Representation of Number in the Brain

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Abstract

Number symbols have allowed humans to develop superior mathematical skills that are a hallmark of technologically advanced cultures. Findings in animal cognition, developmental psychology, and anthropology indicate that these numerical skills are rooted in nonlinguistic biological primitives. Recent studies in human and nonhuman primates using a broad range of methodologies provide evidence that numerical information is represented and processed by regions of the prefrontal and posterior parietal lobes, with the intraparietal sulcus as a key node for the representation of the semantic aspect of numerical quantity.

Contents

INTRODUCTION

Numbers are an integral part of our everyday life; we use them to label, rank, and quantify virtually everything that is imaginable. Symbolic number representations, using Arabic numerals and number words, are uniquely human cultural achievements that have enabled elaborate scientific developments and shaped our technologically advanced culture. For this reason, arithmetic was long thought to be an exclusively human faculty.

Over the past decades, however, it has become clear that basic numerical competence does not depend on language and education, but is rooted in biological primitives that can be explored in innumerate indigenous cultures, infants, and even animals. Comparative psychologists have shown that animals can discriminate numerosities (i.e., the cardinality of a set, set size) (Brannon & Terrace 1998, Davis & Perusse 1988), and field studies have convincingly demonstrated that animals use numerical information on a regular basis to make informed decisions (e.g., in foraging or in social interactions such as fights) (Hauser et al. 2000, McComb et al. 1994, Wilson et al. 2001). These findings highlight the evolutionary significance of numerical competence; processing numerical information is important to guarantee an animal's survival. A breakthrough in developmental psychology was achieved when numerical cognition was demonstrated in human infants (Starkey & Cooper 1980, Feigenson et al. 2004). Research has shown that infants of only a few months of age have the capacity to represent cardinality. Infants can also engage in rudimentary arithmetic, which was first demonstrated in experiments in which five-month-old infants were shown basic addition and subtraction operations on small sets of objects (Wynn 1992). Anthropological studies showed that even human adults who have been deprived of cultural transmission of number symbols, and thus cannot count, are still able to quantify objects (Gordon 2004) and perform arithmetic operations in an approximate fashion (Pica et al. 2004).

Altogether, these behavioral studies underscore that a biological precursor system of elementary arithmetic exists in many species, not just humans. Moreover, this nonverbal quantification system seems to constitute the phylogenetic and ontogenetic foundation of all further, more elaborate numerical skills (Halberda et al. 2008). An understanding of this evolutionary precursor system can thus help to elucidate the symbolic number representations reserved to humans. Here, we specifically review the progress that has been made in our understanding of the neuronal mechanisms of numerical competence in human and nonhuman primates. This review is structured according to the two major concepts that numerical cognition encompasses: numerical quantity and numerical rank (Wiese 2003). Numerical quantity refers to the empirical property of cardinality of sets of objects or events (also called numerosity). It pertains to the question, "How many?". Numerical rank refers to the empirical property of serial order and pertains to the question, "Which position?".

NUMERICAL QUANTITY

Neural Substrates of Cardinal Number

Case studies of the pathology of numerical competence historically provided the first insights into its neural foundation. Acquired calculation deficits (acalculia) occurred after brain damage near the parieto-occipito-temporal junction (Henschen 1919, Gerstmann 1940) or in the frontal lobe (Luria 1966). The first functional imaging studies of mental arithmetic quickly pointed to a reproducible bilateral parietal and prefrontal activation (Appolonio et al. 1994, Dehaene et al. 1996, Roland & Friberg 1985). More specifically, the banks of the intraparietal sulcus (IPS) are consistently activated whenever adults compute simple comparison, addition, subtraction, or multiplication with Arabic numerals (Chochon et al. 1999, Pinel et al. 2001). The IPS is activated even when they merely detect a digit among colors and letters (Eger et al. 2003). The intraparietal region seems to be associated with an abstract, amodal representation of numbers inasmuch as it can be activated by numbers presented in various culturally learned symbolic notations such as Arabic numerals and spelled-out or spoken number words (Eger et al. 2003), even across various countries and cultures including France, the United Kingdom, the United States, Austria, Singapore, China, and Japan (Tang et al. 2006).

Further clarifying the role of the IPS in semantic number representations are neuroimaging studies that have relied on nonsymbolic presentations of number as sets of dots or as series of tones (Castelli et al. 2006; Piazza et al. 2004, 2006, 2007). Attending to the numerosity of such stimuli is enough to induce a strong bilateral activation of the IPS (Castelli et al. 2006, Piazza et al. 2006). Even passively looking at a set of dots suffices to encode its numerosity and adapt to it so that the IPS later shows a rebound functional magnetic resonance imaging (fMRI) response when the number is changed by a sufficient amount (Piazza et al. 2004). This fMRI adaptation method has also been used to demonstrate a convergence of symbolic and nonsymbolic presentations of numbers toward a common representation of quantity in the IPS and prefrontal cortex (PFC) (Piazza et al. 2007).

IPS: intraparietal sulcus

PFC: prefrontal cortex

fMRI and event-related potentials (ERPs) have shown that number-related parietal activations are already present in four-year-old children as they attend to the numerosity of sets (Cantlon et al. 2006, Temple & Posner 1998). To visualize more directly the brain's responses to number in infants, Izard et al. (2008) recorded event-related potentials from three-month-old infants while they were presented with a continuous stream of sets of objects. The right parietal cortex responded to numerical novelty, whereas the left occipito-temporal cortex responded to object novelty (**Figure 1**). This ventral/dorsal double dissociation is similar to what has been observed in adults and four-year-olds (Cantlon et al. 2006, Piazza et al. 2004); the fusiform gryus reacts to changes in object identity but not in number, whereas the parietal regions react to changes in number but not in object identity. The results suggest that number belongs to the parameters that are quickly extracted by the dorsal parietal pathway even in infants. Thus, the parietal mechanism of numerosity extraction seems to be already functional prior to symbolic education in humans. This supports the idea of a language-independent human quantification system whose precursors can also be tackled in nonhuman primates.

Neurons Encoding Numerical Quantity

Recordings in monkeys trained to discriminate numerosity demonstrated the capacity of single neurons to encode the number of items in a motor task (Sawamura et al. 2002) and in visual displays (Nieder et al. 2002, Nieder & Miller 2004). In the basic layout of the visual task, monkeys viewed a sequence of two displays separated by a memory delay and were required to judge whether the displays contained the same number of items (**Figure 2*a***). To ensure that the

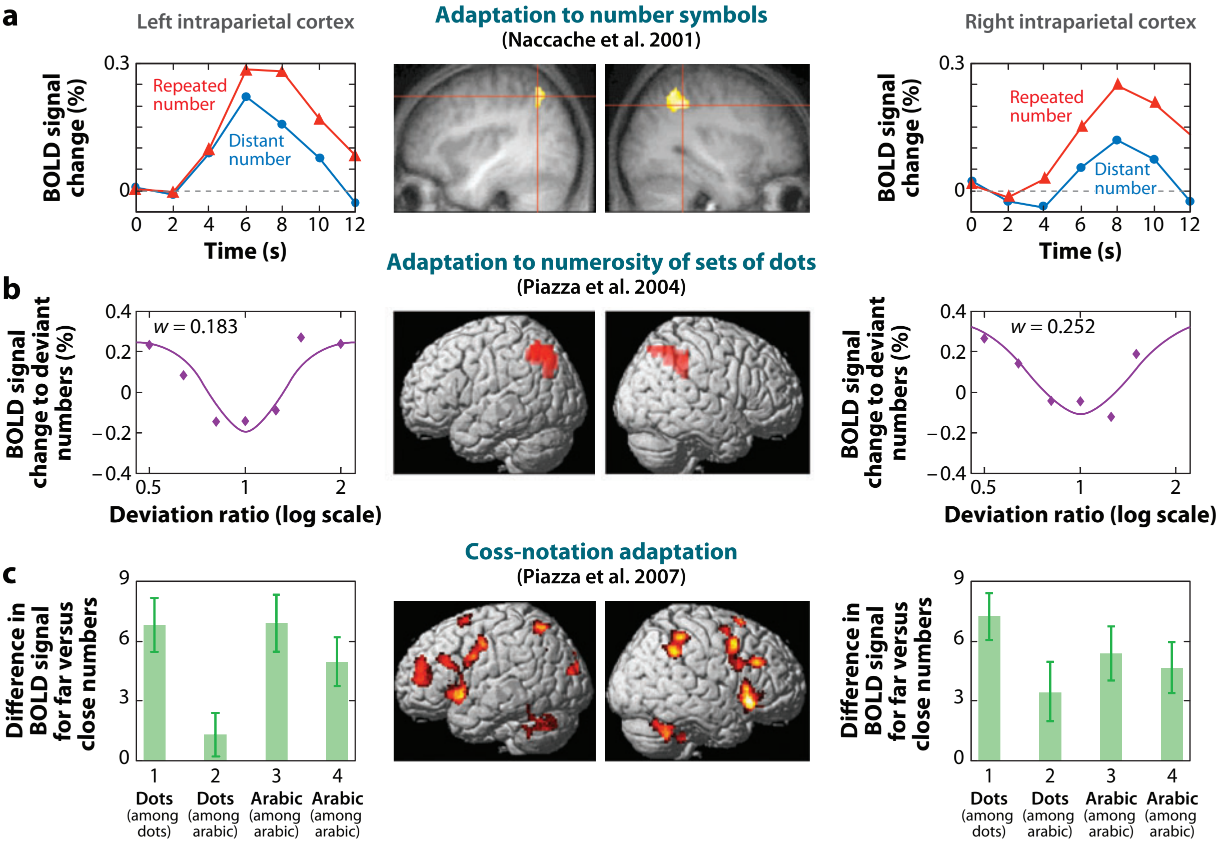


Figure 1

fMRI studies of numerical adaptation in human adults reveal a notation-independent representation of number. The figure puts together three studies that have demonstrated a response to numerical novelty, in the sense of a greater blood oxygen level-dependent (BOLD) fMRI signal to numbers distant from those previously presented than to numbers close to or equal to those previously presented. (*a*) Subliminal priming study showing left and right intraparietal response to numerical novelty for Arabic numerals and number words (data from Naccache & Dehaene 2001). (*b*) Event-related fMRI study of sparse numerosity deviants (sets of dots) presented in the context of a large number of identical adaptation numerosities (data from Piazza et al. 2004). This study manipulated systematically the distance between the deviant and adaptation numerosities, revealing a Gaussian profile of response suggestive of a tuned-cell code for numerosity similar to that observed in nonhuman primates. Precision of coding, as estimated by the Weber fraction w, is somewhat greater in left than in right intraparietal cortex. (*c*) Event-related fMRI study of deviants that could differ in both numerical distance and symbolic or nonsymbolic notation (Arabic numerals versus sets of dots) (data from Piazza et al. 2007). More distant numbers induce a greater signal recovery. Note the lack of left intraparietal response to dot deviants among Arabic numerals, which could be due to a precise coding of symbolic numbers in this region. The additional activation, particularly in prefrontal cortex, could be due to methodological differences, notably in the degree of awareness of deviancy.

monkeys solved the task by judging number per se rather than simply memorizing sequences of visual patterns or exploiting low-level visual features that correlate with number, sensory cues (such as position, shape, overall area, circumference, and density) were varied considerably and controlled for.

Numerosity-selective neurons were tuned to the number of items in a visual display (**Figure 2*c*,*d***), that is, they showed maximum activity to one of the presented quantities—a neuron's preferred numerosity—and a progressive drop off as the quantity became more remote from the preferred number (Nieder et al. 2002, Nieder & Merten 2007). Importantly, changes in the physical appearance of the displays had no effect on the activity of numerosity-selective neurons (Nieder et al. 2002, Nieder & Miller 2004).

As illustrated in **Figure 2*b***, neurons tuned to numerosity were abundant in the lateral PFC and the fundus of the IPS (Nieder & Miller 2004), within or near an association area termed ventral intraparietal area (VIP) (Colby et al. 1993). Neurons encoded numerosity both when the dots were displayed simultaneously as a single set or one by one as a sequence of foveal stimuli (**Figure 2*e*,*f***) (Nieder et al. 2006). The parietal location fits remarkably well with the predictions of human neuroimaging studies (Simon et al. 2002). The parietal cortex, particularly the IPS, seems to be the first cortical stage that extracts visual numerical information because its neurons require shorter latencies to become numerosity selective than do PFC neurons (Nieder & Miller 2004). As PPC and PFC are functionally interconnected (Cavada & Goldman-Rakic 1989, Chafee & Goldman-Rakic 2000, Quintana et al. 1989), numerical information first encoded in PPC might be conveyed directly or indirectly to the PFC where it is amplified and maintained to gain control over behavior. As classical association cortices, the prefrontal and posterior parietal cortices are ideal brain structures for an abstract encoding of quantity. They receive highly processed multimodal input (Duhamel et al. 1998, Lewis & Van Essen 2000, Bremmer et al. 2001, Miller & Cohen 2001)—a prerequisite for numerical competence because the number concept applies equally well to all sensory modalities. Both are also key processing sites for executive functions (e.g., categorization, working memory, decision making, goal-directed behavior, etc.) (Miller & Cohen 2001, Stoet & Snyder 2004, Wallis et al. 2001).

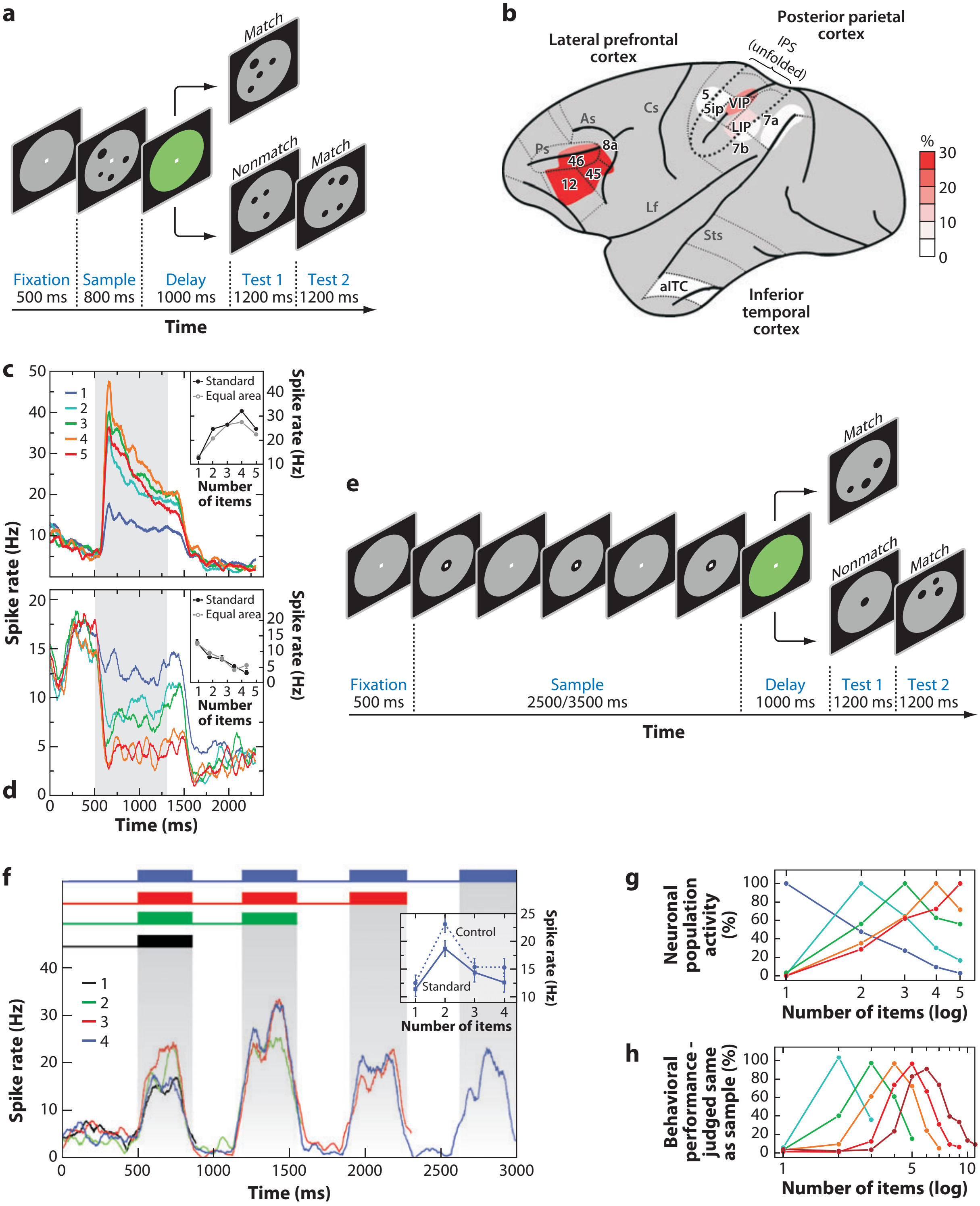
Several findings suggest that the monkey intraparietal neural code for numerosity may be an evolutionary precursor onto which the human invention of arithmetic later encroached. First, the analogy in cerebral location is striking. Numerosity-tuned neurons are mostly found in the depth of the IPS and often show visual flow-field responses, which are compatible with a location in area VIP (Nieder et al. 2006, Tudusciuc & Nieder 2007). Likewise, human fMRI studies have located a plausible homolog of area VIP (Bremmer et al. 2001, Sereno & Huang 2006) at a location remarkably close and overlapping with that of number-related responses (Hubbard et al. 2005, Simon et al. 2002). A recent fMRI study (E. Hubbard, P. Pinel, A. Jobert, S. Dehaene, manuscript submitted) using localizer tasks inspired from monkey physiology [such as saccadic eye movements to determine area lateral intraparietal area (LIP), and visual flow fields and tactile face stimulation to pin down area VIP] indicates partial overlap between VIP and the activation induced by calculation. Together, these studies suggest a (partial) homology between human and macaque parietal regions.

VIP: ventral intraparietal area

LIP: lateral intraparietal area

The activity of all numerosity-selective neurons, each tuned to a specific preferred numerosity, formed a bank of overlapping numerosity filters, mirroring the animals' behavioral performance (Nieder & Miller 2003, Nieder & Merten 2007) (**Figure 2*g*,*h***). Interestingly, the neurons' sequentially arranged overlapping tuning curves preserved the inherent order of cardinalities, an observation that can explain why numerical distance is such a strong predictor of performance in various number discrimination and comparison tasks. An important piece of additional evidence for the contribution of numerosity-selective neurons to behavioral performance came from the examination of error trials. When the monkeys made judgment errors, the neural activity for the preferred quantity was significantly reduced as compared to correct trials (Nieder et al. 2002, 2006; Nieder & Miller 2004; Nieder & Merten 2007). In other words, if the neurons did not encode the numerosity properly, the monkeys were prone to mistakes.

Collectively, numerosity-selective neurons form a distributed representation subject to Weber's law; each number is not coded in an exact manner, but only approximately and with an imprecision that increases in proportion


a
Match
Nonmatch
Match
Fixation
500 ms
Sample
800 ms
Delay
1000 ms
Test 1
1200 ms
Test 2
1200 ms
Time
b
Lateral prefrontal cortex
Posterior parietal cortex
IPS (unfolded)
As
Cs
Ps
8a
46
45
12
5
5ip
VIP
LIP
7a
7b
Lf
Sts
aITC
Inferior temporal cortex
%
30
20
10
0
c
Spike rate (Hz)
1
2
3
4
5
Standard
Equal area
Number of items
d
Time (ms)
0
500
1000
1500
2000
e
Match
Nonmatch
Match
Fixation
500 ms
Sample
2500/3500 ms
Delay
1000 ms
Test 1
1200 ms
Test 2
1200 ms
Time
f
Spike rate (Hz)
1
2
3
4
Control
Standard
Number of items
Time (ms)
0
500
1000
1500
2000
2500
3000
g
Neuronal population activity (%)
Number of items (log)
h
Behavioral performance - judged same as sample (%)
Number of items (log)

to number. Interestingly, symmetric Gaussian tuning functions are only obtained after log-transformation of the number scale (**Figure 2*g***) (Nieder & Miller 2003). This is consistent with Fechner's law, which states that the perceived magnitude (*S*) is a logarithmic function of stimulus intensity (*I*) multiplied by a modality and dimension specific constant (*k*). Therefore, single-neuron representations of numerical quantity in monkeys obey Fechner's Law. The log-Gaussian neural code that was identified in the macaque monkey for a broad range of numerosities (up to 30 items; see Nieder & Merten 2007) is identical to the representation thought to underlie numerical judgments in human and monkey subjects, as derived either from behavioral research (Dehaene 2007, Merten & Nieder 2008, Van Oeffelen & Vos 1982) or from imaging studies. When Piazza et al. (2004) observed that functional MRI adaptation to numerosity was present in human IPS, a read-out of fMRI adaptation revealed peaked tuning profiles which followed Weber's law. A recent study by the same group (Piazza et al. 2007) has shown that numerosity-related information not only exists in the IPS, but also in areas of the human frontal lobe. This commonality suggests that humans and macaques have a comparable labeled-line coding mechanism for the representation of numerosities.

To avoid extensively overlapping tuning curves and to increase discrimination precision among numerosities, neurons should exhibit relatively sharp tuning behavior. Diester & Nieder (2008) recently provided a first glimpse of how this might be achieved mechanistically by local cortical networks within the PFC. They inferred the major cortical cell types—pyramidal cells and interneurons—by characterizing the waveforms of exctracellularly recorded action potentials in monkeys performing a numerosity discrimination task. Putative excitatory pyramidal cells show broad action potential waveforms [broad spiking neurons (BN)], whereas (mainly inhibitory) interneurons are characterized by narrow spike waveforms [narrow spiking (NS)] (Simons 1978, Swadlow 2003, Wilson et al. 1994). Interestingly, adjacent NS and BS neurons recorded at the same electrode tip and, thus, at minimum anatomical distance, often showed inverted numerosity tuning profiles. Importantly, such NS and BS cell pairs were functionally connected (as evidenced by temporal cross-correlation analyses), and the temporal discharge of adjacent NS and BS cells

Figure 2

Representation of visual cardinality in rhesus monkeys. (*a*) Delayed match-to-sample task with visually presented numerosity as the stimulus dimension of interest. A trial started when the monkey grasped a lever and fixated at a central target. After 500 ms of pure fixation, the sample stimulus (800 ms) cued the monkey for a certain numerosity it had to memorize during a 1000 ms delay period. Then, the first test stimulus (test1) was presented, which in 50% of cases was a match showing the same number of dots as cued during the sample period. In the other 50% of cases the test1 display was a nonmatch, which showed a different numerosity as the sample display. After a nonmatch test stimulus, a second test stimulus (test2) appeared that was always a match. To receive a fluid reward, monkeys were required to release the lever as soon as a match appeared. Trials were pseudorandomized and balanced across all relevant features. Monkeys were required to maintain fixation throughout the sample and delay period. (*b*) Lateral view of a monkey brain showing the recording sites in LPFC, PPC, and aITC. The proportion of numerosity-selective neurons in each area is color coded according to the color scale. The IPS is unfolded to show the different areas in the lateral and medial walls. Numbers on PFC indicate anatomical areas. (As, arcuate sulcus; Cs, central sulcus; IPS, intraparietal sulcus; LF, lateral fissure; LS, lunate sulcus; Ps, principal sulcus; Sts, Superior temporal sulcus) (after Nieder & Miller 2004). (*c*, *d*) Responses of single neurons that were recorded from the PFC (*c*) and the IPS (*d*). Both neurons show graded discharge during sample presentation (*interval shaded in gray*, 500–1300 ms) as a function of numerosities 1 to 5 (color coded averaged discharge functions). The insets in the upper right corner show the tuning of both neurons and their responses to different control stimuli. The preferred numerosity was 4 for the PFC neuron (*c*) and 1 for the IPS neuron (*d*) (after Nieder et al. 2002). (*e*) Behavioral numerosity discrimination functions of two monkeys. The curves indicate whether they judged the first test stimulus as containing the same number of items as the sample display. The function peaks (and the color legend) indicate the sample numerosity for which each curve was derived. Behavioral filter functions are symmetric on a logarithmic scale. (*f*) The averaged single-cell numerosity-tuning functions (from PFC) are also only symmetric after logarithmic transformation (after Nieder and Miller 2003).

was negatively correlated (Diester & Nieder 2008); if one neuron discharged, the other neuron was significantly inhibited, and vice versa. Such a feedforward inhibition mechanism may lead to a refinement of numerosity tuning in putative pyramidal cells by lowering the shoulders of the pyramidal cells' tuning functions, thus helping to achieve a more precise distinction among preferred numerosities.

Neuronal Codes for Quantity Representations

Several sensory properties such as binocular disparity, wavelength, and contrast are encoded early on in the sensory pathways (Van Essen & DeYoe 1993). Number, however, is an abstract category devoid of specific sensory features; two cats and two calls have nothing in common, except that the size of their sets is two. How do numerosity-selective neurons tuned to preferred numerosities arise in the course of cortical processing?

Two main models have been proposed to account for the cortical extraction of quantity information from sensory inputs (**Figure 3*a*,*b***). The mode-control model by Meck & Church (1983) works in series and suggests that each item is encoded by an impulse from a pacemaker, which is added to an accumulator (**Figure 3*a***). The magnitude in the accumulator at the end of the count is then read into memory, which forms a representation of the number of a set. Thus, it is assumed that quantity is encoded by summation coding, i.e., the monotonically increasing and decreasing response functions of the neurons (see also the network model by Zorzi & Butterworth 1999, Zorzi et al. 2005).

Another model, the numerosity detector model by Dehaene & Changeux (1993) implements numerosity in parallel (**Figure 3*b***). First, each (visual) stimulus is coded as a local Gaussian distribution of activation by topographically organized input clusters (simulating the retina). Next, items of different sizes are normalized to a size-independent code. At that stage, item size, which is initially coded by the number of active neurons on the retinotopic map (quantity code) is now encoded by the position of active clusters on a location map (position code). Clusters in the location map project to every unit of downstream summation clusters, whose thresholds increase with increasing number and pool the total activity of the location map. The summation clusters finally project to numerosity clusters. Numerosity clusters are characterized by central excitation and lateral inhibition so that each numerosity cluster responds only to a selected range of values of the total normalized activity, i.e., their preferred numerosity. Because the numerosity of a stimulus is encoded by peaked tuning functions with a preferred numerosity (causing maximum discharge) this mechanism is termed a labeled-line code. A similar architecture was proposed by Verguts & Fias (2004) using a backpropagation network. Interestingly, summation units developed spontaneously in the second processing stage (the hidden units) after tuned numerosity detectors were determined as the output stage. Conversely, cells tuned to numerosity developed at the output level in an unsupervised model with summation units at the input level.

Even though numerosity representations derived with both models are noisy (approximate) and obey Weber's law, the two models differ in important aspects. The mode-control model by Meck & Church (1983) operates serially and assumes representation of cardinality on a linear scale, whereas the numerosity detector model by Dehaene & Changeux (1993) encodes numerosity in parallel and represents it on a logarithmic scale [the same holds for the backpropagation model by Verguts & Fias (2004)]. Both models, however, require summation units that accumulate number in a graded fashion prior to feeding into numerosity detectors at the output.

Roitman et al. (2007) recently recorded neurons in area LIP whose responses resembled these summation units. Their discharge rate systematically increased or decreased monotonically with an increase in the numerosity of the stimulus set presented in their receptive field (**Figure 3*c*,*d***), similar to neurons

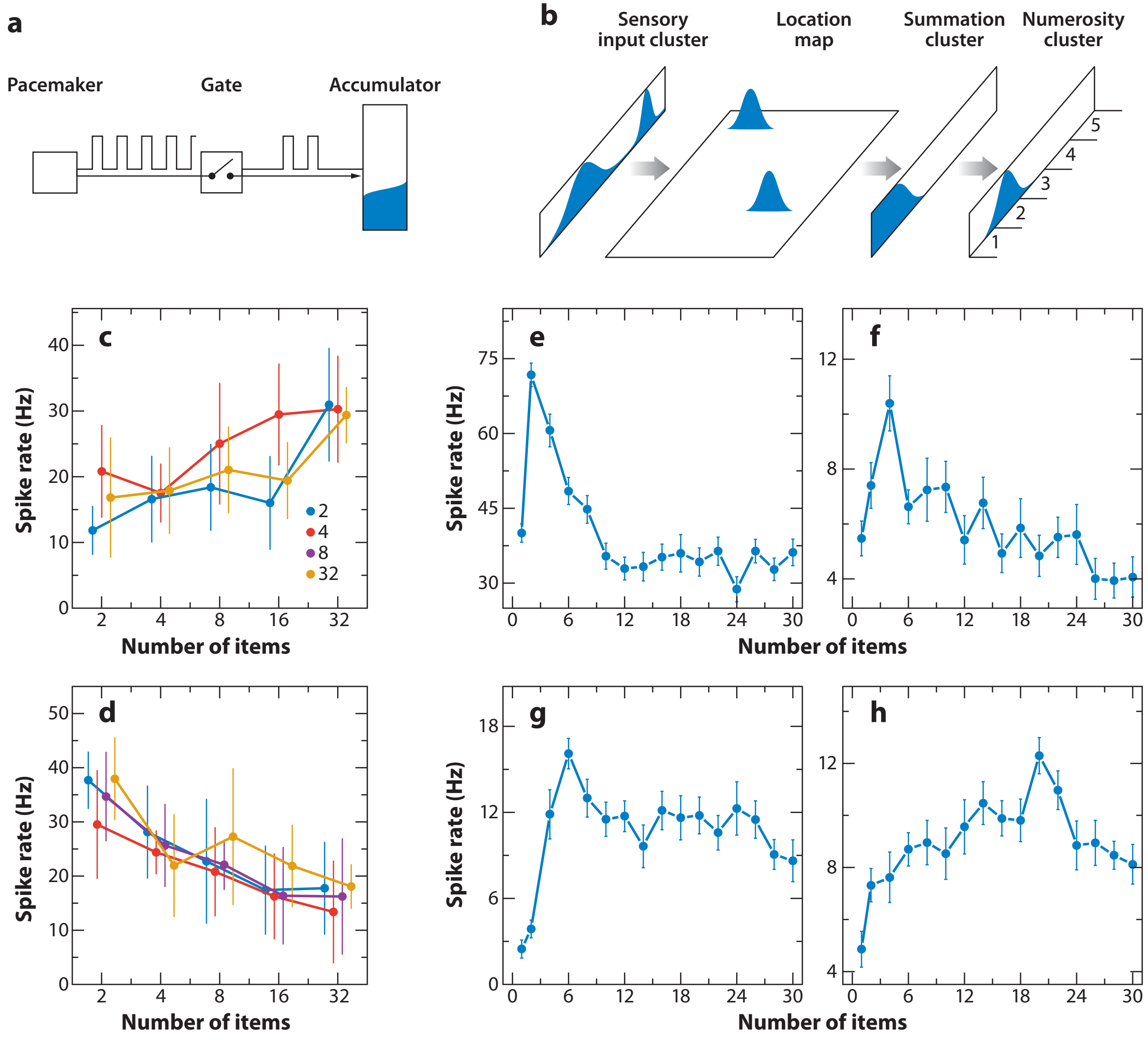


Figure 3

Implementation of neurons sensitive to numerosity. (*a*) Mode-control model (after Meck & Church 1983). (*b*) Numerosity detector model (after Dehaene & Changeux 1993). (*c*, *d*) Neurons in LIP discharge monotonically as a function of set size during an implicit numerosity task. Two single cells are depicted that show an increase (*c*) or decrease (*d*) of discharge rate, respectively, with increasing numerosity. Each neuron was tested with different standard (color code) and deviant numerosities (see text for explanation of the task) (from Roitman et al. 2007). (*e–h*) PFC neurons tuned to preferred numerosities in monkeys performing a delayed match-to-numerosity task. Preferred numerosity was 2° (*e*), 4° (*f*), 6° (*g*), and 20° (*h*) (from Nieder & Merten 2007).

representing other basic sensory magnitudes in a monotonic fashion (Romo et al. 1999, Brody et al. 2003). The authors suggested that the two classes of number-selective neurons (monotonic versus tuned cells) may be the physiological instantiation of the summation units and numerosity units proposed in neural network models of numerical representation; monotonic magnitude coding by LIP neurons may provide input to the tuned neurons in the PPC and PFC (**Figure 3*e–h***). Indeed, LIP and VIP are known to be monosynaptically connected.

Note, however, that the neurons recorded by Roitman and coworkers (2007) cannot be the endstage of number coding as they only encoded the numerosity of sets placed within their spatially restricted receptive fields. Extraction of abstract numerical information requires integration across visual space, and also time and modality for some tasks. Area VIP and the PFC are ideal candidate structures for such a representation of overall numerosity because both areas integrate multimodal input (Duhamel et al. 1998) and their neurons exhibit global cognitive processing properties that are no longer spatially restricted (Everling et al. 2002, Freedman & Assad 2009).

Importantly, in the Roitman et al. (2007) study, the monkeys were actively engaged in a delayed saccade task that did not require any discrimination of the numerosities. Numerosity only served to predict the amount of reward that the animal would get after a correct saccade. In this situation, very few neurons were tuned to numerosity, and monotonic coding was the rule. By contrast, all studies that required the monkeys to use cardinal numerical information explicitly found a labeled-line code, irrespective of stimulus modality, presentation format, and recording site (Sawamura et al. 2002; Nieder et al. 2002, 2006). In the monkey PFC, a labeled-line code was recently also observed for the neural coding of derived quantities such as visual proportions (Vallentin & Nieder 2008). This observation opens the interesting, yet obviously still speculative, possibility that the neuronal representation may change if quantity is encoded as an explicit category.

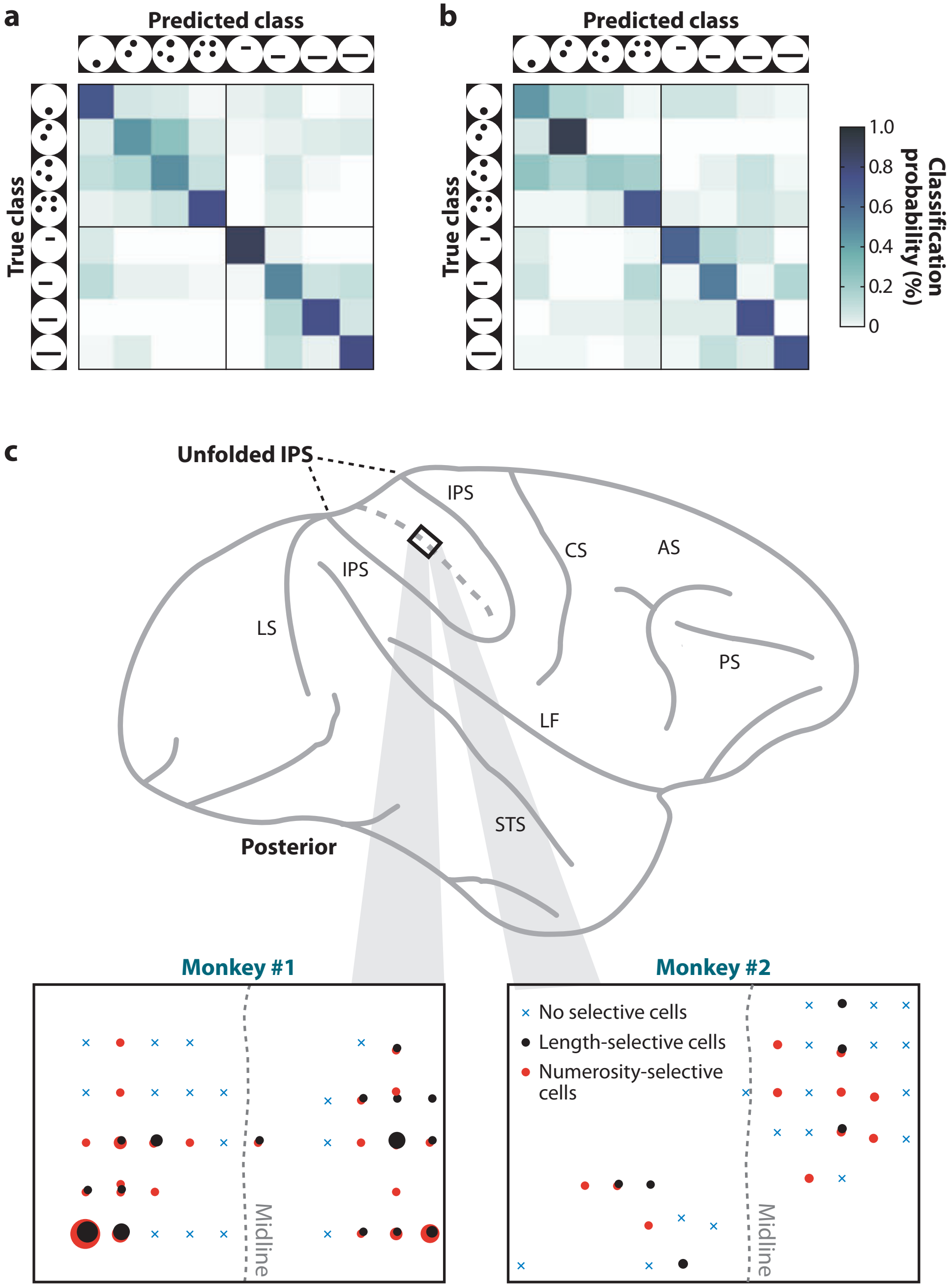
Recent single-cell analyses applying statistical learning algorithms also suggest that, beyond a simple rate code, additional information about numerosity is conveyed by the precise temporal discharge patterns of quantity-selective neurons. To assess the discriminative power of small populations of neurons, Tudusciuc & Nieder (2007) applied a population decoding technique (Laubach 2004, Hung et al. 2005, Averbeck et al. 2006, Laubach et al. 2008) based on an artificial neuronal network. The classifier was trained with neuronal responses (i.e., preprocessed spike trains) of a set of neurons recorded from area VIP while the monkeys made judgments about two stimulus dimensions (numerosity and line length); at this stage, the classifier was informed about the stimulus configuration and learned the neuronal features which were best suited for identifying a given category. In the subsequent test phase, the classifier predicted the categories from novel neuronal responses of the same pool of neurons, i.e., from data it had not used for learning.

The quantitative results based on the statistical classifier demonstrated that the small population of tuned quantity-selective neurons carried most of the categorical information (**Figure 4*a***). Interestingly, however, even a population of untuned neurons (neurons that did not discriminate quantity based on average spike rate) had a remarkable and significant

Figure 4

Neuronal coding of continuous and discrete quantity. (*a*, *b*) Classification performance of a statistical classifier based on spike trains of a population of IPS neurons. Confusion matrices describing the pattern of quantity classification performed on 72 quantity-selective neurons (*a*) and 72 nonselective (untuned) neurons (*b*). The rows in each confusion matrix represent the true classes the monkeys have seen, the columns correspond to the output of the classifier. Color codes the classification probability. The eight classes correspond to the eight stimulus quantities: numerosity 1 to 4 and line length 1 to 4, where length 1 is the shortest line. Thus, the main diagonal shows how often the classifier correctly assigned quantity stimuli to their real category (i.e., a measure of accuracy). (*c*) Anatomical reconstruction of the recording sites in area VIP at the fundus of the IPS. The top image shows a lateral view of a monkey brain. The squares in the bottom panels illustrate the magnified layout of the unfolded fundus of the IPS. The color symbols represent the selectivity of the neurons (one or more) recorded at each of the 174 penetration sites. The sites from which more than one type of neuron were recorded are marked by all corresponding symbols (from Tudusciuc & Nieder 2007).

discrimination ability, albeit to a lesser extent than the tuned neurons (**Figure 4*b***). This suggests that the classifier extracted additional information from the temporal structure of the neuronal responses beyond the averaged spike rate. Moreover, the comparison between the monkeys' neuronal and behavioral responses showed that the brain indeed utilizes this information for decision making; neuronal responses recorded whenever the monkeys



failed to discriminate the quantity categories prevented the classifier from predicting the correct quantity category. The precise nature of information extracted by the classifier, however, remains unknown.

Abstractness and Specificity of Number Coding in the IPS

The IPS hosts neural circuitry necessary for numerical representations. But does the IPS contain a special, locally restricted neural substrate for coding number? If so, are number neurons exclusively coding numerical information? Given the present state of knowledge, the answer is a nuanced one. The IPS clearly contains a specialized subsystem for number in the sense that its activation during calculation cannot be reduced to simpler sensori-motor functions such as attention or response planning. However, there does not seem to be a single, isolated piece of cortex that responds solely to number; parameters of object size and location also seem to be coded by intermingled neuronal circuits distributed within the same general area of IPS.

Is there a spatially restricted area for the coding of numerical information? The parietal activation putatively associated with the semantic quantification system occupies a fixed location relative to other parietal areas involved in sensory, motor, and attentional functions. Dehaene and coworkers (Simon et al. 2002, 2004) used fMRI to study the cerebral organization of six different functions previously associated with parietal systems: finger pointing, manual grasping, visual attention orienting, eye movement, written word processing, and calculation. All subjects showed a reproducible geometrical layout of activations associated with these functions. Most notably, activation uniquely evoked by calculation was observed in the depth of the IPS and was surrounded by a systematic front-to-back arrangement of activation associated with grasping, pointing, attention, eye movement, and language-related activations. The systematicity of this organization was confirmed by subsequent research using more selective experiments specifically designed to isolate grasping, saccade, and attention-related functions (for review, see Culham et al. 2006).

Are number neurons exclusively coding numerical information? Several studies have now contrasted intraparietal activations during judgments of number versus other continuous dimensions such as physical size, location, angle, or luminance (Cohen Kadosh & Henik 2006, Fias et al. 2003, Pinel et al. 2004, Zago et al. 2008). The results indicate that IPS activations do not cluster neatly into distinct regions specific for a given quantitative parameter, but instead show considerable overlap. This overlap is particularly strong for number and size (Pinel et al. 2004) and for number and location (Zago et al. 2008). Pinel et al. (2004) thus proposed that neuronal populations coding for number are highly distributed in the IPS and are intertwined and overlapping with representations of other quantitative parameters. This conclusion is supported by recent monkey physiology. To investigate how continuous quantity is encoded by single nerve cells and how it relates to numerosity representations, Tudusciuc & Nieder (2007) trained monkeys to discriminate the lengths of lines of the number of items in dot sets within a given recording session. Approximately 20% of anatomically intermingled single neurons in the monkey IPS encoded either numerosity, line length, or both types of quantities (**Figure 4*c***). Together, the data from human and nonhuman primates suggest that partly overlapping populations of neurons within this area may give rise to what appears functionally as a general-purpose parietal magnitude representation system (Walsh 2003).

Even within the number domain, numerical information might be partially segregated as a function of input or output modality. Cells in area 5 of the superior parietal lobule (SPL), which are usually not responsive to visual numerosity (Nieder & Miller 2004), have been reported to keep track of the number of hand movements a monkey had to make (Sawamura et al. 2002). Similar segregations in relation to numerical presentation formats can be found within the same sensory channel; during ongoing enumeration, cells in monkey VIP encoding the number of sequential items were not tuned to numerosity in multiple-item displays, and vice versa (Nieder et al. 2006). Only once the enumeration process was completed and the monkeys had to store the information in memory did a third population of neurons encode both temporal and spatial numerosities with cells that were tuned to numerosity irrespective of whether it was cued simultaneously or in sequence. This finding argues for segregated processing of numerosity during the actual encoding stage in the parietal lobe, but also for a final convergence of the segregated information to form an abstract quantity representation. Whether the abstract numerosity-tuned neurons that can be recorded in the delay period arise within the IPS owing to straight feedforward mechanisms or rather owing to top-down recurrent influences between IPS and PFC (Barash 2003) remains to be determined in future experiments.

Toward Symbolic Number Representations

As discussed above, humans and animals share an evolutionarily old quantity representation system that allows the estimation of set sizes. Nonverbal numerical cognition, however, is limited to approximate quantity representations and rudimentary arithmetic operations. Many human cultures, however, have invented number symbols that support precise enumeration and calculation. Even though number symbols are of paramount importance in today's scientific and technological culture, their invention dates back only a few thousand years (Ifrah 2000). Given the time scale of genetic evolution, a de novo development of brain areas with distinct, culturally dependent number symbol functions is more than unlikely (Dehaene 2005). Rather, it is conceivable that brain structures that originally evolved for other purposes are built upon in the course of continuing evolutionary development (Gould & Vrba 1982). According to the redeployment hypothesis (Anderson 2007) or recycling hypothesis (Dehaene 2005, Dehaene & Cohen 2007), already existing simpler cell assemblies are largely preserved, extended, and combined as networks to become more complex.

In the number domain, existing neuronal components in PFC and IPS subserving nonverbal quantity representations can be used for the new purpose of number symbol encoding, possibly without disrupting their participation in existing cognitive processes (Piazza et al. 2007). Guided by the faculty of language, children learn to use number symbols as mental tools during childhood. During this learning process, and as a necessary (but by no means sufficient) step for the utilization of signs as numerical symbols, long-term associations between initially meaningless shapes (which later become numerals) and inherent semantic numerical categories must be established. Indeed, fMRI adaptation studies have revealed that in educated adults, even very quick presentations of number symbols become capable of automatically evoking number-related activation in the intraparietal cortex of both hemispheres (Naccache & Dehaene 2001; see **Figure 1*a***). Cross-notation fMRI adaptation has also been observed in the intraparietal cortex (**Figure 1*c***); after adaptation with a set of 17, 18, or 19 dots, an fMRI recovery is observed when the Arabic numeral 50 is presented, but not when the numeral 20 is presented (Piazza et al. 2007). This observation strongly suggests that in human adults, populations of neurons in parietal and prefrontal cortex have been jointly activated by nonsymbolic numerosities and by number symbols.

Developmental studies indicate that the coding of nonsymbolic numerosity is already present in four-year-olds (Cantlon et al. 2006) and even in three-month-old infants (Izard et al. 2008), particularly in the right intraparietal cortex (see **Figure 5**). The very few cross-sectional neuroimaging studies of numerical development available so far suggest that the left intraparietal cortex exhibits an increase in activation and in the precision of its number code (Ansari et al. 2005, Ansari & Dhital 2006,

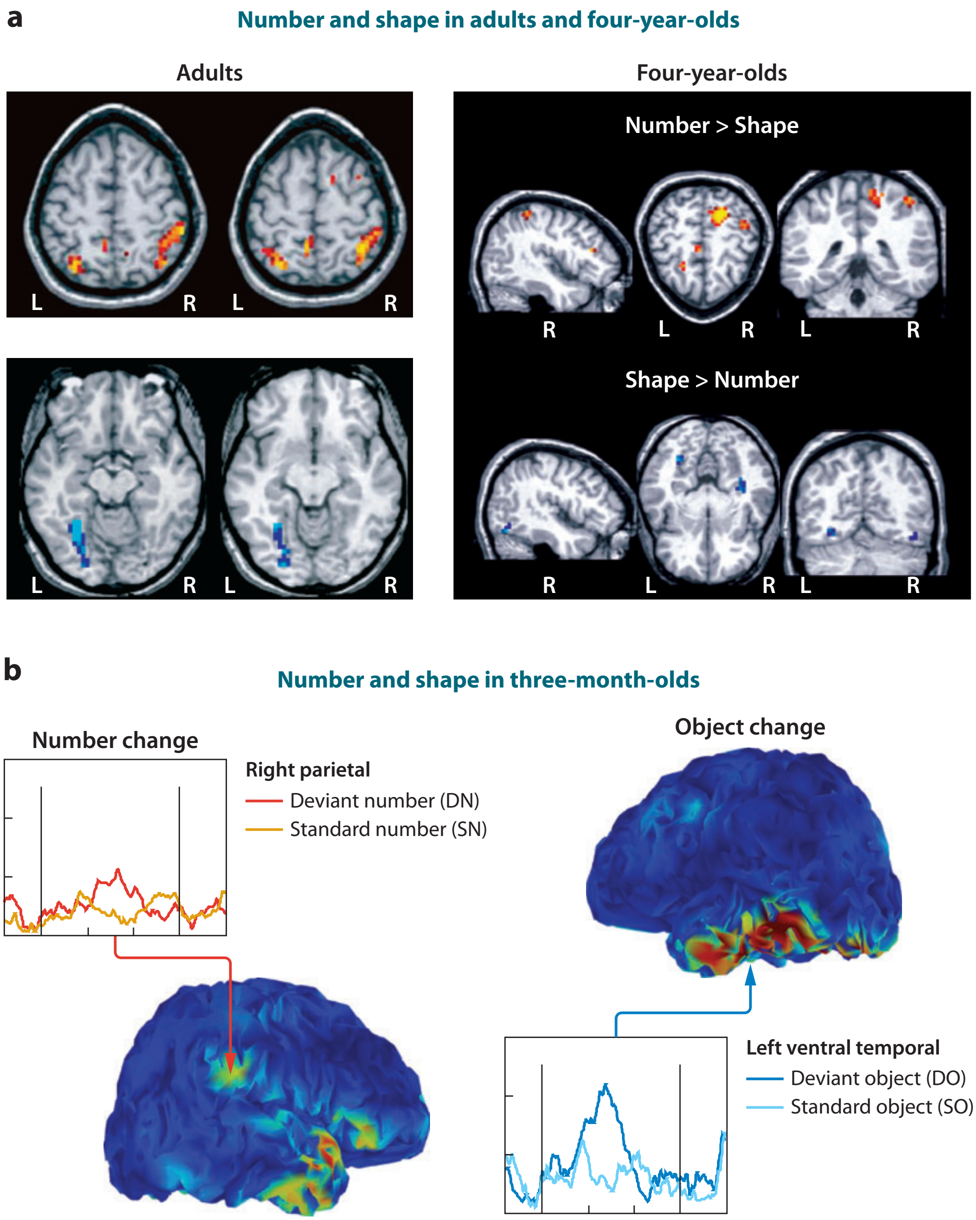


Figure 5

Developmental evidence for an early representation of numerosity in right parietal cortex. (*a*) Cantlon et al. (2006) used 4-Tesla fMRI and an adaptation design inspired from Piazza et al. (2004) to localize cortical responses to changes in either numerosity or object identity of a visual set. A clear dorsal-ventral distinction can be seen in adults (*left panel*), with bilateral intraparietal responses to number change, and left lateralized occipito-temporal responses to object change. A similar ventral-dorsal organization is seen in four-year-olds, with prominent numerical representations in right parietal cortex. (*b*) Izard et al. (2008) used high-density recordings of event-related potentials and cortical-source reconstruction to monitor infants' brain responses to changes in numerosity or object identity. Right parietal cortex responded strongly to number change, whereas left ventral temporal cortex responded strongly to changes in object identity.

Rivera et al. 2005). Thus, this region may play a particular role in the emergence of exact arithmetic abilities in the course of education, corroborating the century-old observation that acalculia is typically caused by left but not right parietal lesions.

Recently, Pinel & Dehaene (2009) obtained indirect evidence that the acquisition of a sophisticated language for number may play a role in this left-lateralized development of the parietal number system. They studied hemispheric lateralization of fMRI activations for calculation and for language in a large group of 209 right-handed subjects (**Figure 6**). Although both arithmetic and sentence processing activated large sets of areas strongly lateralized to the left hemisphere, these two lateralizations were largely uncorrelated, which suggested they might be caused by several independent genetic and developmental variables. However, there was a strong and systematic intersubject correlation between two focal regions; the lateralization of the left superior temporal sulcus during language processing predicted the lateralization of the left IPS during arithmetic. This observation speculatively suggests that education to numerical symbols significantly affects the cerebral representation of number (see sidebar Does Language Affect Numerical Thought? Cognitive Anthropological Studies of Number Sense).

DOES LANGUAGE AFFECT NUMERICAL THOUGHT? COGNITIVE ANTHROPOLOGICAL STUDIES OF NUMBER SENSE

Several recent psychological studies in remote human cultures confirm that the sense of approximate numerosity is a universal domain of human competence (Gordon 2004, Pica et al. 2004, Frank et al. 2008, Butterworth et al. 2008). In the Amazon, for instance, the Munducuru and the Piraha people have very little access to education. Furthermore, their languages have reduced sets of number words, five and two number words, respectively, which are not used for counting and may be similar to the approximate English words “dozen” or “handful.” Yet adults and children of these cultures pass tests of approximate number perception, matching, comparison, and simple arithmetic (Gordon 2004, Pica et al. 2004). A vigorous debate concerns the limits of these native numerical abilities. On the one hand, some who adhere to Whorf’s hypothesis believe the lack of a developed language for number drastically affects numerical cognition and prevents any understanding of exact arithmetic (Gordon 2004). On the other hand, a recent study of Australian children concludes that a reduced number vocabulary does not prevent the emergence of “the same numerical concepts as a comparable group of English-speaking children” (Butterworth et al. 2008), including a thorough understanding of large exact numbers. Studies of the Munduruku, however, show clear cross-cultural differences; unlike Western controls, the Munduruku appear to think of number as an analog, an approximate and logarithmically compressed continuum (Pica et al. 2004, Dehaene et al. 2008), exactly as expected from the neural representation of numerosity observed in human and nonhuman primates (Nieder & Miller 2003, Nieder & Merten 2007, Piazza et al. 2004). Education in counting and measurement, more than spoken language, may play a critical role in bringing about concepts of exact number, a conceptual change whose neural underpinnings probably involve the left intraparietal sulcus (see main text).

To investigate the single-neuron mechanisms by which a number symbol becomes attached to the corresponding numerosity, Diester & Nieder (2007) trained two monkeys to associate the a priori meaningless visual shapes of Arabic numerals with the inherently meaningful numerosity of multiple-dot displays. After this long-term learning process was completed, a relatively large proportion of PFC neurons encoded plain numerical values, irrespective of whether they had been presented as a specific number of dots or as a visual sign (**Figure 7**). Such association neurons showed similar tuning during the course of the trial to both the direct numerosity in dot stimuli and the associated numerical values of signs. Interestingly, the tuning functions of association neurons showed a distance effect for both protocols, i.e., a drop-off of activity with increasing numerical distance from the preferred numerical value. This distance effect indicates that association neurons responded as a function of numerical value rather than visual shape per se. Most cells coded the (direct and associated) numerical values during specific time phases

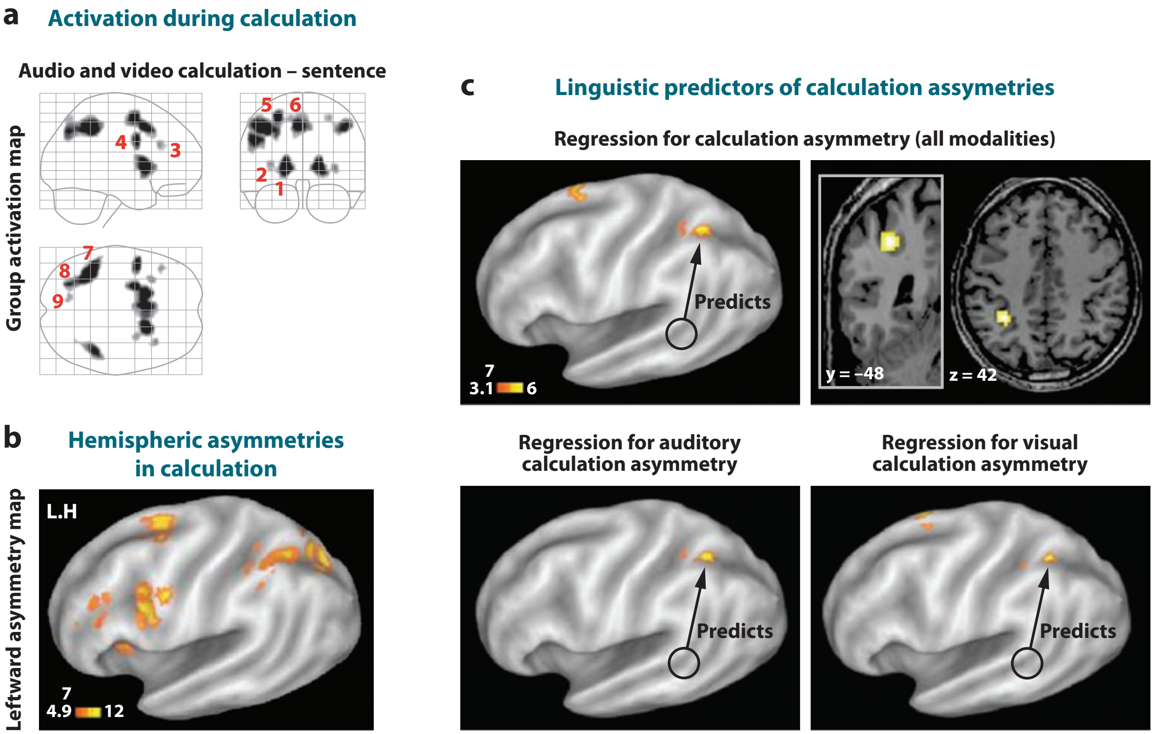


Figure 6

Evidence for a relation between language lateralization and the specialization of the left parietal cortex for exact calculation (Pinel & Dehaene 2009). fMRI activations were monitored in 209 right-handed subjects during a subtraction task with either auditory or visually presented number symbols. (*a*) Compared to sentence listening, listening to numerical problems such as "subtract 7 from 13" caused activation in a set of bilateral intraparietal, left precentral and inferior prefrontal, supplementary motor, and basal nuclei regions. (*b*) Most of these regions showed an asymmetry in favor of the left hemisphere. (*c*) The degree of asymmetry of the left intraparietal activation was quite specifically predicted by the asymmetry index of the left superior temporal sulcus during a nonnumerical sentence listening or reading task, which tentatively suggested that language asymmetry causes a developmental shift in the intraparietal number representation.

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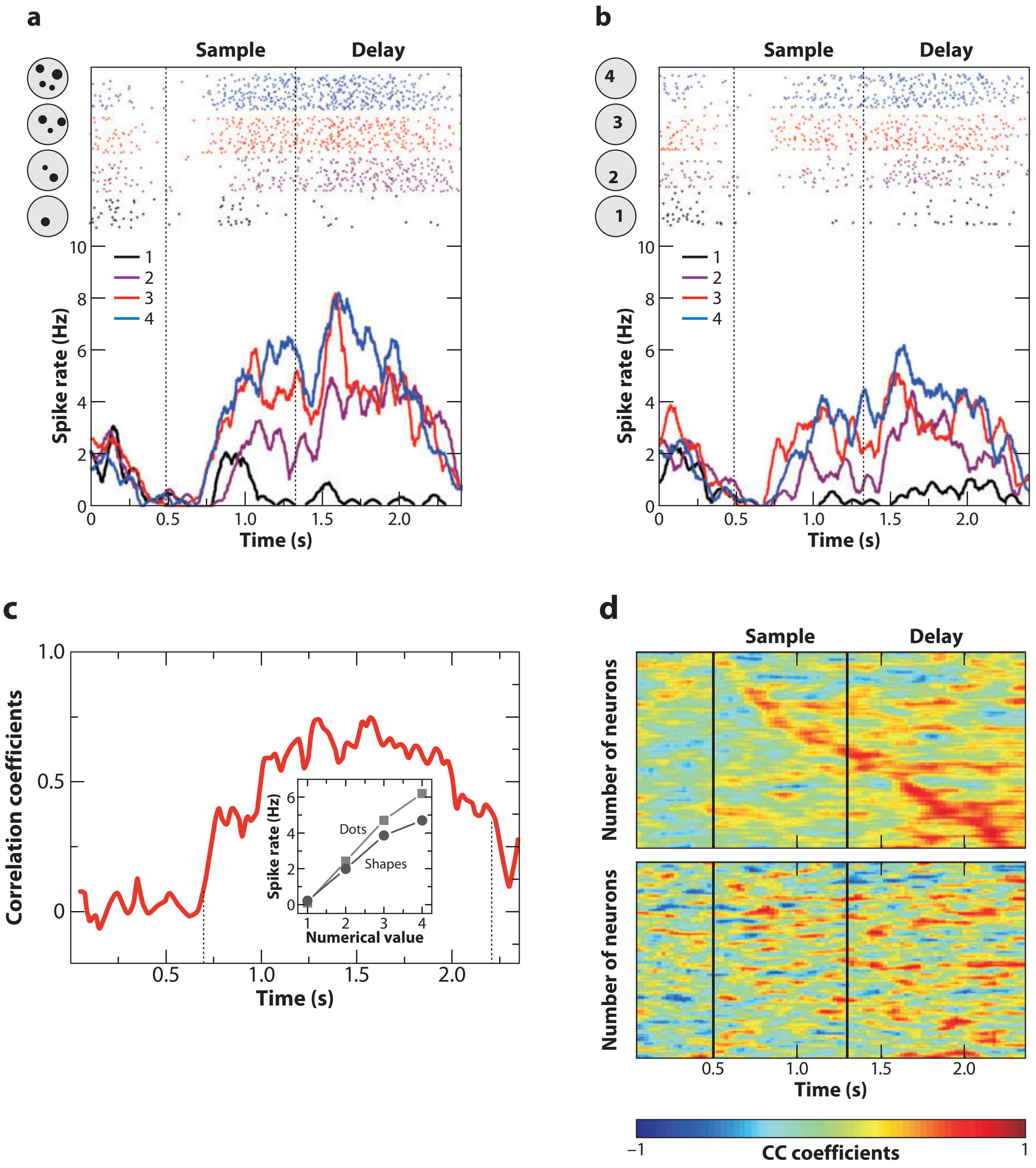
Figure 7

Semantic associations between signs and numerical categories by single neurons. (*a*, *b*) The responses of the same single PFC neuron to both direct numerosities and associated numeral shapes [side panels in (*a*) and (*b*) illustrate sample stimuli]. Neuronal responses in (*a*) and (*b*) are shown as dot-raster histograms (*top*, each dot represents an action potential) and smoothed spike density histograms (*bottom*, colors denote discharge to the corresponding sample numerical value 1 to 4). The first 500 ms indicate the fixation period. Black vertical lines mark sample-onset (500 ms) and offset (1300 ms). This neuron's preferred numerical value in the sample and the delay period was 4. Note the similarity in the association neurons' temporal discharge profiles in response to the multiple-dot displays and the shape of Arabic numerals. (*c*) Time course of cross-correlation coeffcients for the tuning behavior of the neuron to dots (*a*) and shapes (*b*). The interval bordered by vertical dotted lines indicates the time phase of significant cross correlation (as determined by measures from signal detection theory) between tuning to numerical values in the multiple-dot displays and Arabic numerals; in this period, the neuron associated numerical values in the two protocols. The overall tuning functions of this neuron to dots and shapes are shown in the inset. (*d*, *e*) Temporal profile of correlation coefficients during correct trials (*d*) and error trials (*e*) for all association neurons in the PFC (running average rectangular filter, window size 5 data points). Neurons are sorted by time of maximal correlation (after Diester & Nieder 2007).

in the trial (e.g., only at sample onset or toward the end of the delay period). The neuronal population as a whole, however, represented the numerical association throughout the entire trial and thus provided crucial associative information over time. In addition, the activity of association neurons predicted the monkeys' performance; if the monkeys failed to match the correct number of dots to the learned signs, the tuning behavior of a given neuron to numerosities and their associated visual shapes was severely disrupted. These findings argue



for PFC association neurons as a neuronal substrate for the semantic mapping processes between signs and categories. In contrast to PFC, only 2% of all recorded IPS neurons associated signs with numerosities. Moreover, the quality of neuronal association in the IPS was weak and occurred much later during the trial. Therefore, even though monkeys use the PFC and IPS for nonsymbolic quantity representations, only the prefrontal part of this network is engaged in semantic shape-number associations in symbol-training monkeys.

Interestingly, a somewhat similar pattern may exist in human children (Ansari et al. 2005, Kaufmann et al. 2006, Rivera et al. 2005). In contrast to adults, young children lacking ample exposure to number symbols show elevated PFC activity when dealing with number symbols. With age and proficiency, however, the activation seems to shift to posterior parietal and occipito-temporal areas, particularly in the left hemisphere. The PFC could thus be ontogenetically and phylogenetically the first cortical area establishing semantic associations, which might be relocated to the parietal cortex in human adolescents in parallel with the maturing of the language capacities that endow our species with a sophisticated symbolic system (Deacon 1997, Nieder 2009).

NUMERICAL RANK (ORDINALITY)

The sense of ordinality—the knowledge of which number comes first, second, third, etc.—seems to rely on a system that is partially dissociable from cardinality. Experiments by Turconi (Turconi & Seron 2002; Turconi et al. 2004, 2006) have demonstrated that the ordinality and cardinality meanings of numbers, although often associated, are not synonymous to human subjects. Surprisingly, judging whether 2 is smaller than 5 is a different task than judging whether 2 comes before 5. The function that relates response times to numerical distance is distinct; it shows a classical distance for cardinality judgements (faster RTs with larger distances), but a partially reversed effect with ordinal judgements (fast RTs to consecutive pairs such as 4–5) (Turconi et al. 2006). Event-related potentials are also subtly different (Turconi et al. 2004), and knowledge of ordinality and cardinality, although often associated in brain-lesioned patients (Cipolotti et al. 1991), can be dissociated in Gerstmann's syndrome following a left parietal lesion (Turconi & Seron 2002).

The few studies that have attempted to identify the cerebral bases of ordinal knowledge suggest that ordinal and cardinal knowledge may involve overlapping neural circuits within parieto-frontal areas. Number comparison, which involves the cardinal meaning of numbers, and letter comparison, which only involves ordinal knowledge, activate very similar parieto-frontal networks in humans (Fias et al. 2007). Furthermore, during ordinal comparisons, the left intraparietal area shows a distance effect (smaller activation for more distant rank orders) that resembles the effect observed during number comparison (Marshuetz et al. 2006).

Similar networks of ordinal number representations seem to be present in the macaque monkey. Neurons that encode the ordinal position of task-related hand or eye movements have been found frequently in prefrontal (Funahashi et al. 1997) and a subset of motor-related cortical areas, such as the frontal eye field (FEF), caudate nucleus, and anterior cingulate cortex (Barone & Joseph 1989, Kermadi & Joseph 1995, Procyk et al. 2000, Procyk & Joseph 2001); presupplementary (pre-SMA) and supplementary motor area (SMA) (Tanji & Shima 1994, Clower & Alexander 1998, Shima & Tanji 2000); and even primary motor cortex (Carpenter et al. 1999). These neurons were only active when the monkeys reached or saccaded to the first, second, or third target, irrespective of the targets' location and the precise type of movement.

Ordinal categorization of items requires both information about the rank of an item (for example, based on temporal order) and its identity. Neuropsychological studies emphasize the importance of the lateral PFC in maintaining temporal order information (Milner 1971, McAndrews & Milner 1991). In monkeys, lesioning the dorsolateral frontal cortex causes impairments in tasks that require recall of the temporal order of events and stimuli (Petrides 1995). Two recent elegant studies (Ninokura et al. 2003, 2004) addressed the single-neuron correlate of temporal rank order information in visual lists. Monkeys were trained to observe and remember the order in which three visual objects appeared. Subsequently, the animals planned and executed a triple-reaching movement in the same order as previously seen. Neurons in the ventro-lateral PFC selectively encoded visual object properties, whereas neurons in the dorso-lateral PFC were selectively tuned to the rank order of the objects irrespective of the sensory properties of objects. For example, several rank-order selective neurons were active whenever the second item of a shuffled list appeared. A third class of neurons, found in the ventro-lateral PFC, showed the most complex responses, which integrated the objects' sensory and order information. Such neurons would only discharge whenever a certain object appeared at a given position in the sequence.

The representational formats of nonverbal serial order information are still poorly understood. However, behavioral and neuronal data indicate an imprecise representation of discrete numerical rank, which is reminiscent of the approximate-magnitude mechanism that has been proposed for cardinality. To elaborate a computational model of working memory for serial order, Botvinick & Watanabe (2007) recently wove item, numerosity, and rank information together. Their network combined graded neuronal responses to different items (not yet verified experimentally) and tuning functions for sequential enumeration processes (Nieder et al. 2006) with the data showing that neurons in the PFC code the rank of items within a sequence (Ninokura et al. 2004). The model's output, a recalled multi-item sequence, replicated many behavioral characteristics of working memory such as the primacy effect (a recall advantage for initial items) and the recency effect (advantage for the last one or two items). Furthermore, changing the width of the model's rank-tuning curve simulated the developmental finding of improved recall accuracy with age. Thus, this model integrates across several neurophysiological studies to demonstrate how higher cognitive functions may exploit both quantity and rank. It posits that working memory of ordered sequences, at least in part, relies on neuronal assemblies in the parietal and prefrontal cortices that also contribute to numerosity representations.

CONCLUSION

The seemingly narrow domain of number processing has provided a remarkably productive window into the neural basis of a conceptual competence. Numerical cognition is perhaps the only domain of higher cognition in which a series of converge experiments provide seamless links from single-cell recordings in animals to human neuroimaging studies and behavioral competence. Mathematical theories, based on extensions of signal detection theory and evidence accumulation mechanisms, now provide bridging laws that account for the details of human response times and error rates in elementary arithmetic task (e.g., Dehaene 2007). A major question for further research is whether the neurobiological model will continue to prove useful in studying more complex mechanisms of even greater relevance to the human species. The cortical representation of symbols and the emergence of higher representational mechanisms with serial or even recursive computational capacities are two central issues that remain.

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