during mere viewing and memorizing of sample stimuli (He et al., 2014), the latter case very comparable to the situation in our study. However, due to the relatively low spatial resolution used in those previous studies in combination with averaging across subjects in whole brain space, they were not able to attribute these effects to specific subparts of the IPS, and we extend their results by localizing the effects more precisely to the superior/medial bank of the sulcus, to a large degree in overlap with the visual field maps. In that sense, the results obtained with our contrast point into the same direction as the ones obtained by Harvey et al. (2013) and Harvey and Dumoulin (2017b): regions preferentially responsive to viewing of non-symbolic sets of items on the upper bank of the IPS overlap with those showing visual topography, even though our contrast is likely to have recruited a somewhat wider set of regions than Harvey's topographic numerosity maps per se.

The current study further extends and nicely complements the results obtained by Harvey and colleagues (Harvey et al.,2013; Harvey and Dumoulin, 2017b), by dissociating the responses associated with viewing different kinds of numerical stimuli from those elicited by executing numerical operations. Congruently with previous studies using delayed comparison tasks (Cavdaroglu and Knops, 2018; Cavdaroglu et al., 2015) we observed that match trials, during which a comparison was made, elicited stronger signals in intraparietal areas with respect to sample trials. Once again, our analysis methods allowed us to more precisely pin down the location of these activations within the IPS than done previously and compare it to the ones observed during mere viewing. Activity during comparison over mere viewing of sample stimuli was found most strongly outside the IPS0–5 complex, and this part of the IPS located inferiorly and laterally to the retinotopic visual field maps was most strongly activated with respect to the rest of the parietal cortex.

The same inferior/lateral region of IPS was also more strongly activated by calculation over reading. It is important to note that only subtractions were tested in the current experiment and results need not be entirely identical for other types of arithmetical operations. Indeed, there is evidence suggesting that the neuronal correlates of different arithmetical operations show some heterogeneity (Chochon et al., 1999; Lee, 2000; Dehaene et al., 2003; Zhou et al., 2007; De Smedt et al., 2011; Prado et al., 2011; Rosenberg-Lee et al., 2011, 2014, though see: Kawashima et al., 2004). Neuropsychological cases of double dissociations between the ability to solve multiplications and subtractions (reviewed in Dehaene et al., 2003) have led to the suggestion that multiplications may be typically solved by recalling the solution from rote verbal memory, whereas subtractions may require actual computation based on some sort of internal manipulation of numerical quantities on an internal number line, possibly similar to the strategy employed to solve numerical comparisons (Dehaene et al., 2003). Neuroimaging studies on healthy subjects have reported stronger IPS activations for subtraction with respect to multiplication (Chochon et al., 1999; Lee, 2000; Prado et al., 2011) or whenever a procedural strategy is used as opposed to fact retrieval in which case the angular gyrus is more involved (Polspoel et al., 2017; Tschentscher and Hauk, 2014).

In line with the idea of subtraction and comparisons involving potentially similar internal manipulations of quantity, we provide evidence for an overlapping neural substrate supporting these two operations, localized in IPS in the most inferior/lateral part of the sulcus, outside the retinotopic visual field maps which seem on the contrary more involved in visual processing of sets of items over digits. Of course, the fact that a given region is similarly activated during two different tasks (such as number comparison and calculation here) at the univariate level, does not necessarily imply recruitment of identical neuronal populations. Interestingly, one previous study using multi-voxel pattern analyses found a significant correlation across voxels between the strength of numerical distance effects measured during a number comparison task and responses for subtraction over multiplication in the IPS, suggesting that the activation overlap extends to an intermediate scale of neuronal responses (Prado et al., 2011). Future studies should perhaps use related multivariate techniques to probe the neuronal codes underlying internally computed quantities, such as those representing the outcome of a comparison process or an arithmetical operation. Extending the current results to other types of arithmetical operations or to different stimulus formats is also an important goal that future studies should address. Bugden et al. (2019) recently showed that overlapping IPS regions are activated when solving either non-symbolic or symbolic additions. Based on the current results we would expect these activations to be predominantly found in the lateral-inferior part of the intraparietal sulcus, in overlapping locations with the one here recruited for our two types of numerical operations. The ROC analysis performed in the current experiment showed that the voxels most activated for numerical operations are also recruited, although to a smaller extent, by the “Non-symbolic > Symbolic” contrast. A tentative interpretation of this unexpected result might consider this activation as a sort of ‘input signal’ on which calculation procedures can potentially be applied. Such ‘input signal’ might be stronger for non-symbolic compared to symbolic stimuli potentially due to a difficulty effect (discussed in the following paragraphs).

It could be argued that the activations described in the current study might not be specific to number processing, but rather related to associated motor responses, visual features of the stimuli or domain general processes (such as visuospatial attention, memory and task difficulty). These factors are likely contributing to some of the activation differences observed in the current experiment as much as to those described in previous reviews (Dehaene et al., 2003; Hubbard et al., 2005; Harvey et al., 2017) and metanalyses (Arsalidou and Taylor, 2011; Arsalidou et al., 2018) attempting to localize numerical processing-related activation foci during performance of numerical operations (estimation, comparison and simple arithmetic) in different numerical formats (non-symbolic arrays, symbolic numbers, math related sentences). What constitutes an appropriate baseline condition for a numerical operation such as mental calculation or numerical comparison is a non-trivial question on which currently no consensus exists in the field.

Yet, we do not believe that factors unspecifically related to numerical processing are sufficient to completely explain the entire pattern of activation differences observed here and in the literature. For example, in the current study, the contribution of motor responses to the activity elicited by the contrast ‘Comparing vs Viewing’ can hardly explain why these activations were located in overlapping regions along the intraparietal sulcus with those elicited by the contrast ‘Calculation vs Reading’, but not with those elicited by the contrast ‘Non-symbolic vs Symbolic’, given that none of these two latter contrasts involved motor responses. Low-level visual features of the stimuli (e.g. difference in shape) are also unlikely to fully explain the activation localization differences across contrasts. The visual stimuli presented in the mental calculation paradigm, i.e. words and number words, were much different in terms of low-level features from those used in the delayed number comparison paradigm, where digits and non-symbolic arrays were shown. Yet, activations elicited by the contrast ‘Calculation vs Reading’ overlapped with the one elicited by the contrast ‘Comparing vs Viewing’, but not with those obtained in the contrast ‘Non-symbolic vs Symbolic’. While in our study non-symbolic and symbolic stimuli differed in convex hull, a previous study using population receptive field methods found that numerosity models predicted parietal responses better than models of responses to several non-numerical visual features, including convex hull (Harvey and Dumoulin, 2017a). Similarly, the pattern of activity read out from similar parietal regions reflected the numerical information over and above other non-numerical low-level features, including convex hull (Castaldi et al., 2019). These results suggest that the parietal activity within the retinotopic visual field maps is primarily modulated by the numerical content of the stimuli rather than by the stimuli’s convex hull. Task difficulty was not explicitly matched here and although there was no effect of format on response accuracy, reaction times were slightly but significantly longer when comparing non-symbolic match stimuli. However, once again, while task difficulty might have potentially contributed to the activation effects observed here for different contrasts, it can hardly completely explain the entire pattern. Using single-subject analyses, Fedorenko et al. (2013) showed that a large fronto-parietal network, the so-called multiple demand system (Duncan, 2010), activated more for hard compared to easy conditions over a wide range of tasks varying in both the content and operations evoked (including mental arithmetic, holding information in working memory, filtering and suppressing task-irrelevant information, for verbal, numerical and visuo-spatial stimuli). The co-localization of activity elicited by “Comparing>Viewing” and by “Calculation>Reading” might thus be interpreted in term of general task difficulty, comparing and calculation supposedly being more difficult compared to viewing and reading, respectively. Calculation-related activations have, however, been observed by others in the IPS even when the control conditions used were matched in task difficulty (Bugden et al., 2019). Moreover, an interpretation in terms of general task difficulty is not sufficient to explain the regional differences across contrasts observed here, in particular why viewing non-symbolic as opposed to symbolic stimuli (a process more difficulty in terms of RTs, see Fig. S1) activates a different parietal sub-region with respect to calculation and comparison when compared with the respective easier conditions. Overall, while acknowledging the fact that differences in low-level features and task difficulty cannot be formally discarded as potentially contributing to some of the activations observed here, we don't think they are likely to explain the complete pattern of findings.

An animate debate within the field of numerical cognition concerns the question of whether the semantic meaning of numbers is represented in a format specific or format invariant fashion (Dehaene et al., 1998, 2003; Cohen Kadosh and Walsh, 2009; Carey and Barner, 2019). As a result, many functional imaging studies have tried to identify either shared or distinct substrates of number processing in different formats. These have used a variety of approaches, from classic univariate subtraction designs (e.g., Holloway et al., 2010; Chassy and Grodd, 2012; Lyons and Beilock, 2013; He et al., 2014) to methods focusing on within-category distinction employing either fMRI adaptation or multivariate pattern analysis (Piazza et al., 2007; Eger et al., 2009; Kadosh et al., 2011; Bulthé et al., 2014; Lyons et al., 2015; Lyons and Beilock, 2018), leading to a range of different conclusions. A recent metanalysis of univariate activation studies found evidence for both overlapping and distinct brain substrates underlying symbolic and non-symbolic number processing (Sokolowski et al., 2017). Addressing this precise debate was beyond the scope of this manuscript, and although we reported some differential activations between numerical formats, our experimental conditions were not designed to isolate any shared semantic aspect across formats with specific non-numerical control conditions. The contribution of the current work is to highlight some functional heterogeneity between precisely defined subregions of intraparietal cortex. Future studies may combine the methodological approach introduced here with more specific and detailed contrast designs and disentangle whether overlapping activations across formats are mainly encountered in the context of a shared higher-order operation such as a quantitative comparison or arithmetic computation (which predominantly recruited lateral IPS parts in our case), or whether they can also be observed during more basic types of processing (and if so, which are the precise recruited sub-regions in that case).

The main functional landmark in relation to which we mapped numerical processing related activity here are intraparietal retinotopic visual field maps which, as noted in the introduction, are considered the likely human equivalents of the macaque LIP/VIP complex where neurons responsive to the numerosity of non-symbolic arrays have been described by neurophysiological studies (Nieder et al., 2006; Roitman et al., 2007). Identifying equivalence between areas is non-trivial related to the fact that human parietal cortex has differentially expanded and is also recruited by higher-level functions that are not present in monkeys, such as language, sophisticated tool use and higher-level mathematics (Grefkes and Fink, 2005; Kastner et al., 2017). Therefore, the number of areas and their relative localization with respect to IPS anatomy can show some differences across the two species, and suggestions for correspondence should rather emphasize similarities in characteristic functional response properties across areas. Such tentative equivalence, based on functional similarities reviewed in the introduction, has been proposed between lower-level intraparietal field maps and LIP, as well as higher-level visual field maps and VIP (Kastner et al., 2017; Konen and Kastner, 2008).

The mentioned findings led us to investigate separately IPS0, IPS12 and IPS345 subparts here, and to consider our IPS12 and IPS345 ROIs as more likely corresponding to macaque LIP and VIP, respectively. However, we also note that this particular subdivision should be taken with some caution, as no one-to-one correspondence between individual regions in the two species may exist. So far, a higher number of retinotopic visual field maps has been described in humans than in monkeys, and determining the exact equivalence between regions should take into account multiple criteria and is still a topic of ongoing research (Kastner et al., 2017). In the current study, the field map ROIs IPS12 and IPS345 both showed higher activations with respect to IPS0 and to the rest of parietal cortex during viewing of non-symbolic stimuli compared to digits, in line with the preferential neuronal responses to non-symbolic numerical stimuli that have been described in macaque LIP and VIP.

In addition, significant, although less strong, activations where also observed in the IPS12 ROI during numerical comparison and calculation. Some responsiveness of superior parietal regions during numerical operations has been noticed previously (e.g. Dehaene et al., 2003) and been hypothesized to reflect attentional shifts along an imaginary number line. In line with this hypothesis, activity in intraparietal regions identified by their responsiveness to saccadic eye movements could be read out to train a decoder to distinguish leftward from rightward saccades, and this decoder could subsequently be used to predict two different arithmetic operations (subtraction vs addition) presumably associated with leftward as opposed to rightward shifts along the mental number line (Knops et al., 2009). Parietal field maps including IPS2 which carried some effect of numerical operations here have also been implicated in processing spatial information at a relatively abstract level by other recent studies. Despite being defined as visual field maps, these areas were activated during a demanding auditory short-term memory task when the spatial position of the auditory stimuli had to be kept in memory (Michalka et al., 2016). A role in attentional shifts along an internally represented space of numerical magnitude as underlying the activation during numerical operations, although speculative, appears to fit well with these other findings.

However, beyond the minor result in IPS12, the regions most strongly recruited during numerical operations (both comparison and calculation) fell outside the field map ROI which we used here as independent criterion of the human equivalent of the LIP/VIP complex, and into more lateral/inferior portions of the IPS. A correspondence between the areas maximally recruited during these types of numerical operations in humans and macaque regions VIP and LIP, as commonly assumed in the literature, therefore appears unlikely given the present results. Currently, it remains to some extent unclear which, if any, would be the counterpart in the macaque monkey brain of the more lateral human IPS regions shown to be responsive to numerical operations here. Interestingly, a functional connectivity study suggested the existence of evolutionarily novel cortical networks in humans for which no correspondence in the monkeys' brain could be identified (Mantini et al., 2013). One of these networks which was in addition located within the areas having undergone the largest degree of cortical surface expansion between monkeys and humans, encompassed the intraparietal cortex near HIPS (Mantini et al., 2013), and could possibly overlap with the operation-related activations shown here on the inferior/lateral bank of the IPS.

In conclusion, intraparietal cortex is confirmed to play a crucial role in different components of numerical processing tasks, however, our study revealed a sub-regional specialization where more medial versus more lateral parts of the intraparietal sulcus are preferentially recruited during mere viewing of non-symbolic (over symbolic) numerical stimuli and numerical operations (comparison and calculation), respectively. While the former showed a large extent of overlap with the area containing retinotopic field maps, the latter activations were predominantly located outside those regions, and thus likely arise within an area that is distinct from the human equivalent of the LIP/VIP complex. In light of the current results it would be interesting to further investigate what is the more comprehensive functional response profile of the potentially human-specific lateral intraparietal sulcus subparts, and what might be the common computational denominator underlying different tasks recruiting these regions. Finally, future studies should also test whether the sub-regional specialization observed here in adults is already present in children or whether this differentiation emerges during development and mathematical learning.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117210.

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