

COGNITIVE NEUROSCIENCE

Tuning to non-symbolic proportions in the human frontoparietal cortex

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Keywords: fMRI adaptation, human cerebral cortex, intraparietal sulcus, numerosity, proportions

Abstract

Humans share with many species a non-verbal system to estimate absolute quantity. This sense of number has been linked to the activity of quantity-selective neurons that respond maximally to preferred numerosities. With functional magnetic resonance imaging adaptation, we now show that populations of neurons in the human parietal and frontal cortex are also capable of encoding quantity ratios, or proportions, using the same non-verbal analog code as for absolute number. Following adaptation to visually presented constant proportions (specified by the ratio of line lengths or numerosities), we introduced novel relative magnitudes to examine the tuning characteristics of the population of stimulated neurons. In bilateral parietal and frontal cortex we found that blood oxygenation level-dependent signal recovery from adaptation was a function of numerical distance between the deviant proportion and the adaptation stimulus. The strongest effects were observed in the cortex surrounding the anterior intraparietal sulcus, a region considered pivotal for the processing of absolute magnitudes. Overall, there was substantial overlap of frontoparietal structures representing whole numbers and proportions. The identification of tuning to non-symbolic ratio stimuli, irrespective of notation, adds to the magnitude system a remarkable level of sophistication by demonstrating automatic access to a composite, derived quantitative measure. Our results argue that abstract concepts of both absolute and relative number are deeply rooted in the primate brain as fundamental determinants of higher-level numerical cognition.

Introduction

Grasping the concept of magnitude comes naturally to most species. Several lines of evidence indicate that our system to count, measure and rank items is phylogenetically ancient, evolving independently of language (Dehaene, 1997; Nieder, 2005). Simple enumeration or quantification, however, is often insufficient to make decisions and guide behavior. In many instances, we need to relate two quantities, generating a new composite construct: a proportion or magnitude 'ratio'. Proportions are fundamental to mathematics and science, underlie the concept of percentage, and even govern seemingly subjective matters such as aesthetics and the sense of beauty ('golden ratio'; Livio, 2002). Despite its paramount relevance for human culture, however, the neural underpinnings of proportional reasoning are largely unknown.

To represent ratios accurately, humans exploit their symbolic numerical competence by using number fractions. A recent neuro-imaging study showed that fractions are represented by populations of neurons that are tuned to preferred ratios of numbers (Jacob & Nieder, 2009). Activity in the parietal cortex, more specifically in the intraparietal sulcus (IPS), a key region for the processing of absolute magnitude, was modulated as a function of the numerical distance of the presented from the preferred fraction. There were no differences in activation whether subjects viewed fraction numerals (e.g. 3/6) or

fraction words (e.g. 'half') that were intermingled within a single experimental run. This insensitivity to stimulus notation indicates that fractions were encoded by their true numerical value and are not necessarily processed by numerator and denominator in separation. This strongly contrasts with common beliefs grounding on the fact that children and adults have considerable difficulties learning and using fractions (Bonato *et al.*, 2007). The finding of cross-notation encoding of fractions raises the possibility of an abstract processor of magnitude ratios in the human IPS, and is strongly reminiscent of the system described for absolute numbers.

Similar to absolute quantity, which can be judged approximately without symbols, proportion (relational quantity) can also be determined non-verbally. Behavioral similarities are emerging between the non-symbolic representation of numerosities and proportions. For instance, infants can discriminate two ratios sufficiently far apart, long before the concept of proportionality is introduced during formal schooling (McCrink & Wynn, 2007). Electrophysiological recordings have shown that, in the monkey, single neurons respond to preferred non-symbolic proportions as described for absolute number (Vallentin & Nieder, 2008). Taken together, these observations suggest that quantity ratios are accessed automatically prior to the acquisition of language, possibly using cortical networks similar to those processing absolute quantity. However, a circuit to non-verbally represent magnitude ratios has not been described in humans. The identification of such a system would provide the much needed link between the infant and animal data on non-verbal proportions and the experiments addressing the processing of fractions (Jacob & Nieder, 2009). It could

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Received 29 April 2009, revised 5 August 2009, accepted 8 August 2009

demonstrate that the neuronal representation of fractions co-opts the phylogenetically older circuits for non-symbolic proportions, giving rise to a truly notation-invariant representation of magnitude ratios. Furthermore, joint activation of the IPS during processing of both absolute and relative magnitude would constitute a strong argument for the existence of an overarching, most abstract quantity processor. No data exist so far that allow for a direct comparison of the representation of numerosity and proportions.

Here, we use functional magnetic resonance imaging (fMRI) adaptation to investigate the non-verbal processing of relative quantity in the human brain. fMRI adaptation (Grill-Spector *et al.*, 1999; Grill-Spector & Malach, 2001) is based on the finding that repetitive presentation of an invariant stimulus property reduces the activity of neurons processing this feature and with it the blood oxygenation level-dependent (BOLD) signal at this site. A sudden deviation in the stimulus property is encoded by a different, non-adapted pool of neurons processing this novel aspect, resulting in a net BOLD signal recovery from adaptation. By parametrically varying stimulus features, the tuning characteristics of interspersed neural populations can be read-out with superior sub-voxel spatial resolution. Several neuroimaging experiments in humans have validated fMRI-adaptation protocols for the study of the mechanisms of the representation of numerosity, successfully disentangling processing of magnitude from unspecific novelty effects (Dehaene *et al.*, 2003; Piazza *et al.*, 2004; Cantlon *et al.*, 2006). Supporting single-cell recordings in monkeys (Nieder *et al.*, 2002; Nieder & Miller, 2004), these studies suggest that neurons in the IPS and prefrontal cortex (PFC) are tuned to preferred numerosities.

Extending established fMRI-adaptation protocols, we now report tuning of neural populations in the human parietal and frontal cortex to non-symbolic proportions, bridging the gap between monkey electrophysiology and neuroimaging of human high-level mathematical cognition.

Materials and methods

Participants

Fifteen healthy volunteers (aged 21–37 years) recruited from an academic background were included in each experiment after obtaining informed written consent. All were right-handed as determined by the Edinburgh Handedness Inventory, and had normal or corrected-to-normal vision. Subjects received financial compensation for their participation. The local ethics committee of the University of Tübingen approved all experiments, which conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Experimental protocol

General remarks

We performed two separate, however related, experiments to investigate the neuronal coding of magnitude ratios (dot and line proportion protocol). A third experiment (numerosity protocol) was added to compare the extent of cerebral activation. A rapid event-related fMRI-adaptation design was used to exploit the neurophysiological finding that repetitive presentation of invariant stimulus features induces a reduction of activity in the neurons processing this particular property (repetition-suppression or adaptation). We measured changes in the BOLD signal, a surrogate for neuronal activity, during adaptation and in response to abrupt introduction of stimuli that deviate in the dimension of interest.

Subjects passively viewed rear-projected stimuli through a mirror system inside the MRI-scanner. Stimulus presentation was controlled with Presentation (Neurobehavioral Systems, Albany, CA, USA). All stimuli were programmed with MATLAB (The Mathworks, Natick, MA, USA) and comprised a large gray background circle subtending 9.2° of visual angle to focus the subjects' attention and a central white fixation spot. Stimuli were divided into two sets. Adaptation stimuli were designed to keep the dimension of interest constant while varying all other parameters. In the deviant stimuli, the feature of interest changed to one of four levels, increasing in numerical distance from the adaptation magnitude. To control for novelty effects, half of the deviants included a salient change in a dimension unrelated to numerical properties. Stimuli were flashed for 300 ms, allowing enough time to perceive the key features but not to enumerate items. The background circle and fixation point were then presented for an additional 900 ms to fix the inter-stimulus interval at 1.2 s. Each experiment opened with an adaptation phase, during which 33 adaptation stimuli were presented without intervening deviants (totaling 39.6 s). For the remainder of the experiment, deviant stimuli were randomly interspersed among the adaptation images, separated by 3–11 stimuli (inter-deviant time 3.6–13.2 s). In both proportion protocols, the first deviant was chosen to signal a maximal change in the dimension of interest. For all subjects, it occurred directly after the adaptation phase. A total of 240 stimuli were presented in the numerosity and dot protocols, of which 32 were deviants. There were 320 stimuli in the line protocol, of which 40 were deviants. Each protocol was repeated once. The sequence of experimental runs (protocols) was the same for all subjects.

Subjects were shown exemplary images (adaptation and deviant stimuli) from all experiments before entering the scanner. Importantly, subjects were not given any explicit task, but merely instructed to fixate and attend to the features of the visual display. Upon informal questioning after the experiment, subjects readily reported changes in the salient non-numerical control condition (color and shape, see below), while differences in proportion were less conspicuous. This confirmed that the images' feature of interest (proportion) did not exert unreasonably large effects on arousal and attentional processing compared with controls. To the eight subjects performing all three experiments, the numerosity and dot protocol were not disclosed as two separate experiments but were referred to as necessary repetitions.

Stimulus design in individual protocols

Line proportions

Proportions were specified by the ratio of the length of two horizontal solid lines arranged above and below the fixation spot. Subjects were adapted to 1 : 5. Deviants were 2 : 5, 3 : 5, 4 : 5 and 5 : 5. Adaptation stimuli were chosen randomly before each run from a pre-calculated set of 72 images. There were 72 images for each deviant proportion. Both image sets were composed of three groups: in the first, the reference line length (bottom, long) varied randomly, and the test line (top, short) was chosen correspondingly for each proportion. In the second, the length of the test line was fixed, determining the reference line length for each proportion, and vice versa in the third set. One third of the presented adaptation and deviant images were selected randomly from each of the three groups. Absolute line lengths did thus not co-vary with proportion. Line lengths varied between 0.6° and 7.3° of visual angle. The reference line was centered and placed 0.5° below the fixation spot. The test line's position was allowed to vary randomly along the x-axis as long as it

did not overlap the edges of the reference line by more than 0.6° , ensuring that information about the relative position of the edges did not inform about proportional magnitude. The test line's offset from the screen center in the y -direction was fixed at 0.5° . Bars were colored in red, except for half of the deviants, which were blue. Red and blue were equiluminant.

Dot proportions

Proportions were specified by the ratio of the number of items in two groups comprising equiluminant red and blue dots. Item size was equal within any given stimulus. Subjects were adapted to one half (5 : 10). Deviant proportions were 6 : 10, 7 : 10, 8 : 10 and 9 : 10, with more dots in the blue group. Adaptation stimuli were chosen randomly before each run from a pre-calculated set of 540 images. There were 120 images for each deviant proportion. All deviant stimuli comprised 20 items, chosen to fall in the range of the set sizes presented in the numerosity protocol and permitting the number of elements in both groups to assume integer values. Set sizes for the adaptation stimuli assumed even numbers between 4 and 32 including 20 to assure the numerosity of the deviant stimuli was not perceived as novel. As in the numerosity experiment, half of the deviant images were composed of triangles instead of dots (identical item size). Item diameter varied as above for all stimuli and did not correlate with proportion. Overall dot density was equated across all stimuli, as were the dot densities for both the red and the blue group.

Numerosity

Random dot patterns were used to represent numerosity. Subjects were adapted to a display with 18 items, and 6, 12, 24 and 30 dots were used as deviants. Adaptation stimuli were chosen randomly before each run from a pre-calculated set of 60 images. There were 60 images for each numerosity deviant. All items in a single display were equally large. To ensure that numerosity did not co-vary with any low-level features, we controlled for several other parameters. For the adaptation images, dot diameters varied between 0.3 and 0.7° of visual angle, entailing changes of individual item size and total occupied area. The latter was equated across all deviants, meaning that item diameter and size were fixed for a certain deviant numerosity. Importantly though, these parameters were not novel and fell in the range of diameters and total occupied area encountered during the adaptation stimuli. Mean dot density, calculated as the average inter-item distance, was equated for all stimuli (adaptation and deviants). In half of the presented deviant images and four adaptation stimuli shown in between deviants (separated by at least three images), dots were replaced by triangles (identical item size). Items were separated by a specified minimum distance from the background circle border and fixation spot and were not permitted to overlap. To ensure maximal similarity to the dot proportion protocol, dots were assigned to two groups by equiluminant red and blue coloring. The ratio of set sizes varied in steps of 1 : 6 from 1 : 6 to 5 : 6 but was not correlated with numerosity.

Image acquisition

T2*-weighted functional images (TR 2.4 s, TE 37 ms) sensitive to the BOLD contrast were acquired in gradient echo-planar imaging sequences on a Siemens Tim Trio scanner (Siemens, Erlangen, Germany) operating at 3 T. Thirty-six slices with a 0.5-mm gap were acquired for complete coverage of the cerebral cortex in descending order at $3 \times 3 \times 3$ mm isotropic resolution (flip angle 90° , FOV 192 mm, image matrix 64×64). Anatomical scans used the 3D

gradient-echo T1-weighted Siemens MPRAGE sequence (TI 1.1 s, TR 2.3 s, TE 2.92 ms) acquiring 176 slices in the sagittal plane at $1 \times 1 \times 1$ mm isotropic resolution (flip angle 8° , FOV 256 mm, image matrix 256×256).

Data analysis

Functional images were analysed using the SPM5 software package (Wellcome Department of Imaging Neuroscience, London, UK). The first three scans were discarded to allow for equilibration of T1 magnetization. The remaining volumes were unwarped with the FieldMap toolbox, corrected for motion by realignment to the first image in the session, slice-time corrected, normalized to the Montreal Neurological Institute (MNI) standard space using the parameters obtained during segmentation of the anatomical scans and smoothed with an isotropic Gaussian kernel of 8 mm at full-width half-maximum. Data were high-pass filtered (320 s) before analysis within the general linear model framework. In brief, data were approximated by a linear combination of regressors obtained by convolution of the canonical hemodynamic response function with the onsets of the deviant and an equal number of randomly selected adaptation stimuli (in the numerosity protocol, four stimuli with shape changes were already fixed, see above), separated by at least three images from a preceding or following deviant. Every deviant level was modeled with separate regressors for the standard and control shape (numerosity and dot protocol) as well as color change condition (line protocol) in a two-factorial design [factors distance (four levels) and shape/color (two levels)]. Time and dispersion derivatives were included to capture additional variance. BOLD signal adaptation was approximated by a regressor decreasing linearly during the adaptation period. Realignment parameters were included as regressors of no interest. Contrasts identifying voxels with significant adaptation, main effect of numerical distance (far vs. close deviants) and main effect of shape/color change were entered in a second-level random effects analysis. The adaptation regressor was orthogonal to the event condition regressors, meaning they accounted for independent components of the BOLD signal variance. Thus, there was no selection bias by using the adaptation regressor to narrow the subsequent search for voxels showing an effect of numerical distance. To ensure comparability to previous studies of magnitude processing (Piazza *et al.*, 2004, 2007; Cantlon *et al.*, 2006), thresholds for statistical inference were set at $P < 0.01$ uncorrected at the voxel level, corrected at the cluster level to $P < 0.05$ with a cluster extent of 30 voxels. Student's non-directional, paired t -test was used for testing BOLD signal time courses, Gaussian fits and fitted slopes. Repeated-measures two-way ANOVAs were calculated for the tuning curve data with factors distance (four deviant levels) and shape/color (two levels, standard or control).

Results

In two fMRI-adaptation experiments (Fig. 1), participants were exposed to a stream of visual stimuli. The stimulation protocols tested selectivity for proportions between a test and a reference line (continuous quantity), and for proportions between two sets of dots (discrete quantity). The stimuli were designed to initially maintain constant either the ratio of the length of two lines (line proportion protocol, Fig. 1A) or the ratio of the number of items in two groups (dot proportion protocol, Fig. 1B), while varying other non-numerical low-level features. We allowed sufficient time for adaptation, and then measured the BOLD signal recovery to abrupt changes in proportion (Fig. 1C).

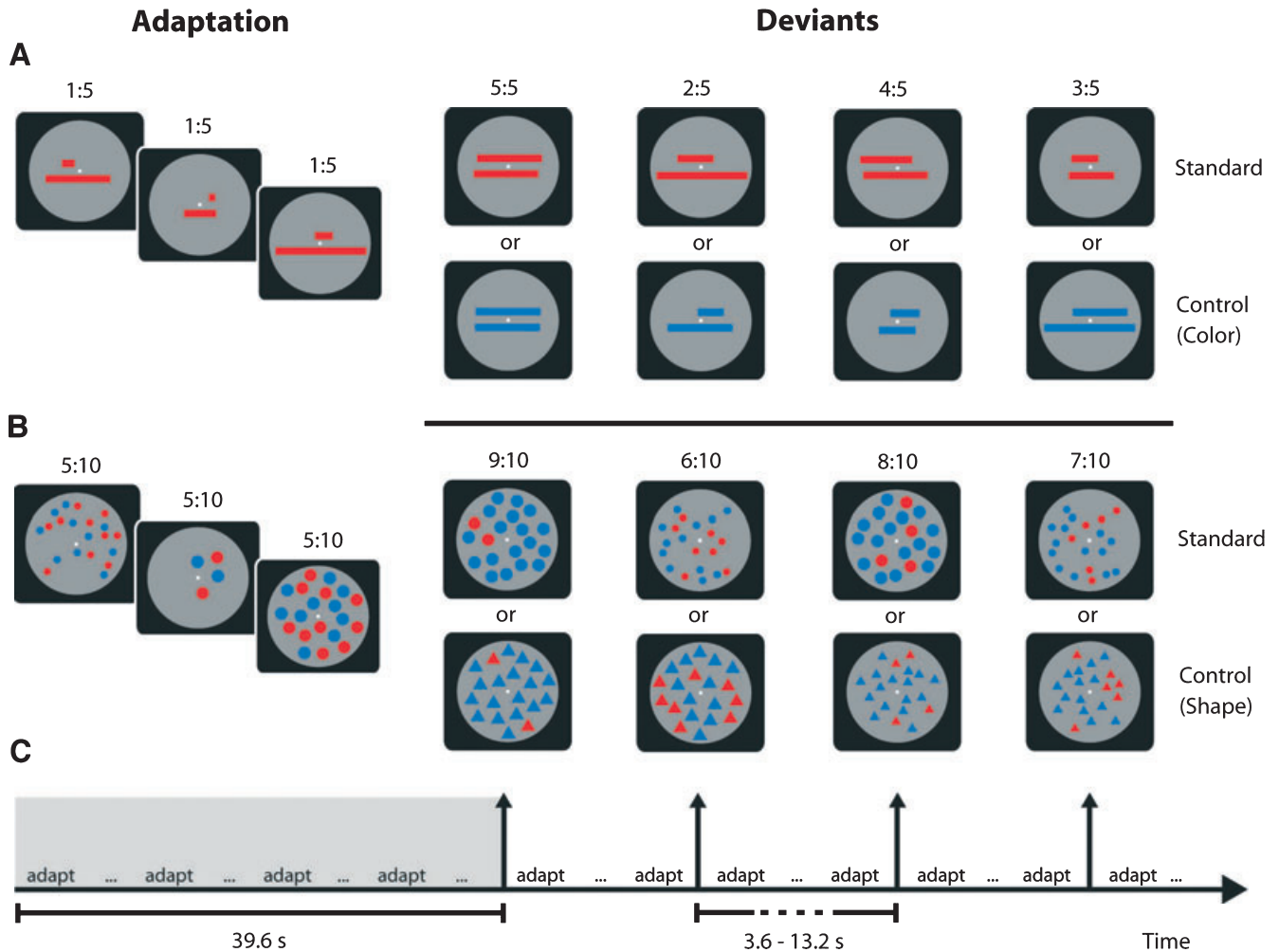


FIG. 1. Experimental protocols and example stimuli. Following an adaptation period with rapid repetitions of invariant magnitudes (total duration 39.6 s, inter-stimulus interval 1.2 s, 33 consecutive stimuli), a stimulus deviating maximally from the adaptation quantity was introduced abruptly. Deviants could assume one of four levels, and were separated by random intervals between 3.6 and 13.2 s during which adaptation stimuli were shown. (A) In the line proportion protocol, proportions were specified by two horizontal bars of different lengths (reference line at the bottom, test line at the top). Numerical values were 1 : 5 during adaptation, and 5 : 5, 4 : 5, 3 : 5 and 2 : 5 for deviants. Line length was uncorrelated with proportion. A color change from red to blue was introduced in half of the deviants (bottom row). (B) In the dot proportion protocol, proportions were specified by the ratio of two set sizes. Red and blue denoted the two groups. Proportions were kept constant at 5 : 10 (1 : 2) during adaptation, and changed to 9 : 10, 8 : 10, 7 : 10 and 6 : 10 in deviants. All deviants comprised 20 items. In the adaptation period, overall numerosity varied from 4 to 32 and was not correlated with proportion. In half of the deviants, dots were replaced by triangles (bottom row). (C) Experimental protocol for the line and dot experiment.

Distinct cortical regions for processing magnitude ratios and non-numerical novelty

For both experiments, we first conducted a full-brain second-level analysis of the distance contrasts (main effect of distance; voxels responding stronger to the two deviants furthest from the adaptation stimulus than to the two closest deviants; Fig. 2A and C). Despite the entirely distinct notations, we obtained the same pattern of activated structures. The most consistent effects were observed in the bilateral parietal cortex as well as in the PFC. Particularly significant involvement of the anterior IPS was present in both hemispheres (areas circled, Fig. 2A and C). Precentral and inferotemporal cortex were also activated in the dot proportion experiment (Fig. 2C), whilst the latter did not survive the threshold in the line proportion experiment (Fig. 2A).

Because the distance effect *per se* does not rule out confounding effects of non-numerical novelty, we searched for brain areas showing a main effect of color change (line proportion protocol; Fig. 2B) and shape change (dot proportion protocol; Fig. 2D). Strong responses

were present in the inferotemporal cortex. In the dot proportion experiment, we observed an involvement of the most 'posterior' part of the parietal cortex in the right hemisphere. Importantly, the overall activation pattern was very different from that seen in the analysis of the quantity distance effect, and the distance-sensitive areas in the 'anterior' IPS and PFC did not overlap with the areas processing the more salient shape and color changes. Allocation of attention and stimulus novelty typically activate the posterior IPS (Dehaene *et al.*, 2003; Gur *et al.*, 2007), whereas it is the anterior IPS that is considered selective for the representation of magnitudes. To avoid contamination by unspecific stimulus novelty *a priori*, the posterior IPS did not undergo further analysis.

Adaptation to constant magnitude ratios in bilateral IPS

We next identified cortical regions in which the BOLD signal decreased during the adaptation period in response to the ongoing

repetitive visual stimulation. Processing of the adaptation images' invariant dimension (i.e. proportional magnitude in the dot and line experiments) should entail a signal decrease that we approximated by a regressor decreasing linearly throughout the adaptation period. A very stereotypical and reproducible pattern was observed in both experiments. Despite the profound variation in appearance of the images within and, most of all, across our experiments, signal adaptation was strongest in the bilateral parietal cortex, precisely coinciding with the regions identified with the previous distance contrasts. We determined for each subject and both hemispheres within the anterior IPS, which was defined by the group analysis of the adaptation effect, the single voxel that showed the strongest BOLD signal adaptation (i.e. strongest correlation with the adaptation regressor). BOLD signal time courses from these voxels averaged over both hemispheres are plotted for the line and dot proportion experiment (Fig. 3A and B, respectively). In both experiments, there was a marked increase compared with rest in response to presentation of the first stimuli. The signal then gradually decayed to a minimum towards the end of the adaptation period (a consequence of our voxel selection). More importantly, upon abrupt introduction of the first deviant, chosen to deviate maximally from the habituation stimulus in both experiments (5 : 5 for lines, 9 : 10 for dots), the BOLD signal clearly recovered from adaptation. To statistically compare different response phases, we pooled data from three consecutive scans in four time bins positioned identically for both experiments (Fig. 3A and B): rest (scan 1–3), peak (scan 5–7), end of adaptation phase (scan 17–19) and first deviant (scan 20–22). Differences were significant between all time bins [rest vs. peak: $t_{14} = 9.94$, $P = 10^{-7}$ (line), $t_{14} = 9.05$, $P = 3.2 \times 10^{-7}$ (dot); peak vs. adaptation: $t_{14} = -2.99$, $P = 0.01$ (line), $t_{14} = -4.65$, $P = 3.7 \times 10^{-4}$ (dot); adaptation vs. deviant: $t_{14} = 2.37$, $P = 0.03$ (line), $t_{14} = 2.56$, $P = 0.02$ (dot)].

Several other regions processing non-quantitative features also showed a BOLD signal adaptation, including striate and extra-striate visual cortex, the insular cortex, thalamus, basal ganglia and cingulum (Supporting information, Tables S1 and S2).

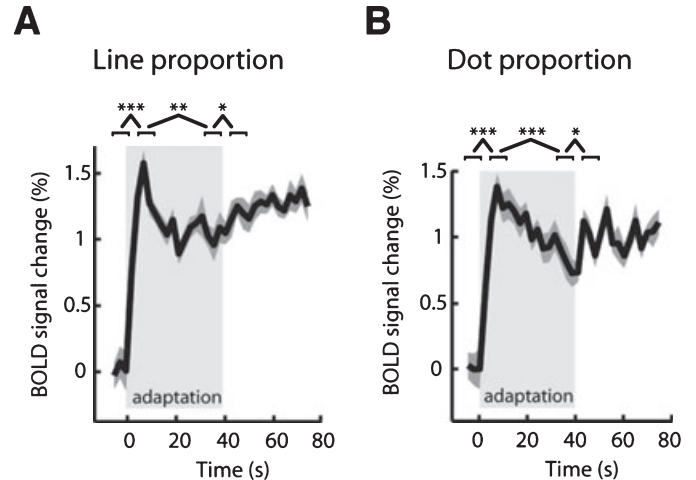


FIG. 3. Blood oxygen level-dependent (BOLD) signal adaptation in bilateral anterior IPS. (A and B) Voxels in the anterior IPS with the strongest BOLD signal decrease during the adaptation phase were identified for each subject. Time course of BOLD signal change extracted from these voxels, averaged over subjects and hemispheres, in the line (A) and dot experiment (B). Following the adaptation period (marked in gray) there is a clear signal rebound upon introduction of the first deviant. Significant signal changes are also evident between rest and peak signal and between peak signal and last adaptation stimuli. A, anterior; P, posterior; L, left; R, right; *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

Tuning to proportions specified by continuous quantity

Compared with the dot experiment, proportions in the line experiment (Fig. 1A) were perceptually very different, unambiguous and determined by ratios of continuous quantity. We identified for each subject and hemisphere the voxel within the anterior parietal cortex that responded strongest to far (deviants 5 : 5 and 4 : 5) than to close deviants (deviants 3 : 5 and 2 : 5). The independent adaptation

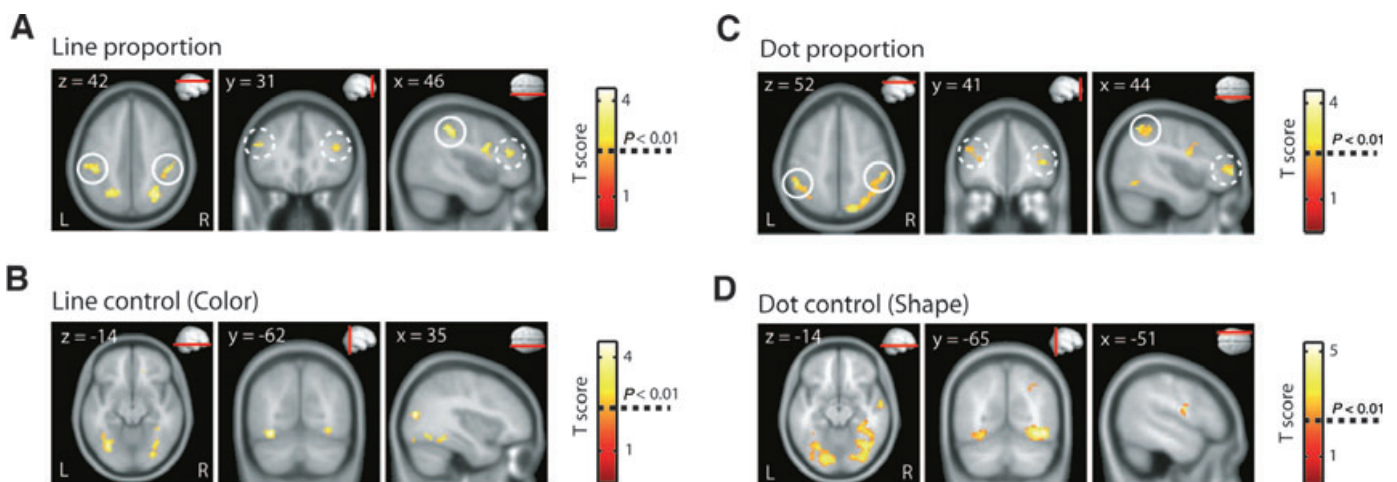


FIG. 2. Segregated representation of proportional magnitude and non-numerical novelty. (A) Full-brain search for cortical regions responding stronger to more distant ratio deviants than to stimuli closer to the adaptation proportion in the line protocol. Voxels are overlaid on a template brain averaged over 152 healthy subjects. Sections in the transverse, frontal and sagittal plane are shown in the left, middle and right panel, respectively. The exact slice position is given in the upper left-hand corner in MNI coordinates and symbolized on the right by the red line superimposed on a schematic brain. Images are oriented following neurological convention (left is left and right is right). Large clusters were observed in bilateral IPS (anterior regions marked with circles) and PFC (dashed circles). ($P < 0.01$ at the voxel level, corrected at the cluster level to $P < 0.05$.) (B) Distinct cortical regions responded to changes in stimulus color (control condition) in the line protocol. (C) In the dot proportion protocol, a network comparable to the line proportion experiment was activated extending to anterior cingulate and inferotemporal cortex. Same layout as in (A). (D) Regions sensitive to shape changes (control condition) in the dot protocol differed from the areas processing magnitude ratios.

regressor served as a localizer only to define the parietal brain areas and was orthogonal to the distance regressors, ensuring an unbiased analysis.

There was a graded BOLD signal response to deviants increasing in distance from the adaptation proportion (supporting Fig. S1, A). Plots of the averaged beta weights for each regressor as a function of deviant proportion are shown for both hemispheres (negative weights for the adaptation stimulus indicate continuing BOLD adaptation; Fig. 4A). As a consequence of our voxel selection (and reported in the following sections for completeness only), the repeated-measures two-factorial ANOVA revealed a significant effect of distance [main effect of distance: $F_{3,7} = 25.53$, $P = 5.0 \times 10^{-9}$ (left), $F_{3,7} = 7.72$, $P = 4.2 \times 10^{-4}$ (right)]. More importantly, there were no effects of the control condition, color change [main effect of color change: $F_{1,7} = 0.13$, $P = 0.73$ (left), $F_{1,7} = 1.04$, $P = 0.37$ (right)], confirming the whole-brain analysis presented earlier. Of special note, the salient color change did not interact with the relatively inconspicuous, small proportion deviants [distance \times color: $F_{3,7} = 1.83$, $P = 0.16$ (left), $F_{3,7} = 1.36$, $P = 0.27$ (right)]. This analysis closely resembles a control condition where a salient change in a non-numerical dimension is 'not' accompanied by a novel proportion. The lack of interactions therefore adds to ruling out confounds caused by unspecific attention or novelty effects. In a second approach, more robust to noise, slopes of linear fits to the beta weights of all deviants were calculated for individual subjects. Slopes were significantly larger than zero [$t_{14} = 7.51$, $P = 7.1 \times 10^{-6}$ (left standard color), $t_{14} = 5.91$, $P = 7.1 \times 10^{-5}$ (left control), $t_{14} = 5.1$, $P = 2.8 \times 10^{-4}$ (right standard), $t_{14} = 5.48$, $P = 1.4 \times 10^{-4}$ (right control); Fig. 4B]. There were no differences in slope between the standard and control conditions [$t_{14} = -0.97$, $P = 0.35$ (left), $t_{14} = 0.66$, $P = 0.52$ (right)].

For each subject, we also determined the voxel with the largest effect of numerical distance within the bilateral PFC, as localized by the independent orthogonal regressor for signal adaptation. There were

no effects of shape or interactions in the left or right PFC – the effect of distance was again due to voxel selection [repeated-measures two-way ANOVA: main effect of distance: $F_{3,7} = 12.93$, $P = 5.2 \times 10^{-6}$ (left), $F_{3,7} = 15.79$, $P < 7.1 \times 10^{-7}$ (right); main effect of color: $F_{1,7} = 0.04$, $P = 0.84$ (left), $F_{1,7} = 0.36$, $P = 0.56$ (right); distance \times color interaction: $F_{3,7} = 0.86$, $P = 0.47$ (left), $F_{3,7} = 0.89$, $P = 0.46$ (right); Fig. 4C]. Slopes of all linear fits were significantly larger than zero [$t_{14} = 4.5$, $P = 5.6 \times 10^{-4}$ (left standard color), $t_{14} = 3.88$, $P = 0.002$ (left control), $t_{14} = 3.56$, $P = 0.004$ (right standard), $t_{14} = 7.15$, $P < 7.5 \times 10^{-6}$ (right control); Fig. 4D] and equal for standard stimuli and color controls [$t_{14} = -0.59$, $P = 0.56$ (left), $t_{14} = 1.45$, $P = 0.16$ (right)]. In conclusion, neither the analysed parietal nor the prefrontal regions were sensitive to changes in a non-quantitative dimension (color), arguing that the distance effect for continuous proportions was not caused by general stimulus novelty.

Representation of ratios of discrete quantity

The data set from the dot proportion experiment (Fig. 1B) was subjected to the same analysis. Subjects were adapted to ratio 1 : 2 (equal number of red and blue dots with varying overall item numbers). Within the anterior parietal regions localized by the group analysis of BOLD signal adaptation, we searched for voxels with a greatest recovery to far (9 : 10, 8 : 10) compared with close proportions (7 : 10, 6 : 10) across subjects. All deviants comprised 20 items to rule out influences of numerosity changes.

BOLD signal time courses were graded with greater rebound as the distance in quantity between the deviant and the habituation proportion increased (supporting Fig. S1, B). The plot of beta weights as a function of deviant proportion was similar to the line proportion experiment, though data were noisier (Fig. 5A). Given our voxel selection, a repeated-measures two-way ANOVA with factors distance

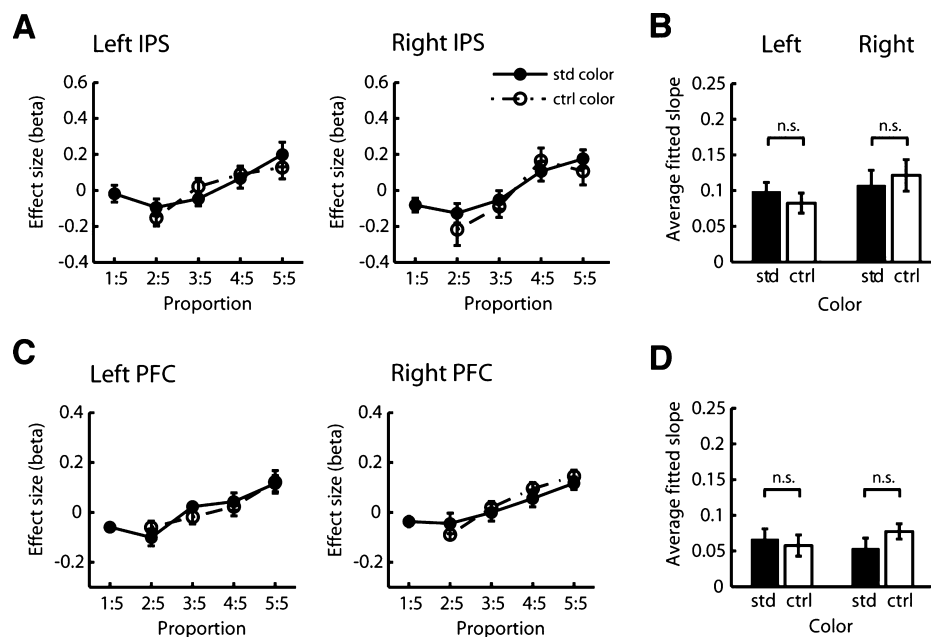


FIG. 4. Encoding of line proportions in the bilateral frontoparietal cortex. (A) Differential activation to proportions as expressed in averaged beta weights for standard and color control deviants (closed and open circles, respectively) in the left and right intraparietal sulcus (IPS; left and right panels, respectively). Negative weights indicate continuing adaptation. (B) Slopes of linear fits to the individual beta plots averaged over all subjects for the bilateral parietal cortex. (C) Averaged single subject betas to adaptation and deviant stimuli in the prefrontal cortex (PFC), plotted as a function of magnitude ratio, are shown for the standard and control color condition and for both hemispheres. (D) Slopes of linear fits to the data in (C) were equal for the left and right PFC. n.s., not significant.

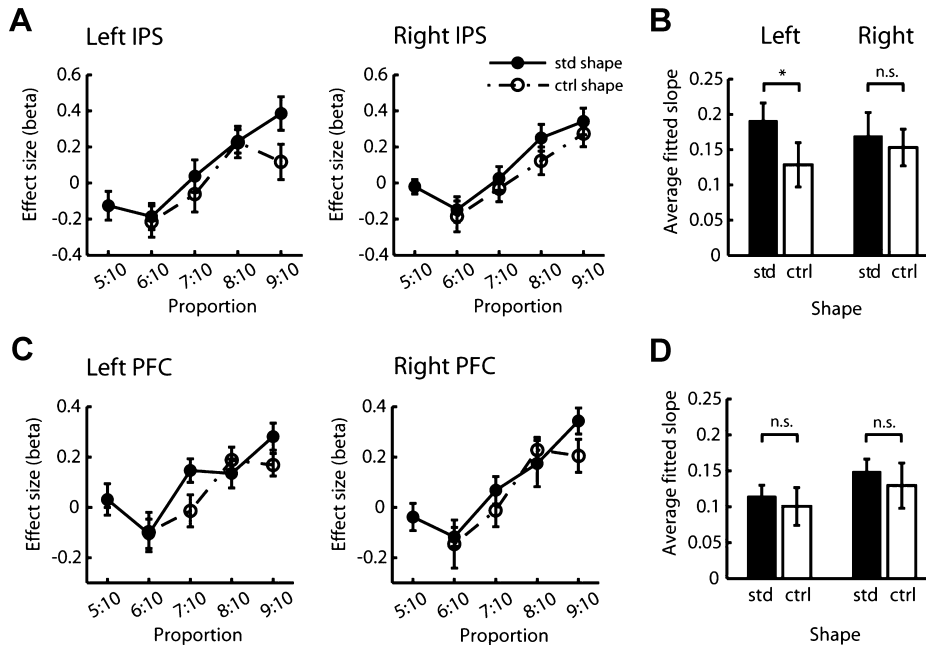


FIG. 5. Representation of dot proportions in parietal and frontal cortex. (A) Beta weights for the adaptation and deviant stimuli were averaged over subjects for standard and control shapes (closed and open circles, respectively) and the left and right intraparietal sulcus (IPS; left and right panel, respectively). (B) Linear functions were fitted to the deviant beta weights for each subject and both hemispheres. Differences in slopes between standard and shape control deviants reached statistical significance in the left IPS only. (C) Beta weights plotted for both shapes and the left and right prefrontal cortex (PFC; left and right panels, respectively). (D) Averaged slopes of linear fits to the data in (C) for both hemispheres and standard and control shapes. There were no statistically significant differences. n.s., not significant. * $P = 0.04$.

and shape showed increased rebound to far compared with close deviants [main effect of distance: $F_{3,7} = 15.86$, $P = 4.8 \times 10^{-7}$ (left), $F_{3,7} = 23.32$, $P = 4.8 \times 10^{-9}$ (right)]. The effect of shape became significant in the left parietal cortex only, owing to a disproportionately 'decreased' signal recovery to the largest deviant in the shape control condition – a response to unspecific novelty leading to 'increased' rebound can therefore be excluded [main effect of shape change: $F_{1,7} = 5.89$, $P = 0.03$ (left), $F_{1,7} = 1.93$, $P = 0.19$ (right); Fig. 5A]. Most importantly, as in the line experiment, there were no interactions [distance \times shape: $F_{3,7} = 1.71$, $P = 0.18$ (left), $F_{3,7} = 0.22$, $P = 0.88$ (right)]. For both hemispheres, the slopes of linear fits to beta weights of all deviants were positive [$t_{14} = 7.62$, $P = 2.4 \times 10^{-6}$ (left standard shape), $t_{14} = 4.19$, $P = 0.001$ (left control), $t_{14} = 5.08$, $P = 1.7 \times 10^{-4}$ (right standard), $t_{14} = 5.86$, $P = 4.1 \times 10^{-5}$ (right control); Fig. 5B]. The difference in slopes reached significance on the left only ($t_{14} = -2.26$, $P = 0.04$) because of the outlier. There was no significant difference on the right ($t_{14} = -0.47$, $P = 0.65$).

In the PFC voxels with maximal adaptation, the repeated-measures two-way ANOVA of the deviants' beta weights (Fig. 5C) revealed no effect of shape change in either hemisphere [main effect of shape change: $F_{1,7} = 1.71$, $P = 0.21$ (left), $F_{1,7} = 1.71$, $P = 0.21$ (right); main effect of distance: $F_{3,7} = 22.54$, $P = 7.5 \times 10^{-9}$ (left), $F_{3,7} = 20.55$, $P = 2.4 \times 10^{-8}$ (right)]. The distance \times shape interaction was significant for the left PFC only [$F_{3,7} = 3.21$, $P = 0.03$ (left), $F_{3,7} = 0.82$, $P = 0.49$ (right)]. Reducing the effect of unsystematic noise, slopes of linear functions fitted to the deviant regressors' beta weights were positive [$t_{14} = 7.4$, $P = 5.2 \times 10^{-6}$ (left standard shape), $t_{14} = 3.79$, $P = 0.002$ (left control), $t_{14} = 8.64$, $P = 9.5 \times 10^{-7}$ (right standard), $t_{14} = 4.11$, $P = 0.001$ (right control); Fig. 5D], and there were no differences between the standard and shape control condition [$t_{14} = -0.58$, $P = 0.57$ (left), $t_{14} = -0.67$, $P = 0.52$ (right)].

Compressed tuning to numerosity

With a third stimulus set, we determined the brain regions sensitive to changes in absolute numerosity. Images were designed to resemble the dot proportion stimuli but were rearranged with regard to order of presentation (supporting Fig. S2). In a perceptually comparable stream of images, indistinguishable to the participants from the previous experiment, deviant stimuli now differed with regard to absolute magnitude. We conducted a full-brain second-level analysis of the distance contrast (main effect of distance; numerosities 6 and 30 contrasted against 12 and 24; Fig. 6A) to reproduce the results from a previous fMRI-adaptation study (Piazza *et al.*, 2004). Significant activation was identified in a frontoparietal network, again extending well into the anterior IPS in the parietal cortex. Plots of the averaged beta weights against stimulus numerosity in IPS (from maximal adaptation voxels in anterior IPS) resulted in inverted peak functions centered on the adaptation numerosity 18 (Fig. 6B). A repeated-measures two-way ANOVA with factors distance and shape revealed no interactions [$F_{4,5} = 1.32$, $P = 0.27$ (left), $F_{4,5} = 0.73$, $P = 0.57$ (right)]. Importantly, identical BOLD responses were found for adaptation numerosity 18 irrespective of presentation format (standard or shape change controls).

Recovery slopes for deviants smaller and larger than the habituation numerosity were different, resulting in symmetric tuning functions when plotted on a logarithmic scale (Fig. 6B). To quantify this finding, we fitted symmetric Gaussian functions to the tuning curves (averaged over standard and control shape conditions) plotted both on a linear and logarithmic scale for each of the 15 subjects. Gaussian distributions described the data plotted on a logarithmic scale significantly better [r^2 statistics; left: 0.71 (linear), 0.85 (log); right: 0.70 (linear), 0.84 (log)] for both hemispheres [$t_{14} = 2.47$, $P = 0.03$ (left), $t_{14} = 3.0$, $P = 0.01$ (right); Fig. 6C]. Tuning curve width, a direct measure of the precision of numerosity representation, was

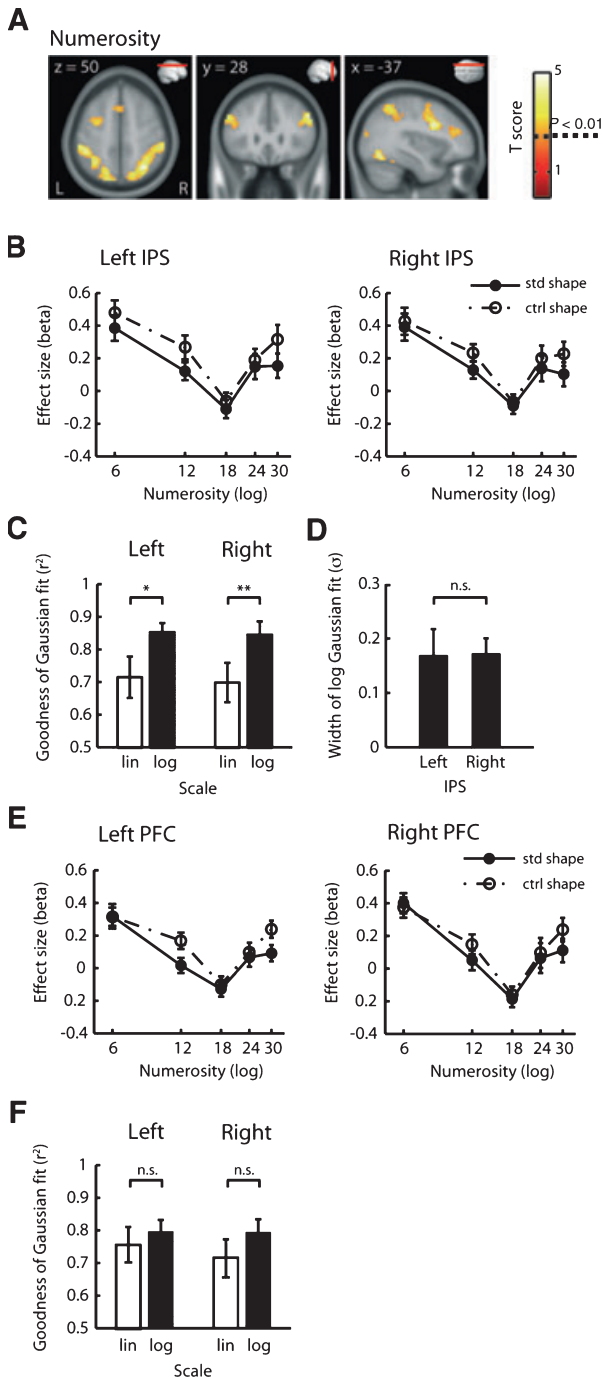


FIG. 6. Logarithmic tuning to numerosity. (A) Full-brain search for cortical regions responding stronger to more distant numerical deviants than to stimuli closer to the adaptation numerosity. Activation was observed in the bilateral intraparietal sulcus (IPS), precentral and prefrontal areas, as well as in the anterior cingulate and inferotemporal cortex. (B) Averaged beta weights plotted as a function of deviant numerosity on a logarithmic scale for standard and control shapes (closed and open circles, respectively) and the left and right IPS (left and right panel, respectively). (C) Goodness of Gaussian fits (r^2) to beta weights for each individual subject, averaged over standard and shape control conditions. On a logarithmic scale, data were more symmetrical around the adaptation numerosity and provided a significantly better fit bilaterally compared with plotting on a linear scale. (D) There was no inter-hemispheric difference in the width of the Gaussian fit. (E) Tuning curves plotted for bilateral prefrontal cortex (PFC). (F) Gaussian fits to both hemispheres on linear and logarithmic scales. ** $P = 0.01$; * $P = 0.03$; n.s., not significant.

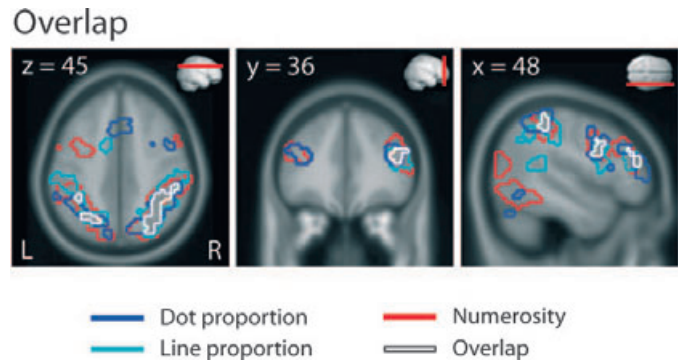


FIG. 7. Overlap of fMRI-adaptation distance effect for proportions and numerosities. Borders of cortical regions showing an effect of numerical distance are superimposed on a template brain for the numerosity (red), dot proportion (dark blue) and line proportion (light blue) experiments. Joint activation in all three experiments is outlined in white. Significant overlap was restricted to the bilateral parietal cortex surrounding the IPS, the precentral and prefrontal cortex.

equal in the left and right parietal cortex ($t_{14} = -0.10$, $P = 0.92$; Fig. 6D). In bilateral frontal areas, the graphs closely resembled those obtained in the parietal cortex with a tendency towards superior Gaussian fits on a logarithmic scale [r^2 left: 0.76 (linear), 0.80 (log); right: 0.71 (linear), 0.79 (log); $t_{14} = 0.71$, $P = 0.49$ (left), $t_{14} = 1.50$, $P = 0.16$ (right); Fig. 6E and F].

Overlapping representation of magnitude ratios and numerosities in the frontoparietal cortex

We observed a high degree of congruency between the individual regions for the proportion and numerosity experiments (Fig. 7). Joint activation in all three experiments, indicative of a shared substrate for the representation of absolute and relative magnitude, was seen around the IPS, in particular on the right, and in bilateral prefrontal and precentral regions, also with a right-sided predominance.

Discussion

In this study, we investigated the neural representation of non-symbolic proportions using fMRI adaptation. We made three key observations in our experiments. First, non-symbolic proportions (quantity ratios) are automatically (implicitly) represented in the human brain, because BOLD signal adaptation was seen in the absence of any task involving the explicit manipulation of stimuli. Second, populations of neurons are tuned to preferred proportions and, thus, recovery from BOLD signal adaptation was a function of ratio distance. Third, both numerosity and proportion are processed by the same dedicated brain areas as revealed by strong overlap of the distance effect for all three protocols. Our results therefore indicate that the human brain uses the same coding scheme for both absolute and relative quantities. The parietal lobe is thought to host a generalized magnitude system to represent very different classes of abstract quantity from spatial extent to number symbols (Walsh, 2003; Pinel *et al.*, 2004; Piazza *et al.*, 2007; Tudosciuc & Nieder, 2007). We now describe a novel, equally remarkable characteristic of this neural circuitry: non-verbal, automatic access to quantity ratios, a composite, derived measure of magnitude.

In the frontoparietal cortex, BOLD signal recovery (i.e. release from BOLD adaptation) increased as the numerical distance between adaptation and deviant proportion grew larger. This observation

closely resembles previous findings for absolute numerosities (Piazza *et al.*, 2004, 2007) and indicates that populations of neurons exist that are tuned to specific quantity ratios using an approximate, analog magnitude code. Neuronal activity and, consequently, changes in cortical blood flow are maximal for preferred proportions and fall off gradually as the deviant becomes more remote from the adaptation stimulus. The distance effect was invariant to the exact visual arrangement of individual stimuli, excluding an influence of low-level features. Rapidly and widely varying absolute line lengths and dot numerosities also did not allow subjects to precisely calculate an absolute number equivalent for the presented magnitude ratios (whereby our findings would reflect adaptation to and processing of absolute rather than relative quantity). Importantly, we reproduced the distance effect with two stimulus sets with fully distinct notations (continuous and discrete quantity; Verguts & Fias, 2004), arguing that magnitude ratios are represented as an abstract category in the human brain.

fMRI-adaptation protocols have proven a valuable tool for investigating human numerical cognition by determining not only 'where' magnitudes are processed, but importantly, 'how' this is accomplished from a mechanistic point of view (Piazza *et al.*, 2004, 2007; Shuman & Kanwisher, 2004; Ansari *et al.*, 2006; Cantlon *et al.*, 2006; Cohen Kadosh *et al.*, 2007). They circumvent some of the potential confounds of conventional fMRI protocols, including intentional response selection, which are known to engage parietal cortex (Gobel *et al.*, 2004). Moreover, adaptation approaches have the potential to achieve a sub-voxel resolution by 'tagging' a specific neuronal population that is sensitive to changes in a particular stimulus property (Grill-Spector *et al.*, 1999; Grill-Spector & Malach, 2001). Yet, these advantages come at a cost. Without the inclusion of careful controls, adaptation experiments investigating processes localized in the partial lobes struggle to exclude attentional influences, because BOLD rebound also scales with the degree of general stimulus novelty. The protocol presented here was therefore modified from previously published experiments to include different stimuli while maintaining the well-established core design.

We can confidently exclude the possibility that the observed distance effect was in fact a reflection of non-numerical stimulus novelty, whereby parietal activation could be due to an attentional pop-out effect that becomes more prominent as the difference in magnitudes increases. First, stimulus design ensured that low-level features such as dot array density (homogeneity) or the absolute difference in line lengths (outline shape) did not inform about the respective quantity dimension. Second, in the adaptation stimuli, we extensively varied the total number of display items as well as the individual set sizes in the dot proportion protocol and the absolute line lengths in the line proportion protocol. We argue that the presence of an effect of distance by itself is not easily explained by unspecific novelty, because more salient dimensions exerting stronger influences on attentional processing did not co-vary with proportion. Third, our results show that overlapping regions represent absolute and proportional magnitude but that there was no dependable effect of changes in more salient stimulus dimensions (as verified by the participants, see Materials and methods) such as shape and color in these same areas (Fig. 2). Fourth, interactions were consistently absent in all experiments with a lack of difference in cortical activation between the standard and control conditions in particular for the quantitatively close deviants (Figs 4–6). This closely approximates the control situation we also explicitly included in the numerosity experiment, in which a strong 'non'-numerical shape deviant was contrasted with a standard stimulus of the same magnitude (numerosity 18). Identical BOLD responses demonstrated that the regions we analysed in the

proportion and numerosity experiments were exquisitely sensitive to changes in the magnitude dimension. Fifth, and most importantly, novelty effects in fMRI experiments are localized to the more 'posterior' part of the superior parietal lobule (e.g. Dehaene *et al.*, 2003; Gur *et al.*, 2007). However, our results indicate an additional involvement particularly of the 'anterior' IPS in coding of relative magnitude (Fig. 2). This region is clearly segregated from the novelty areas, which did not enter our analyses, and has been established as the key structure for the representation of absolute number (for a meta-analysis of fMRI studies, see Dehaene *et al.*, 2003). Anatomically, it lies posterior to the somatosensory cortex and borders the inferior parietal lobule (e.g. angular gyrus) superiorly. It comprises the anterior ascending portion of the IPS (inferior postcentral sulcus) as well as parts of the horizontal segment (Brodmann areas 7, 40, 39; Molko *et al.*, 2003). In a similar vein, it has been proposed that 'violation of expectation' could account for the effects of adaptation in fMRI experiments, whereby the rebound from adaptation is a mere consequence of unpredicted stimuli (Summerfield *et al.*, 2008). Given the parametric stimulus design in our study, this concept falls short of explaining our results: the deviants occurred with equal frequencies, yet influenced the size of BOLD signal recovery as a function of their numerical distance from the adaptation stimulus. In summary, our results demonstrate domain-specific coding of magnitude ratios in the anterior IPS and PFC.

We selected the voxels to analyse for numerical tuning from the regions with significant BOLD signal adaptation. The regressors for distance and adaptation effects were orthogonal; thus, there was no bias in voxel selection. Whole-brain analyses for distance effects showed widespread activation in the frontoparietal cortex (Fig. 2), meaning our results were also not exaggerated by choosing the 'best-fit' noisy voxel. Furthermore, the frontoparietal regions with the strongest adaptation to constant magnitude coincided with the areas identified in the full-brain analysis of the distance effect; again, selection of voxels for the tuning plots was therefore not biased towards posterior 'novelty areas'. Eye movements are typically associated with activation in more posterior and medial areas of the parietal cortex (Simon *et al.*, 2002) and therefore did not confound our analyses. Finally, influences of task difficulty or response selection can be excluded (Piazza *et al.*, 2004; Cantlon *et al.*, 2006), for in our passive viewing protocols we intentionally avoided any explicit instructions to the subjects, asking them only to fixate and attend to the stimuli.

Our numerosity experiment extended previous studies by providing several interesting additional points. Besides corroborating the role of the parietal cortex in number processing, we found that similar mechanisms are operating in the PFC, a structure that has been implicated in magnitude processing in studies of human infants (Cantlon *et al.*, 2006) and non-human primates (Nieder *et al.*, 2002). A typical finding in primate single-cell electrophysiology is compressed scaling of number representations (Nieder & Miller, 2003; Nieder & Merten, 2007), whereby differences in neuronal firing rates for adjacent numerosities decrease as the magnitudes increase (reflecting the behavioral 'size effect': the ability to discriminate two equidistant numerosities deteriorates as their magnitude increases). Tuning curves become symmetric and Gaussian-like only when plotted on a logarithmic scale. By comparing plots on linear and logarithmic scales across subjects, we now provide quantitative evidence that this principle holds true in the human brain also. On a behavioral level, mapping of number to a compressed scale has been demonstrated in an Amazonian indigene culture that lacks number words and formal education (Dehaene *et al.*, 2008). Our study now reveals the neurobiological basis for this logarithmic intuition of number. In further accord with these findings, our statistical analyses

demonstrate that tuning curve width, a measure of the precision of numerical coding, is equal for the left and right parietal cortex. Whereas neuropsychological studies have often reported deficits in arithmetic following left-sided lesions (particularly, but not restricted to, the angular gyrus), we interpret the absent lateralization to reflect the fact that processing of non-symbolic quantities does not rely on or profit from language-associated networks in the left hemisphere. Finally, the experimental design in the proportion protocols, strictly speaking, did not fully address coding of bi-directional 'more deviant than', but rather uni-directional 'greater than' (because all deviants were chosen to be larger than the adaptation stimulus). However, the numerosity protocol with deviant stimuli both smaller and larger than the adaptation number showed that the frontoparietal cortex is indeed sensitive to changes in magnitude in both directions.

Interestingly, we found greater neuronal discriminability (steeper slopes of the linear fits) for discrete compared with continuous proportions, in spite of a considerably smaller inter-deviant numerical distance (1 : 10 vs. 1 : 6, respectively). A possibility is that discrete, countable stimuli (dots) provide more exact numerical representations than continuous, uncountable stimuli (line lengths; Gallistel & Gelman, 2000). Fractions with Arabic digits convey even higher precision using verbal access to absolute quantities via number symbols (Jacob & Nieder, 2009). This recent fMRI-adaptation study challenged the commonly held belief that the human brain necessarily processes the two components of a fraction in separation (Bonato *et al.*, 2007). Examining non-symbolic proportions, we now link up single-cell electrophysiological recordings in the monkey reporting neurons sensitive to changes in proportion (Vallentin & Nieder, 2008), with human neuroimaging showing that even fractions can be represented by their true numerical value. Our experiments identify in the human brain a phylogenetically conserved system for non-verbal representation of magnitude ratios that may serve as the basis to encode even symbolic proportions (fractions) following the acquisition of language and symbolic knowledge.

The experiments described here suggest that, akin to numerosities, proportions can be encoded and accessed automatically, and that the populations of neurons tuned to preferred quantity ratios give rise to a non-symbolic, language-independent and therefore intuitive representation of proportions. We therefore expect to find an implicit understanding of proportionality in adult humans lacking number words (Gordon, 2004; Pica *et al.*, 2004; Dehaene *et al.*, 2008), infants and even in other species. Indeed, our data are in full agreement with the fact that non-verbal animals (Wilson *et al.*, 2002) and human infants (McCrink & Wynn, 2007) understand the concept of magnitude ratios and utilize it for making decisions. Our results now establish tuning to proportions in the human brain as on a par with the well-characterized cortical representation of numerosity, suggesting that the same analog magnitude code is used to create concepts of both absolute and relative quantity.

Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1. Blood oxygenation level-dependent (BOLD) signal time courses for individual deviants.

Fig. S2. Numerosity adaptation protocol.

Table S1. Cortical regions showing a decrease in BOLD signal during the adaptation phase of the line proportion experiment.

Table S2. Cortical regions showing a decrease in BOLD signal during the adaptation phase of the dot proportion experiment.

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Acknowledgements

This work was supported by a junior research group grant (C11/SFB 550) from the German Research Foundation (DFG) and a Career Development Award by the International Human Frontier Science Program Organization (HFSP) to A.N.

Abbreviations

BOLD, blood oxygenation level-dependent; fMRI, functional magnetic resonance imaging; IPS, intraparietal sulcus; PFC, prefrontal cortex.

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