The neuronal code for number

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Abstract | Humans and non-human primates share an elemental quantification system that resides in a dedicated neural network in the parietal and frontal lobes. In this cortical network, 'number neurons' encode the number of elements in a set, its cardinality or numerosity, irrespective of stimulus appearance across sensory motor systems, and from both spatial and temporal presentation arrays. After numbers have been extracted from sensory input, they need to be processed to support goal-directed behaviour. Studying number neurons provides insights into how information is maintained in working memory and transformed in tasks that require rule-based decisions. Beyond an understanding of how cardinal numbers are encoded, number processing provides a window into the neuronal mechanisms of high-level brain functions.

Number rules the universe. Pythagoras

One of the central concepts we use in thinking about the world is the number concept. The number concept encompasses cardinal numbers, which are the focus of this Review, ordinal numbers and nominal numbers[1,2]. Cardinality (also known as numerosity) corresponds to the empirical property of quantity, and is the number of countable elements in a given group (for example, five runners). From basic needs, such as finding enough food items, to more advanced requirements, such as calculating the flight trajectories of spacecraft, survival depends on processing numerical quantity.

Numbers are intriguing because they are abstract representations. When assessing numerosity, the sensory appearance of the elements is meaningless. For example, three fingers, three calls and three hand movements can all be classified by the cardinal number 'three'. Numbers are also fascinating because they can be logically transformed according to a finite set of rules; for example, two plus two equals four. Such simple and many more complex operations are the building blocks of arithmetic, the elementary branch of mathematics. Numerical operations require mental feats such as abstraction, memorization, rule following and decision making. Therefore, number processing provides a means to decipher the neuronal mechanisms of cognitive control functions.

Several lines of evidence suggest that number estimation is ubiquitous in the animal kingdom and deeply rooted in human ancestry. First, numerate humans who are presented with stimuli that are displayed too briefly to be counted can still estimate numerosity[3,4]. Second, innumerate humans who have never learned to count verbally are still able to process numerosity[5,6]. Third, prelinguistic infants can discriminate the number of objects[7,8], and, last, both trained and wild animals (insects[9,10], fish[11,12], amphibians[13,14], birds[15,16] and mammals) exploit set size to arrive at adaptive decisions[17–22]. Three different processes, subitizing[23], number estimation (also known as analogue magnitude representation) and a texture-like mechanism are thought to underlie the (nonverbal) representation of number in humans and other animals[24]. Collectively, these findings argue that humans share a nonverbal quantification system with non-human animals.

This quantification system resides in a dedicated parieto-frontal brain network in primates[25,26]. Over the past 15 years, studies in non-human primates have identified cellular mechanisms that give rise to numerical competence. This Review discusses how single 'number neurons' in selected regions of the primate association cortices encode the number of elements in a stimulus. Beyond a mere understanding of how cardinal numbers are represented, the investigation of number neurons elucidates the processing and transformation of numerical information in tasks that require cognitive control as a preadaptation for arithmetic.

Neurons represent abstract number
Coding across space, time and modality. Determining whether number representations are abstract or are influenced by non-numerical variables is notoriously difficult because number is intrinsically correlated with many other features of a physical stimulus. Varying the number of items in a set inevitably changes spatial and/or temporal parameters, and fixing one parameter causes another to vary with the number of items. For example, the total area covered by all items in an array can only be fixed if the size of the individual items is decreased for each item that is added to the array. Responses made by a neuron or a subject to such an addition could in fact represent changing item size rather than number. The best

Ordinal numbers
Numbers that relate to the empirical property of 'rank' in a sequence (for example, 'fifth place').

Nominal numbers
Strictly linguistic labels to identify objects (for example, 'Bus number 5').

Number estimation
(Also known as the analogue magnitude system and the analogue number system). A process of representing small and large set sizes that becomes systematically less precise with increasing numbers. Thus, number estimation obeys Weber's law.

Subitizing
(Also known as object file representation or object tracking system). The rapid tracking for up to approximately four items by assigning 'files' or 'pointers' to individual items.

way to tackle this problem is to control — unbeknown to the individual — one parameter after another in separate stimulus configurations. If a neuron (and the subject) responds equally to systematically varied (that is, controlled) numerosity stimuli, it is safe to conclude that the neuron responds to number. Therefore, one important past research agenda was to test the activity of neurons to various number stimulus formats.

In monkeys trained to judge cardinal values (FIG. 1a), neurons in the lateral prefrontal cortex (lPFC) and the intraparietal sulcus (IPS) of the posterior parietal cortex (PPC) responded selectively to a specific number of items (that is, numerosity) in visual multiple-dot displays[27–31] (FIG. 1b,c), including a numerosity of zero[32,33]. Number neurons respond most strongly to their preferred numbers, but they also respond to a lesser extent to adjacent numbers, and thus they have a bell-shaped (Gaussian) response function. The visual appearance of stimulus displays, such as the spatial arrangement, the density or the total area of the dots, had no effect on neuronal activity in the studies described above, confirming that the neurons represented numerosity rather than the co-varying sensory features of the displays.

Number neurons not only signal the numerosity in simultaneously displayed visual items but also encode the number of elements that appear sequentially one by one, irrespective of the temporal intervals between the elements[34] (FIG. 1d). In functional MRI (fMRI), the activation of number neurons is mirrored by bilateral blood oxygen level dependent (BOLD) activation in the human IPS during numerosity estimation in both spatial (item arrays) and temporal (sequential items) modes of display[35]. Sequential processing is particularly important in the motor system, and cells in the superior parietal lobule (SPL; area 5) are tuned to different numbers of hand movements[36]. Transient pharmacological inactivation of neuronal activity in parietal area 5 led to individual movements being omitted in monkeys that had been trained to perform between one and five hand movements, thus preventing the monkeys from performing the correct number of movements[37]. Controls showed that the errors were not caused by motor deficits or an impaired ability to select between actions. This finding demonstrates that the activity of number neurons is causally related to number estimation.

Given its abstract nature, a number needs to be encoded not only across time and space in single sensory domains but also independently of the sensory modality (that is, encoding must occur supramodally). In monkeys trained to assess both the number of sequential visual dots and auditory sounds within the same session (FIG. 1d,e), neurons in the lPFC and in the ventral intraparietal (VIP) area of the IPS encoded the number of auditory pulses, the number of visual items, or both[38]. Interestingly, many randomly selected neurons (11% of the total number) in the PFC responded to the same number of items in both the visual and the auditory stimulation protocols; that is, they responded supramodally to number (FIG. 1f). In the VIP area, however, intermingled neurons represented either visual or auditory numerosities, but not both[38]. In humans, modality-independent

(visual or auditory) BOLD activation during numerosity estimation has been observed in a right fronto-parietal network[39]. The same network was also identified during verbal counting of visual and auditory items, with additional activation in prefrontal, parietal and premotor areas[39]. In contrast to monkeys, the human parietal lobe seems to be recruited more strongly with age and number proficiency[40,41], giving rise to supramodal (spoken or written) and notation-independent (numerals or number words) symbolic number activation[42].

The idea that numerical representations are abstract has previously been rejected as premature based on the behavioural differences that are found for the processing of different number formats and number task-specific BOLD responses[43]. Whether the issue of abstract representation can be resolved on the basis of behavioural outcome effects and the methodological limitations of BOLD signals is a question in itself[44]. However, the idea of the abstractness of numbers does gain support if 'abstract representation' is operationalized as "neuronal populations that code numerical quantity and are insensitive to the form of input in which the numerical information was presented" (REF. 43). Number neuron responses in the PFC were generalized across spatial features in visual item arrays[27,29,31], spatiotemporal visual presentation formats[34], visuo-auditory presentation formats[38], and the number of dots and associated number signs[45]. That the extraction of numerosity is only minimally influenced by the processing of physical stimulus features has also recently been demonstrated in human imaging studies[46,47]. Of course, if neurons operate on lower, more sensory levels of the cortical hierarchy, such generalized responses cannot (and should not) be expected for all selective neurons. Abstract number information could also be extracted from population activity.

Computational advantage of abstract number neurons. Before the first electrophysiological recordings of number neurons, the influential triple-code model of number processing[48] proposed that number representations initially involve a lower step of modality-specific analysis, followed by a higher processing stage in which these representations reach an abstract, amodal format. The number-selective responses of supramodal neurons could easily be associated with arbitrary signs, such as visual shapes or auditory sounds, to establish symbolic representations of numbers in humans through numerals and number words[40,49,50]. Neurons in the PFC of monkeys that were trained to associate the number of dots with visual shapes (for example, ⠇ with '3') responded equally well to the cardinal values in both displays[45]. This linking capacity of PFC neurons might constitute a pre-adaptation in monkeys that may have evolved to become symbolic linking in humans.

Number as a spontaneously represented category. For a long time, number neurons were investigated in monkeys that had been trained to discriminate set sizes. Could it be that number neurons are only a by-product of intense experience rather than a reflection of a native quantitative faculty that resides in the primate brain? After all,
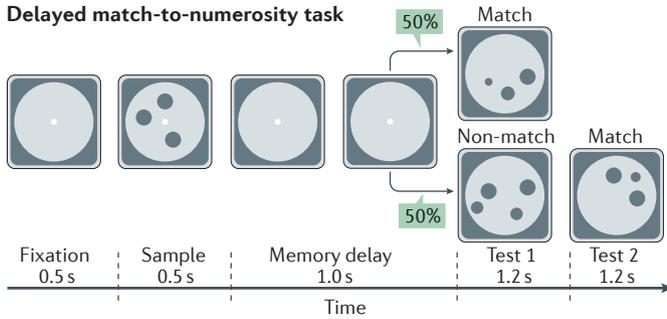

Texture-like mechanism
A mechanism that allows the representation of very many and densely packed items and does not obey Weber's law.
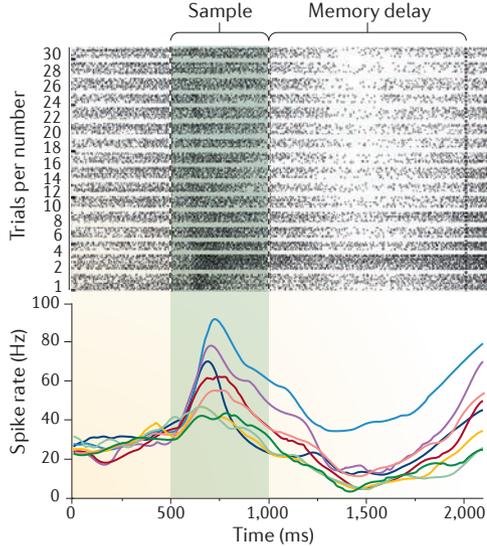
Preadaptation
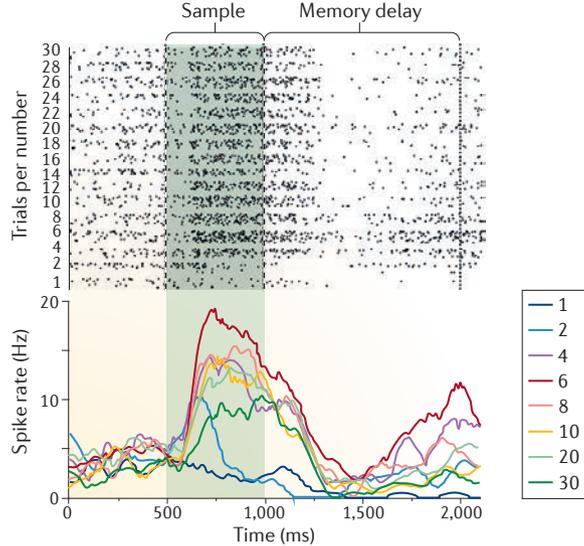A trait that serves a different purpose from the one for which it evolved.

a Delayed match-to-numerosity task

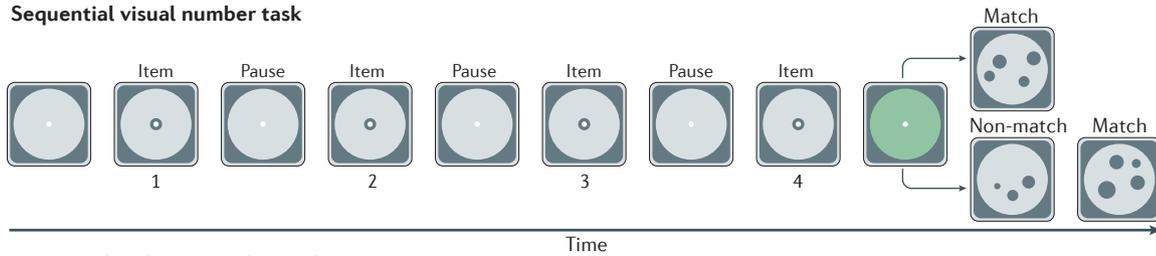| Fixation 0.5 s | Sample 0.5 s | Memory delay 1.0 s | Test 1 1.2 s | Test 2 1.2 s |

Time

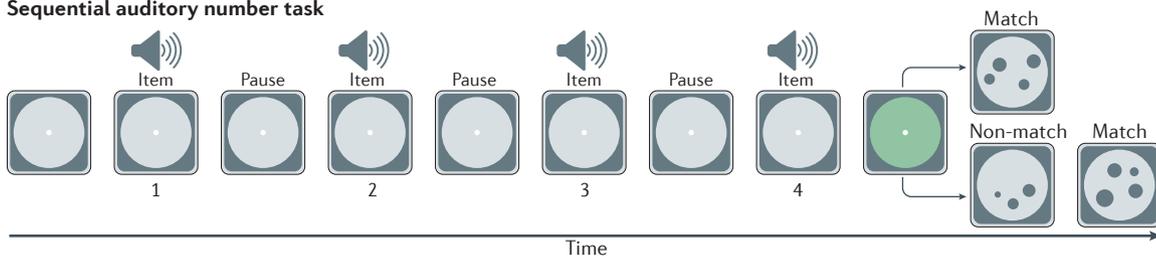**b** Cell tuned to the number 2

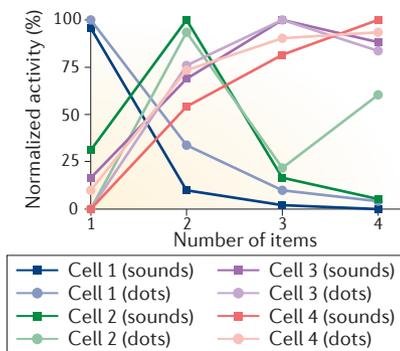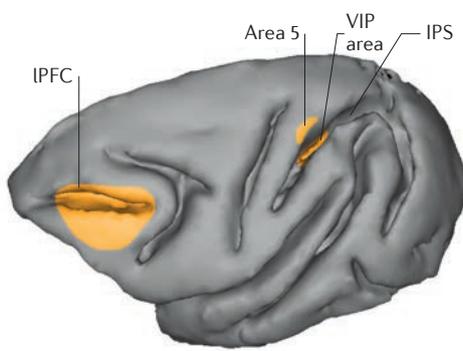**c** Cell tuned to the number 6

d Sequential visual number task

Time

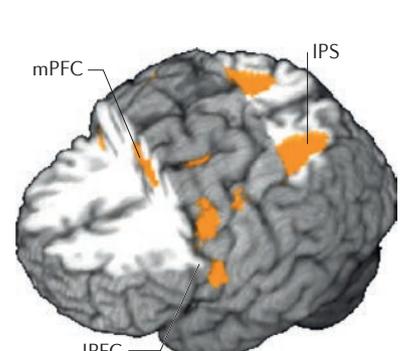**e** Sequential auditory number task

Time

f Supra-modal number-tuning curves

g Number network in the monkey brain

h Number network in the human brain

◄ Figure 1 | **Representation of number in the primate brain. a** | A delayed match-to-numerosity task is commonly used to explore the representation of numbers. A trial begins when the monkey grasps a lever and fixates at a central target on a screen. After fixation, a sample stimulus comprising a number of dots (which varies between trials) is displayed and the monkey memorizes this stimulus during a delay period. The monkey needs to respond whenever the numerosity displayed in the sample phase is shown again in the test phase. In this case, the test stimulus is a match in 50% of the cases. Trials are pseudo-randomized and each numerosity is indicated with many different images. **b** | Neurons of the primate association cortex (here the prefrontal cortex (PFC)) selectively respond to specific numbers. The time course of neuronal activity during the trials shows that this example neuron preferentially responded to two dots (that is, it preferred the number 2). Note that this neuron signalled '2' both during the sample presentation and during the following delay phase (that is, in working memory). Discharges to all even numbers (and 1) up to 30 for many stimulus repetitions are plotted as dot-raster histograms (top panel; each dot represents an action potential) and averaged spike density functions (bottom panel; neural activity is averaged and smoothed, and only a selection of the numbers are shown for clarity). Colours correspond to specific tested numbers. **c** | Different neurons exhibit different preferred numbers. This example neuron selectively responded to 6 items both during sample presentation and memory delay. **d** | To assess how neurons encode the number of items presented over time, a sequential visual enumeration protocol has been used. In this task, the monkey needed to enumerate items one by one and respond if the sample period and test display showed the same number of visual items, and it had to withhold a response if they did not (probability = 50%). Sample numerosities '1' to '4' were cued by sequentially presented dots separated by blank displays. The temporal succession and duration of individual dots were varied systematically within and across numerosities, thus controlling for temporal cues. **e** | To find out whether number neurons generalized across sensory modalities, different numbers of sounds (indicated by speaker icons) had to be enumerated by monkeys and matched to the number of visual items in multi-dot displays. This sequential auditory enumeration task was presented alternately with the sequential visual protocol (see part **d**) in a given session. In this way, the neuronal responses of single neurons to both visual and auditory numbers could be tested. **f** | Supramodal number neurons responded to the same preferred numbers of visual dots and auditory sounds. Tuning functions (normalized average responses) of four example neurons with preferred numerosities of 1 to 4. Each neuron shows almost identical tuning to the number of auditory sounds or visual items. **g** | A frontolateral view of a monkey brain shows the areas of the number network with a high proportion of number neurons. **h** | A frontolateral view of a human brain depicts areas that are consistently activated by numbers in functional imaging studies. IPS, intraparietal sulcus; lPFC, lateral PFC; mPFC, medial PFC; VIP, ventral intraparietal. Parts **b** and **c** are based on data from REF. 31. Part **f** is based on data from REF. 38. Part **h** is adapted with permission from REF. 82, Elsevier.

it is well known that neuronal responses in the association cortex can be modified by learning[51,52]. However, recordings in monkeys that had not been trained to judge number showed that single neurons in both the VIP area and the lPFC spontaneously responded to numerosity and were tuned to preferred numerosities[53]. Similarly, recent imaging evidence has suggested that the direct and automatic extraction of numerosity also occurs in the human brain[46,47].

Strong support for the direct and spontaneous assessment of number resulted from psychophysical experiments that showed that approximate visual number assessments are subject to adaptation (that is, set sizes are underestimated after adaptation to a high numerosity)[54,55]. This adaptation is even present for sequentially presented items, across modalities and across spatio-temporal presentation formats[56]. Because adaptation is a characteristic of sense organs, number may be regarded as a sensory-like attribute[54]. Importantly, numerosity adaptation is spatially selective. Thus, adaptation may be mediated by number-selective neurons that show a spatially restricted response field, such as lateral intraparietal[57] or

VIP area neurons[58]. Cells in the IPS that were number-selective in both space and time[34], and number cells in the PFC that integrate across modalities[38], are probably neural substrates for cross-format and supramodal adaptation. Collectively, these results from psychophysics, brain imaging and single-neuron recordings support the classic idea of a 'sense of number' (BOX 1).

Cortical topography

Hierarchical number processing. Across many studies in monkeys, the highest proportions of number neurons have been found in the lPFC (20–30%) and in the VIP area (15–20%) in the IPS[27,29–31,34,45] (FIG. 1g). Both of these brain areas, which constitute the core number network, have also recently been activated in a monkey fMRI study of number processing[59]. Neurons in the inferior temporal lobe, however, do not seem to be involved in numerosity processing[29]. The lPFC and PPC are anatomically[60–63] and physiologically[64,65] interlinked, classic association cortices. They are ideally positioned for number processing because both the lPFC and the VIP area receive highly processed input from nearly all senses, which is a prerequisite for representing number abstractly across multiple sensory modalities. In addition, both areas are connected to premotor output structures, allowing them to guide behaviour in an adaptive manner[66].

Physiological parameters suggest that number information is processed hierarchically between the IPS and the lPFC. Simultaneous recordings from parietal and frontal lobes have repeatedly found that IPS neurons respond markedly earlier to number than do PFC cells[29,30,53,67]. In addition, single PFC neurons are less sensitive to co-varying sensory features of numerosity displays than are IPS neurons[29] and, in contrast to IPS neurons, PFC neurons respond supramodally to numerosity[38]. Finally, in monkeys trained to associate cardinal values with visual shapes, PFC neurons signify this association across time, whereas IPS neurons do not[45]. These findings suggest that the IPS is the first cortical hub to extract quantitative information. As a putative recipient of information about numerosity from the IPS, the PFC can then process numerical information in a goal-directed way.

Human number system. The cortical number network in the non-human primate cortex is mirrored in the human brain. Damage to parts of the association cortices causes acquired deficits in processing numbers in humans[68–70], leading to a neuropsychological syndrome that is known as acalculia[71–73]. Acquired numerical impairments have revealed a crucial role for the parietal lobes in number and calculation skills, besides other frontal and temporal association areas (reviewed in REFS 74,75). Collectively, recent neuropsychological studies in patients have suggested a cortical number network rather than a one-to-one correspondence between number abilities and one specific brain area[76]. In agreement with findings from lesion studies, it is thought that underdeveloped neuronal circuitries in the number network cause dyscalculia, which is a developmental disorder that is characterized by impairments in the ability to understand numbers and perform calculations[77]. Dyscalculia is associated with reductions

in grey matter volume in the right IPS[78] and frontal areas, such as the anterior cingulum, the left inferior frontal gyrus and the bilateral middle frontal gyri[79].

Functional imaging studies in humans also suggest that frontal lobe areas and posterior parietal areas subserve the nonverbal and symbolic representation of quantities[80], with the posterior parietal areas even showing a spatially organized numerosity map[81]. The findings of dozens of fMRI studies exploring BOLD activation during number tasks were summarized in a recent quantitative meta-analysis[82], which showed that numerical processing is repeatedly and robustly associated with activation mainly in the inferior and superior parietal lobules and the IPS, as well as in frontal lobe areas such as the inferior and middle frontal gyrus of the lPFC, and the cingulate gyrus of the medial PFC (mPFC) (FIG. 1h).

Reading number from neuronal responses

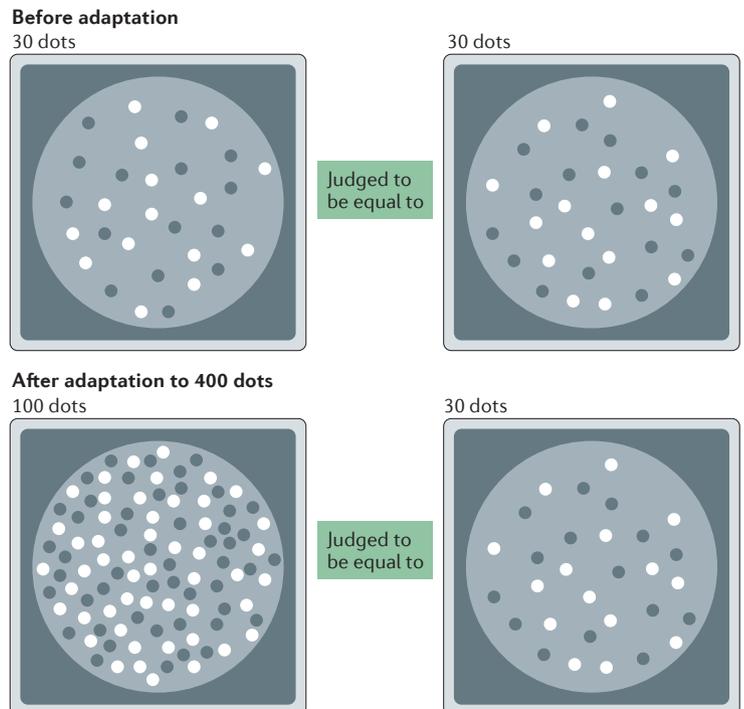**Labelled-line code for number.** A number neuron shows a maximum discharge rate to its preferred numerosity (FIG. 1b,c,f). When the presented number becomes more remote from the preferred one, the neuronal activity of single neurons progressively drops off, thus forming a peak-tuned response curve[27–31]. Such a labelled-line rate code for number has been shown to exist in the monkey brain, across spatiotemporal presentation formats, modalities and sensory-motor domains[34,36,37,83].

The tuning functions of neurons explain the behavioural phenomenon known as the numerical distance effect[4,28], which is the finding that numerically distant numbers are easier to discriminate (for example, 2 versus 6) than numerically closer numbers (for example, 5 versus 6). This is because the read-outs from neurons that are tuned to distant numbers are unequivocal given that the tuning functions hardly overlap. Neuronal coding properties also explain the numerical size effect[4,28], which captures the finding that it is easier to discriminate numbers with low magnitudes (for example, 2 versus 3) than numbers with high magnitudes (for example, 8 versus 9) at a given numerical distance (a distance of 1 in this example). The numerical size effect is related to the finding that the number-tuning curves (FIG. 2a) and population activity

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Box 1 | A 'sense of number'

The classic idea of a 'sense of number' (REFS 179,180) suggests that humans and animals are endowed with an innate faculty to perceive the number of items in a set (that is, numerosity). This idea argues that numerosity is intuitively assessed as a perceptual category by hard-wired sensory brain processes, without the need to be learned. Similar to perceptual categories such as faces, numerosity is susceptible to adaptation[54–56]. For example, after adaptation to 400 dots, subjects judge 100 dots as being equal to 30 dots (see the figure). Supporting sensory access to numerosity, visual numerosity emerges as a statistical property of images in computational network models[91].

Recently, this core idea of the 'number sense' was tested neurophysiologically by recording single-cell activity in numerically naive monkeys. Numerosity-selective neurons were present both in the ventral intraparietal (VIP) area of the posterior parietal cortex (PPC) and the lateral prefrontal cortex (lPFC) of the primate brain without numerical training[53]. Moreover, recordings in naive monkeys revealed neurons that were spontaneously tuned to preferred numerosities. This finding argues for a labelled-line code of numerosity and against summation coding. Finally, numerosity was encoded earlier in the PPC, suggesting that numerical information is automatically extracted in the parietal cortex and then conveyed to the frontal lobe. Indeed, when the same initially numerically naive monkeys were re-trained to actively discriminate visual numerosity, contrasting neuronal effects on PFC and VIP area neurons were witnessed as a result of numerosity training[84]: although PFC neurons became more responsive and more selective during active numerosity discrimination, none of these effects was observed for VIP area neurons. These data indicate the elevated engagement of PFC neurons for executive control, whereas the VIP area continues to encode numerosity as a perceptual category regardless of behavioural relevance. Collectively, these findings suggest that numbers reflect a natural perceptual category. The intuitive sense of number may well be present at birth in both humans and monkeys, and number neurons probably provide the neurobiological substrate of this sense.

Before adaptation
30 dots   30 dots
Judged to be equal to

After adaptation to 400 dots
100 dots   30 dots
Judged to be equal to

Weber–Fechner law
Classic psychophysical law about the perception of magnitudes in relation to the physical intensity of a stimulus; it states that linear increments in sensation S are proportional to the logarithm of stimulus magnitude I (S = k * log(I)).

(FIG. 2b) become progressively broader and thus less selective with increasing magnitudes. Further evidence that monkeys rely on the activity of number neurons to solve a trial comes from recordings during behavioural errors. The discharge rate to the preferred number is markedly reduced in error trials compared with correct trials[27,29–31,84]. Thus, if the neurons do not properly encode their preferred number, the monkey is at risk of confusing numerosities. Together with the numerical deficits seen after pharmacological inactivation (described above)[37], these findings suggest that the activity of number neurons is indispensable for numerical judgments.

Close examination of the shape of the tuning curves reveals asymmetric peak functions on a linear number scale. The neuronal tuning functions (and the behavioural performance functions)[4,85] are better described (that is, symmetric) by a nonlinearly compressed, logarithmic number scale (FIG. 2c) than a linear scale[28,31] (FIG. 2a). The logarithmic coding scheme resulting in bell-shaped curves has physiological advantages. First, it forms a scale-invariant set of neurons that have the same widths of tuning for all numbers. Second, it ensures that the variability of neuronal responses is independent of number preference. Third, logarithmic coding agrees with the psychophysical Weber–Fechner law, which predicts that the discrimination of stimuli diminishes in proportion to the increasing quantity of the stimuli. Logarithmic scaling may be a mathematical approximation, but so far this compression has provided the most symmetric number tuning functions in comparison with other compression schemes, such as peak power functions[4,28,31]. Symmetric Gaussian tuning functions are extensively used in neural models of information coding because they show computational advantages over nonsymmetric functions and their analytical expression can be easily manipulated in mathematical derivations[86].

Number neurons as described electrophysiologically in the monkey brain have been postulated in humans[87,88] on the basis of BOLD signals in fMRI adaptation protocols. This fMRI adaptation assumes that neurons tuned to a preferred number should habituate (that is, they should decrease their discharge rates) with repeated presentations of the same preferred numerosity. Such a habituation effect can then be read out by recording the BOLD activation to individual deviant numerosities, resulting in a release from adaptation to the preferred numerosity and thus a BOLD recovery signal. The fMRI number-tuning curves in the human IPS were shown to become symmetric and Gaussian only when plotted on a logarithmic scale[87,88]. Interestingly, this way of coding numerical information by number neurons showing logarithmically compressed tuning functions seems to have evolved independently in vertebrate endbrains with very different anatomies and thus is an example of convergent evolution (BOX 2).

Tuned and logarithmically scaled 'numerosity detectors' were originally predicted by a numerosity detector model[89] that encoded numerosity from parallel inputs. Numerosity detectors may arise by combining the activity from upstream 'summation units', which are neurons that monotonically increase and decrease discharge rates as a function of numerosity (that is, the 'summation code')[57,89–91]. Summation units representing number in a graded manner are also the basis of the serial mode-control model[92,93], which was originally developed to model animal timing behaviour. It suggests that accumulator units encode pacemaker impulses for each element to be enumerated. Both the numerosity detector model and the mode-control model result in analogue representations of number and predict the Weber–Fechner law. So far, neurophysiological data for the assessment of number from spatial item arrays can be reconciled well with the numerosity detector model. Whether this model could be adjusted to serially presented items — a strength of the mode-control model — awaits further investigation.

Population rate code. A problem of single-cell tuning curves is that they only allow predictions about how neurons will respond on average to a given number. The readouts for single trials of neuronal responses are noisy, and smooth and unequivocal tuning functions only emerge after the discharges of a cell to many identical trial repetitions have been averaged (FIG. 1b,c), or after the tuning functions of many equally tuned single cells have been pooled (FIG. 2b). The brain, however, needs to decipher a presented number within a single trial. To cope with noisy discharge patterns, it must take the activity of a population of other tuned neurons into account. The important information in a population code is thus the relative, rather than the absolute, amounts of activity in different neurons.

Just like a democratic election involves many voters, the coding of a particular number may involve many neurons, and the signal of each number neuron represents an independent vote for a specific number[94]. The independent signals of number neurons may be overlapping and may need to be averaged over large populations to clearly indicate a number. When the activity profiles of all selective neurons are grouped together, an array of overlapping number tuning functions emerges[28,29] (FIG. 2a). This array preserves the ordinal relationship of numerosities in relation to one another. By reading out the activity of labelled lines across the population of cells, all numbers along the number line can be deciphered. For example, if a stimulus with two items is shown, the highest response is elicited in the neuron tuned to 2 (FIG. 2a). However, depending on the amount of tuning overlap, '2' may also, to a lesser degree, activate neurons with a preference for adjacent numbers on the number line. Thus, the stimulation by specific numbers of items ('2' and '4' in FIG. 2a) results in unique activation patterns in the neuronal population of number neurons for these numbers (FIG. 2b).

Clues to how the activity of number-selective neurons could be read out are provided by population-coding models developed for sensory and motor systems that also rely on Gaussian-shaped tuning functions[86]. In the population vector approach applied to the coding of sensory or movement direction information[95–97], each neuron is assigned a vector — the length of which is proportional to the activity of the neuron and the direction of which corresponds to its preferred orientation. All the individual vectors are summed to form a population

vector that allows the preferred orientation to be estimated from its angle. As an alternative population code model, maximum likelihood estimators based on a template derived from the Gaussian-shaped tuning curves of the cells have been suggested[98]. With adaptations, standard models of population coding could be suited to modelling a population code for number representations.

Population coding has several advantages in coding information compared with single neurons, including the reduction of uncertainty caused by neuronal variability, relative insensitivity to the loss of cells, the ability to code different stimulus features simultaneously and the option to compute with representations, such as the transformation (for example, from specific to abstract) and the combination (for example, across modalities) of internal representations[86,97]. Moreover, population activity can reflect changes in stimulus or task conditions much faster than single-neuron rates, which need to be integrated over time, and the same sensory information

can be represented over time via the different spatial firing patterns of a neuronal population[99]. This dynamic population coding for categories has been observed in the monkey parietal cortex[100] and PFC[101], and could be especially important for cognitive control functions that are based on number[102].

Rate and time code. Can functionally overlapping groups of parietal neurons provide sufficient information for a monkey to make correct quantity judgments? To find out, a population decoding technique[103] (that is, a statistical classifier)[104] was used to read out spike trains that were recorded from behaving monkeys[105]. Indeed, a small group of numerosity-selective neurons conveyed categorical information about numerical quantity with high accuracy (FIG. 2d). These tuned neurons were behaviourally relevant, because the classifier was no longer able to predict the numerosities that the monkey had seen based on the firing rates during error trials[105].

a Visual number tuning

b Population activity

c Logarithmic number scale

● Neurons tuned to '1'   ● Neurons tuned to '2'   ● Neurons tuned to '3'   ● Neurons tuned to '4'   ● Neurons tuned to '5'

d Classification with average firing rate

e Classification with temporal firing pattern

Surprisingly, however, even populations of neurons that were not numerosity-tuned based on classic spike-count measures (that is, neurons that showed flat tuning functions) carried reliable information about quantity category[105], albeit with less accuracy than the tuned neurons (FIG. 2e). This suggests that the classifier extracted additional information from the temporal structure of the neuronal responses. These temporal discharge patterns were behaviourally relevant, because the population decoding technique was no longer able to classify numerosities based on spike trains during error trials. Thus, in addition to a classical firing rate code, a temporal code (time code) provides supplementary information about number in the neuronal population.

Discrete and continuous quantities. Many neurons in the parietal and prefrontal association cortices respond not only to discrete numerical magnitudes but also to continuous magnitudes, such as length[30,105], distance[106] and time[107,108]. In both the VIP and PFC, anatomically intermingled neurons have been found that encode length, numerosity or both types of quantities[30,109]. Thus, judging the type and value of magnitude to be processed from individual neurons alone would be not informative

◄ Figure 2 | **Responses of neuron populations to number. a** | Information about number is carried by neurons that form overlapping visual number-tuning functions. Normalized and averaged (according to preferred visual numerosity) tuning functions of number neurons, each tuned to a different preferred numerosity. Different colours represent the distinct preferred numerosities of the neurons. The functions are overlapping and cover the entire range of tested numerosities from 1 to 5. The stimulus display with two dots elicits the highest response in the neuron tuned to '2', but also activates neurons tuned to all the other numerosities to a certain degree. Similarly, the stimulus display showing four dots maximally excites the neuron tuned to '4', but to a lesser extent also excites the other tuned neurons. **b** | Stimulation by specific numbers of items ('2' and '4', respectively) results in unique activation patterns in the neuronal population of number neurons shown in part **a. c** | Numerosity tuning functions shown in part **a** are not symmetric on a linear number axis but show a shallower slope towards higher numerosities. After logarithmic transformation of the number axis, the tuning functions become more symmetric, as predicted by the Weber–Fechner law of logarithmic scaling of perceived magnitudes. **d** | The average firing rate of a population of number-selective neurons conveyed robust information about number. A statistical classifier (neuronal network algorithm) extracted information from neuronal responses recorded from monkeys discriminating numbers. Based on the information acquired from average firing rates of a population of number neurons, the classifier was able to predict the number judged by the monkey from novel recordings. The confusion matrix ('checkerboard') describes the pattern of numerosity classification performed on neuronal population of tuned neurons. The rows in each confusion matrix represent the true classes the monkey had seen and the columns correspond to the output of the classifier. Colour codes the classification probability, and the four classes correspond to numerosity 1 to 4. The main diagonal shows how often the classifier correctly assigned numerosity to their real category. Averaging the classification probabilities over the diagonal parallel to the main diagonal results in the average performance of the classifier as a function of distance from the real numerosity, which is plotted as a tuning function at each end of the main diagonal. **e** | The temporal discharge pattern of a population of unselective neurons also conveyed reliable information about number. Based on the information acquired from the temporal patterns of spikes of a population of neurons, the classifier was able to predict the number seen by the monkey from novel recordings. Same analysis as in part **d**, but performed on neurons that were not tuned based on firing rates. Parts **a**–**c** are based on data from REFS 28 and 29. Parts **d** and **e** are adapted with permission from REF. 105, Tudusciuc, O. & Nieder, A. Neuronal population coding of continuous and discrete quantity in the primate posterior parietal cortex. *Proc. Natl Acad. Sci. USA* **104**, 14513–14518 (2007). Copyright (2007) National Academy of Sciences, U.S.A.

(if a neuron is tuned to a magnitude and value that is not currently relevant) or highly ambiguous (if a neuron encodes more than one magnitude).

To disentangle the effects of two or more types of magnitudes on the response of a neuron, the aforementioned concept of a population code can be extended. The magnitude system would benefit from detecting patterns in the relative responses of a population of neurons that are differently tuned to, for example, number, extent and duration, and on the basis of those patterns, the actual numerical value, length or time interval of a stimulus could be determined. This distributed tuning of single neurons probably causes the activation of overlapping regions by different types of magnitudes in brain imaging studies[47,88,110,111] and could explain the well-known interactions and interference effects between magnitudes. Based on the commonalities between the neural and behavioural representations of number, space, time and other magnitudes, common processing mechanisms for different types of abstract magnitudes have been proposed[112].

Microcircuits sculpturing numerosity selectivity. Narrow numerosity tuning functions are advantageous for a precise read-out of the population responses. At the level of local neocortical microcircuits, inhibitory interneurons have a vital role in sculpturing tuning curves, even though they are outnumbered 4:1 by excitatory neurons (mainly pyramidal projection neurons)[113,114]. In extracellular PFC recordings, pyramidal cells tend to exhibit broad action potential waveforms and low rates of discharge, whereas interneurons display narrow action potential waveforms and high discharge rates[115–119] (FIG. 3).

By exploiting the established differences between putative pyramidal cells and inhibitory interneurons that were recorded extracellularly in the PFC of behaving monkeys, the functional roles that these two classes of neurons exhibit during numerical cognition in local microcircuits have been addressed. Anatomically adjacent pyramidal cells that were functionally connected (indicated by temporally correlated discharges)[120] showed similar numerosity tuning functions[121] (FIG. 3a). The synchronous excitation of neighbouring pyramidal cells probably reflects a shared excitatory input[116]. By contrast, functionally connected inhibitory interneurons and pyramidal cells showed inverted numerosity tuning profiles that were negatively correlated in time (FIG. 3b). That is, whenever an inhibitory interneuron discharged, the pyramidal cell was markedly inhibited, and vice versa. A similar mechanism with opposite tuning of nearby inhibitory interneurons and pyramidal cells accounts for spatial tuning in the PFC[115,117] (see REF. 116 for contrasting results), and blockade of GABAergic inhibition leads to the broadening of the tuning profiles of these neurons[122].

These findings suggest that inhibitory interneurons systematically inhibit numerosity-tuned pyramidal cells, as proposed by recurrent network models for spatial working memory[123]. As the preferred numerosities of the inhibitory interneurons represent the non-preferred numerosities at the flanks of the tuning function of a pyramidal cell, the shoulders of the tuning curve are lowered by this lateral inhibition, thus sharpening the tuning

curve of the pyramidal cell (FIG. 3c). After a number has been encoded, a population of pyramidal cells exhibits tuned persistent activity through recurrent excitations. These tuned pyramidal cells activate local inhibitory interneurons, which, in turn, inhibit pyramidal cells with a different numerosity preference. Remarkably, the outlined wiring scheme not only illustrates the encoding and sharpening of numerosity from sensory input but also suggests reverberation of numerosity-selective activity after a stimulus has ceased based on positive feedback loops of activity between excitatory pyramidal cells. This is the type of activity that is needed for working memory[124].

Robust numerical working memory

The noncanonical association cortex. The controlled processing of numerical information towards a goal requires, first and foremost, that number representations are actively maintained in our 'mental sketchpad'. Working memory, which is the ability to briefly retain and manipulate information, is the fundamental basis of cognition. It allows us to 'think about' quantitative information, and to weigh and measure it in relation to previous experiences and current goals as a hallmark of cognitive control. Consider the simple calculation '2 + 3': it relies on the ability to mentally maintain '2' before it can be incremented by '3' to end up with the result, '5'. Without working memory, we would be lost.

The reciprocally connected association areas that host the number network are particularly well suited to maintaining information across time and to exerting cognitive control. The PPC and lPFC are connected not only to one another but also to >12 other widely distributed cortical areas[125], which are interconnected by a common thalamic input from the medial pulvinar nucleus[126]. The areas in this network display noncanonical circuit properties[127]: in contrast to canonical circuits of the sensory and motor cortices, many connections within this network lack a clear sensory-motor hierarchical polarity with consistent feedforward and feedback laminar termination patterns. Instead, the noncanonical network seems to be designed for parallel and re-entrant processing. It constitutes a global neuronal workspace (GNW) that is thought to enable access to the conscious processing of mental representations[128,129]. According to the GNW model, a behaviourally relevant representation is maintained by a sudden, late and sustained activation (conscious 'ignition' (REF. 129)) of a proportion of the GNW neurons, with only one such conscious representation being active at any given time.

Therefore, a key neurophysiological signature of recurrent loops of the noncanonical association cortex is persistent (or sustained) neuronal activity. Persistent activity is typically witnessed during delayed response tasks that include a short gap in time between a sensory

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Box 2 | Convergent evolution of numerical representations

The sophisticated circuitries in the six-layered neocortex of the frontal and parietal lobes endow both humans and non-human primates with numerical competence. Interestingly, this six-layered neocortex, which is thought to enable primates with the highest levels of cognition, is not present in non-mammalian vertebrates such as birds. The last common reptilian-like ancestor of mammals and birds lived 300 million years ago, at a time when the neocortex had not yet developed[181]. Since then, mammals and birds have independently been through a parallel evolution of endbrains. The bulk of the endbrain in both mammals and birds stems from the ontogenetic mantle, the pallium, and thus shares common ancestry (homology)[182,183]. The overall architectures of the endbrains, however, are very different and developed independently to give rise to similar functions owing to similar selection pressures (homoplasy)[184,185]. Despite these structural differences, birds are known to rival primates in quantitative competence in the laboratory[186–188] and in the wild[189–191].

To explore where and on which basis neuronal code numerosity is represented in avian brains, crows were trained to discriminate the visual number of items in controlled displays[192]. At the same time, single-cell activity was recorded from an endbrain association area that is known as the nidopallium caudolaterale (NCL) in crows[193], which is a brain area considered to be the avian analogue of the primate prefrontal cortex[194–196] (see the figure). The behavioural and neuronal data show an impressive correspondence of neuronal mechanisms found in the avian brain with those described earlier in the primate brain[193]: NCL neurons were tuned to individual preferred numerosities, and neuronal discharges proved to be relevant for the correct performance of the crows in a delayed number discrimination task. Both the neuronal and the behavioural tuning functions were best described on a logarithmic number line. This argues for a nonlinearly compressed coding of numerical information, just as predicted by the psychophysical Weber–Fecher Law[28], not only in primates but also across vertebrates.

Even though crows and primates have very differently organized endbrain structures, they show the same code for number, which suggests that this way of coding numerical information has evolved based on convergent evolution because it exhibits a superior solution to a common computational problem. A comparative approach is indispensable for deciphering evolutionary stable neuronal mechanisms and codes. This proves true not only in the realm of numerical competence but also for all neurobiological questions.
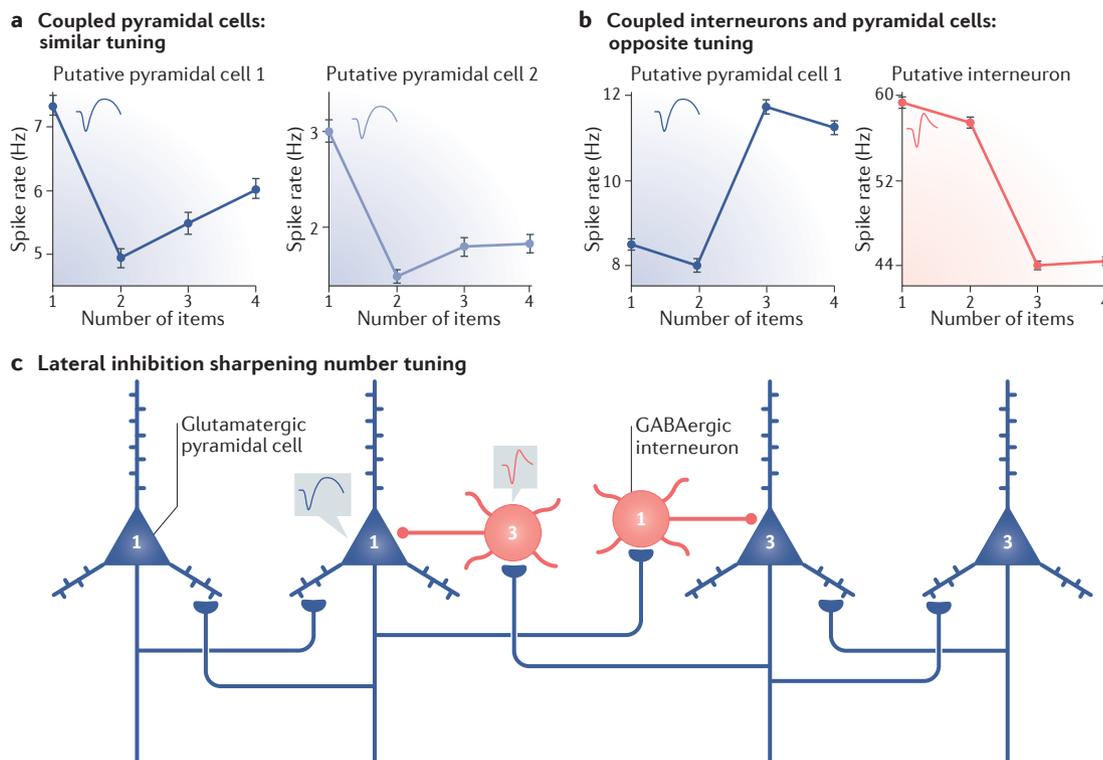

PFC

Nidopallium caudolaterale

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a Coupled pyramidal cells: similar tuning

Putative pyramidal cell 1

Putative pyramidal cell 2

b Coupled interneurons and pyramidal cells: opposite tuning

Putative pyramidal cell 1

Putative interneuron

c Lateral inhibition sharpening number tuning

Glutamatergic pyramidal cell

GABAergic interneuron

Figure 3 | **Microcircuit interactions of number neurons. a** | Putative (excitatory) pyramidal cells seem to receive common inputs about number information rather than being engaged in reciprocal interactions. This is suggested by functionally connected and synchronously excited putative pyramidal cells (broad-spiking neurons) recorded simultaneously at the same electrode tip, with both cells tuned to a numerosity of 1. **b** | The number tuning of putative (excitatory) pyramidal cells seems to be shaped by inhibitory interneurons that show opposite number tuning. This is evidenced by putative inhibitory interneurons (narrow-spiking neurons) and putative pyramidal cells (broad-spiking neurons) that were recorded simultaneously at the same electrode tip and showed inverted (opposite) tuning profiles. These cells were functionally coupled and inhibited each other. **c** | Putative schematic of the lateral inhibition microcircuit in the prefrontal cortex that acts to sharpen number tuning. Tuned broad-spiking pyramidal cells excite each other through glutamatergic synapses on the spines of basal dendrites, thus causing recurrent persistent excitation. Narrow-spiking inhibitory interneurons provide lateral inhibition through GABAergic synapses. Numbers in each model neuron depict the respective preferred numbers. Parts **a** and **b** are republished with permission of the Society for Neuroscience, from: Complementary contributions of prefrontal neuron classes in abstract numerical categorization. Diester, I. & Nieder, A. *J. Neurosci.* **28** (31), 2008; permission conveyed through Copyright Clearance Center, Inc.
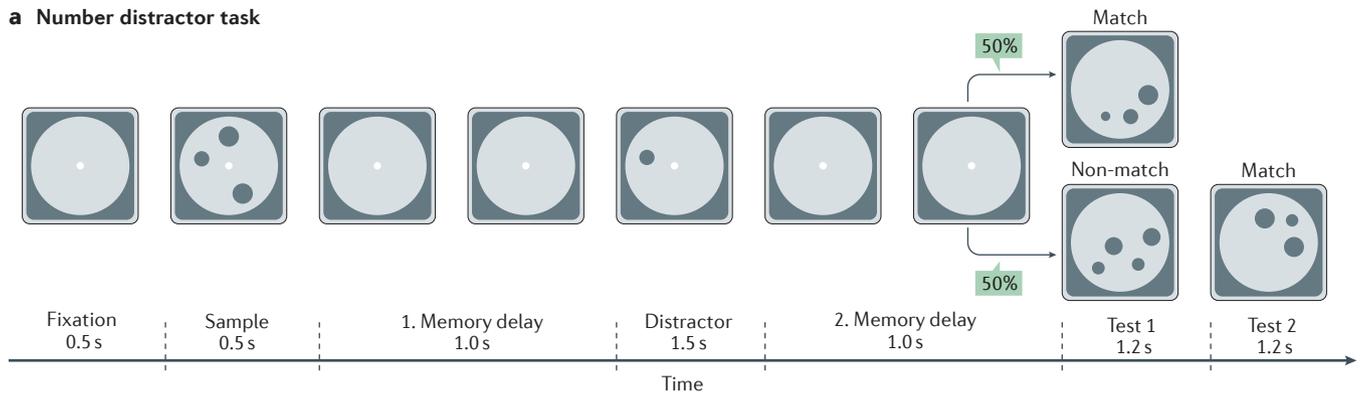
stimulus and an instructed response[130,131]. By sustaining activity, neurons actively buffer and process information to bridge the gap until an adaptive output is selected[132]. High-level cognitive functioning would be impossible without persistent activity offering 'freedom from immediacy' (REF. 133).

The delayed match-to-numerosity task (FIG. 1a) allows the investigation of persistent activity during numerical tasks because it requires animals to retain a number of items over a delay period to subserve a future selection process. As a putative physical correlate of working memory for number, a notable proportion of neurons (20–30% in the PFC and 10–20% in the PPC) show persistent activity during delay periods when monkeys memorize the numerosity that they have just sensed (FIG. 1b). Similar to neurons that are active during sensory stimulation, delay-selective number neurons are tuned to the remembered numerosity[27–31]. Neurons are even tuned to the same numerosity in both the sample and the delay periods (FIG. 1b). In addition, many delay-selective neurons integrate across spatial and temporal presentation formats[34] and visual–auditory modalities[38]. Therefore, numerical delay selectivity is abstract and is found irrespective of the exact spatial or temporal appearance of the memorized sets.

Cognitive inhibition. Working memory has severely limited capacity. Thus, transient representations of numerical information in working memory are vulnerable to distractions that potentially replace important representations with different content encoded by another discrete combination of neurons in the workspace population. The process of restraining or overriding irrelevant representations to keep hanging on to relevant information is known as 'cognitive inhibition' (REF. 134). Crucial questions include where and how number representations that each compete to gain access to the global workspace are selected.

a Number distractor task

b Sorted by sample number

c Sorted by distractor number

d Information about number

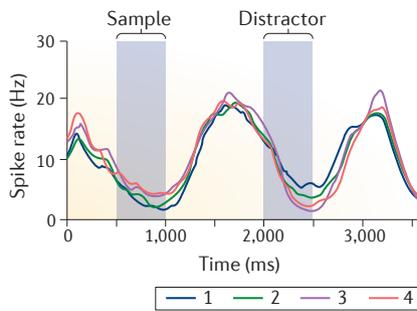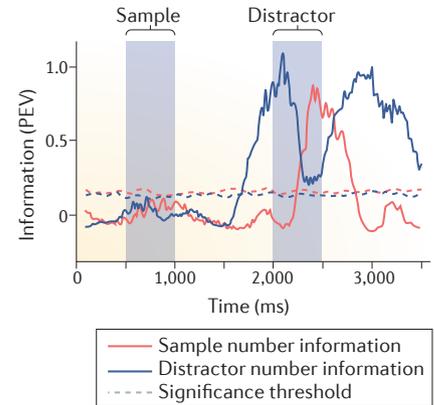Figure 4 | **Cognitive inhibition of a prefrontal cortex cell during numerical distraction. a** | How neurons may cope with the interference caused by an irrelevant number was studied in a modified delayed match-to-sample task (see FIG. 1a). Here, a behaviourally irrelevant numerosity (distractor) presented in the prolonged delay period needed to be ignored to solve the task correctly. Numerosities from 1 to 4 were shown both as the sample and as the distractor numerosities, with all possible combinations used. **b** | An example neuron in the prefrontal cortex encoded a working memory trace of the relevant sample numerosity even after a distracting numerosity had been shown in the aforementioned distractor task. When trials are sorted by sample numerosity, the time course of activation (spike density histogram) shows that the neuron was equally tuned to number 4 both before (1. memory delay) and after presentation of a distractor number (2. memory delay). Interestingly, tuning was apparent during the distractor presentation. The plot is temporally correlated with the task layout that is shown in part **a**. **c** | When the responses of the same neuron as in part **b** were sorted by distractor numerosity, temporary tuning to the distractor numerosity during the end of the distractor period was evident. **d** | The same neuron that is featured in parts **b** and **c** carried information about both the sample and the distractor numerosity in different trial epochs. Information about either the sample or the distractor numerosity is quantified by a sliding window percent explained variance (PEV; ω^2) analysis, which is derived from an analysis of variance (ANOVA). This analysis conveys how much of the discharge variation over time can be explained by the sample numerosity or the distractor numerosity. Information about the sample numerosity (blue line) is encoded during the end of the first memory delay and during the second memory delay, but is briefly lost at the end of the distractor phase. Conversely, information about the task-irrelevant distractor numerosity emerges towards the end of the distractor phase and the beginning of the second memory delay, but vanishes towards the end of the second memory delay. Thus, information about target numerosity was not permanently replaced by irrelevant distractor information but regenerated in the second delay after the distraction, just in time to solve the task. Dashed lines mark the significance threshold. Parts **b**–**d** are adapted with permission from REF. 135, Elsevier.

As challenging abstract categories, number representations place high demands on cognitive inhibition. Consider a simple example: you look up your friend's phone number to call for a chat but while you pick up the phone someone utters an arbitrary number. Only with considerable effort will you be able to ignore the distracting number and still manage to call your friend's number. Monkeys were confronted with a situation mirroring the abovementioned phone call situation[135]. To that aim, a behaviourally irrelevant number display was inserted as a distractor in the delay period of a delayed match-to-number task (FIG. 4a). Because cognitive inhibition cannot entirely eradicate distracting influences, a worsening of performance reflects increased distraction. Indeed, the monkeys managed to resist the distractor numbers most of the time but made slightly more errors than when no distractors were present[135].

While the monkeys performed this task, single-unit activity was simultaneously recorded from the PFC and the VIP area. After sample presentation, PFC neurons encoded the relevant sample number during the first delay period and exhibited the well-known tuning curves and persistent activity (FIG. 4b). However, when the distractor number was subsequently shown, the neurons did not resist interference. Rather, sample information was overwritten and the PFC neurons responded strongly and in a tuned manner to the distractor numbers, sometimes with different preferred numerosities (FIG. 4c). Surprisingly, however, target number representations were not permanently lost but were regenerated in the second delay after the distraction, just in time to solve the task (FIG. 4d). Neurons in the VIP area, by contrast, were mostly unaffected by the distractor numbers and continued to retain the working memory representation of the sample numbers.

These results were unexpected, given the findings from previous studies in which neurons in the PFC and PPC were not activated during the memorization of stimulus features but were instead activated by stimulus location. In spatial working memory tasks, PFC neurons only mildly respond to distractors, suggesting that the suppression of distracting information in the PFC is the key mechanism that protects working memory from interference and gates access to it[136–139]. By contrast, PPC neurons responded strongly to distractors and encoded the physical properties of any stimulus irrespective of its relevance. Thus, the activity of PPC neurons was considered to be an inferior correlate of working memory[139–141].

These new results point towards the PFC as a control or selection stage in the global noncanonical network. Activity in the PFC might be better understood not as a signature of memory storage per se[142], but as a top-down signal[143] that influences other members of the global workspace, such as the VIP, where the actual working memory representations seem to be maintained. To adopt this position of a selection stage, the PFC needs representations of both relevant and not immediately relevant information to attentionally filter[144] and flexibly guide stimulus selection for the upcoming response later in the task. This could explain why the ability to resist interfering stimuli is compromised in monkeys[139,145] and humans with lPFC lesions[146] — not because stored information is lost, but because control and selection processes in the global workspace are dysfunctional.

Rule-based decisions with numbers
Although they are important first steps, the representation and memorization of numerical quantity alone do not constitute behavioural advantages. After quantities have been extracted from sensory input and maintained in short-term memory, numbers need to be processed according to rules or general principles. Rules can be understood as conditional 'if–then' statements that determine the logic of a goal-directed task. Rules are crucial to arithmetic: they constitute mathematical syntax. For example, in equations, we first solve multiplication and division terms, but only if addition and subtraction terms are not in brackets, in which case addition and subtraction need to be calculated first. Because numerical principles operate on abstract numerical categories, quantitative rules in particular require high degrees of cognitive structuring.

A fundamental operation when dealing with numbers involves 'greater-than' and 'fewer-than' rules of the form: if 'x > y' then 'a' versus if 'x < y' then 'b'. These relationships can also be mastered by non-human primates[147–149]. To gain insight into the neuronal processing of numerical rules, rhesus monkeys were trained to flexibly switch between 'greater-than' and 'fewer-than' rules[148,150,151]. In each trial (FIG. 5a), a sample stimulus indicated the reference numerosity that the monkey needed to remember over a brief time interval (the 'memory delay'). Next, a rule cue instructed the monkey to follow either a 'greater-than' or a 'fewer-than' rule. After a second delay (the 'rule delay'), the monkey needed to respond according to the currently valid rule cue to a greater or fewer number of dots, respectively, than it had previously seen in the sample display. The monkeys performed this task with different numbers of items and generalized to novel numerosities, indicating that they had learned an abstract numerical principle[148].
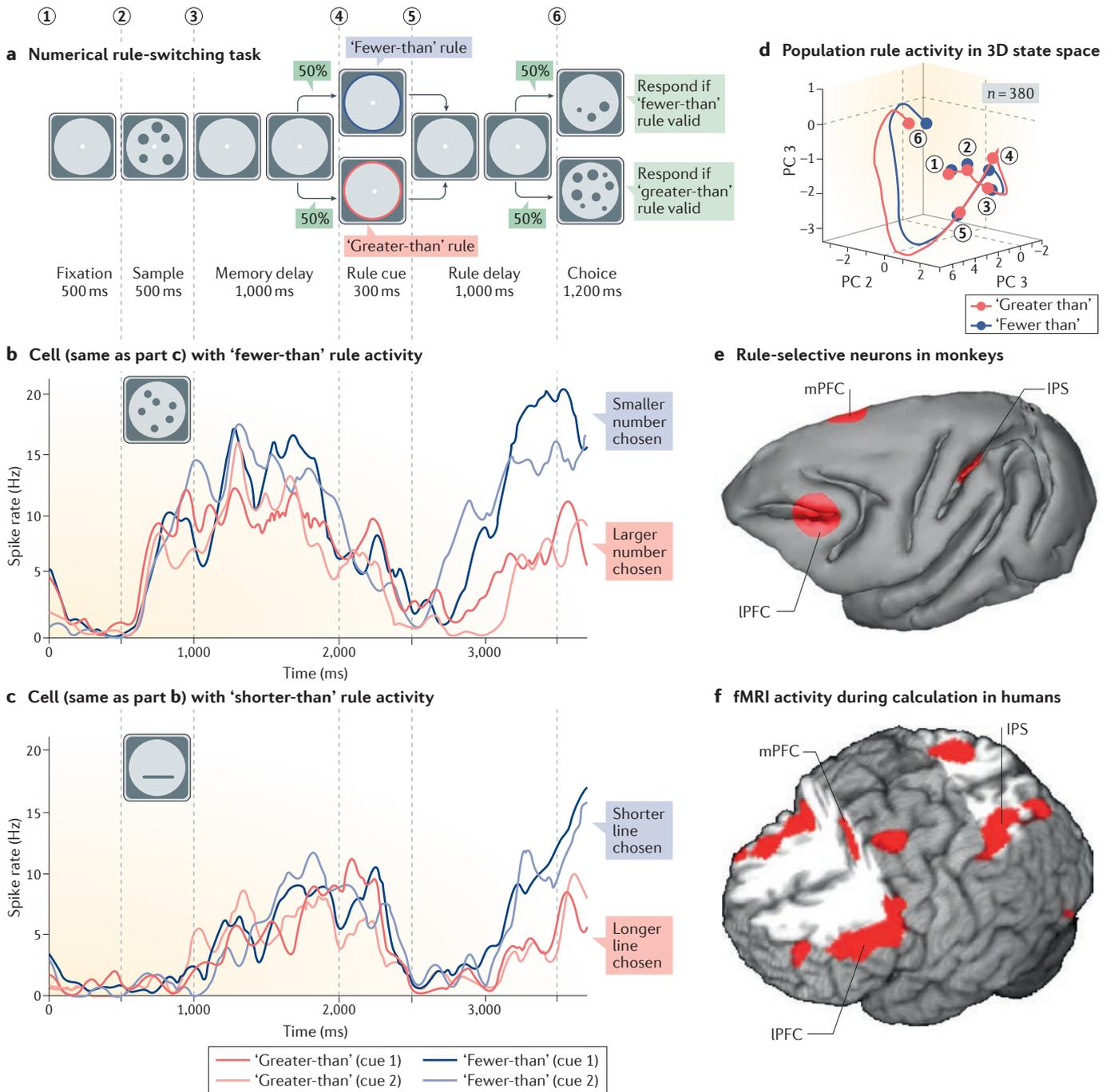
PFC neurons are known to flexibly group information into behaviourally meaningful categories according to task demands[152–154], and they also encode these basic mathematical rules. In the rule-switching task described above, approximately 20% of the PFC neurons reflected 'greater-than' or 'fewer-than' rules[148] (FIG. 5b). Rule-selective neurons responded strongly to the preferred rule during the rule delay phase with an increase in discharge rate, irrespective of the particular sample numerosity to which the rule applied[148]. Importantly, the sensory appearance of the rule cue had no impact on the activity of rule-selective neurons. Moreover, responses in the rule delay could not be explained by motor preparation, because the comparison number was still missing in this phase and therefore the monkey could not know which response was to be prepared. Rule selectivity gradually evolved with time in the rule delay, with approximately one-half of the rule-selective neurons preferring the 'greater-than' rule and the other one-half preferring the 'fewer-than' rule.

The responses of such rule-selective neurons correlated with the behaviour of the monkeys: if the animals made wrong decisions, the responses of the neurons to the preferred rule in the rule delay phase were markedly reduced[148]. This observation indicates that there is a direct relationship between the rule selectivity of the neurons and task performance. Rule-selective neurons were prevalent in the frontal lobe but were also found, although less frequently, in the VIP area of the IPS[150].

'Greater-than–fewer-than' rules can be applied not only to numbers but also to any magnitude. Could neurons represent overarching 'magnitude rules' instead of rules applied to individual magnitudes? In monkeys that applied these quantity rules to both numbers and the lengths of lines[151], most rule-selective neurons responded only to the quantitative rules applied to one specific magnitude type: for example, to the longer lines

but not to more items. Such neurons can be regarded as 'rule specialists'. However, other neurons generalized the magnitude principle and encoded the overarching concept of magnitude rules by equally representing the quantitative rules related to both magnitudes. Such neurons are known as 'rule generalists' (FIG. 5c). This indicates that the primate brain uses a mixture of selective neurons[155]. Rule generalist neurons provide a computational advantage compared with rule specialist neurons and could operate at a higher functional hierarchy[156]; indeed, they allow the generalization and adaptation of quantitative rules to new circumstances.

During mathematical problems, a limited set of neurons needs to be able to solve several tasks throughout time and changing task demands. Thus, brain activity needs to be highly dynamic and neurons may adaptively switch coding properties[157] to join different populations as time goes on[102]. Even though PFC neurons signal number, when appropriate, many of them may dynamically switch to encoding cognitive control functions such as rule-guided decisions. At the population level, the temporal evolution of rule-selective activity can be expressed as a dynamic trajectory through activity state space (FIG. 5d). Once high-dimensional population data

a Numerical rule-switching task

Fixation 500 ms | Sample 500 ms | Memory delay 1,000 ms | Rule cue 300 ms | Rule delay 1,000 ms | Choice 1,200 ms

'Fewer-than' rule
'Greater-than' rule
50%
Respond if 'fewer-than' rule valid
Respond if 'greater-than' rule valid

b Cell (same as part c) with 'fewer-than' rule activity

Smaller number chosen
Larger number chosen

c Cell (same as part b) with 'shorter-than' rule activity

Shorter line chosen
Longer line chosen

'Greater-than' (cue 1)   'Fewer-than' (cue 1)
'Greater-than' (cue 2)   'Fewer-than' (cue 2)

d Population rule activity in 3D state space

n = 380
'Greater than'
'Fewer than'

e Rule-selective neurons in monkeys

mPFC   IPS
lPFC

f fMRI activity during calculation in humans

mPFC   IPS
lPFC

are compressed to a three-dimensional space, the distinct trajectories resulting from PFC population activity indicate robust differentiation of the 'greater-than' and 'fewer-than' rules. (FIG. 5d). This does not apply only to individual neurons — the entire population encodes quantitative rules dynamically.

Rule coding is under the influence of neuromodulators. In the PFC, the neuromodulator dopamine affects the basic coding properties of neurons[158,159] via the two major (D1 and D2) receptor families. Recent experiments probing single neurons by combining single-cell recordings and simultaneous micro-iontophoretic drug applications showed that both the D1 and D2 dopamine receptor families cooperatively enhance number coding, albeit by distinct physiological mechanisms[160]. Thus, numerical operations can be instrumental in deciphering the influence of neuromodulation in high-level processing.

Numerical rule-related activity is most frequently and selectively found in the lPFC and mPFC of monkeys but can also be detected in the VIP area[150] (FIG. 5e). Corresponding brain areas show activity during calculation tasks in humans (FIG. 5f). Pronounced prefrontal

◀ Figure 5 | **Numerical rules. a** | How primates and their neurons process numerical rules has been investigated using a rule-switching task. Here, monkeys needed to decide whether there was a greater or fewer number of dots at the choice stage than the number presented in a sample display (five different numerosities were used in the task). A cue showed in the delay phase indicated whether a 'greater-than' (bottom) or a 'fewer-than' rule (top) needed to be applied (the probability of each rule being displayed was 0.5). Each rule was signified by two pairs of different sensory cues (only colour cues shown). **b** | Neurons recorded in monkeys that were engaged in this numerical rule-switching task selectively responded to one or the other of these numerical rules. The activity averaged over all trials (spike density histogram, smoothed with a 150 ms Gaussian kernel) of an example neuron was systematically higher during the rule delay when the 'fewer-than' rule was cued, irrespective of the sensory features of the rule cue (activity coded by cool colours). The plot is temporally correlated with the task layout that is shown in part **a**. **c** | The neuron featured in part **b** also signalled a 'fewer-than' rule applied to the length of lines. The task design was very similar to the numerical rule-switching protocol depicted in part **a**. In this task, however, monkeys saw lines of different lengths that they needed to process according to 'shorter-than' and 'longer-than' rules. This neuron showed elevated firing rates also to the 'shorter-than' rule, thus generalizing rules across magnitude types. The neuron shown in parts **b** and **c** was thus termed a 'rule generalist'. **d** | The temporal dynamics of information about numerical rules during the numerical rule-switching task (as shown in part **a**) is encoded not only by single rule-selective neurons but also by an entire population of prefrontal cortex (PFC) neurons. Multi-dimensional state space analysis was applied to extracted shared activity patterns in a population. At each time during a trial, population activity is represented by an n-dimensional vector in n-dimensional state space ($n = 380$ dimensions for 380 neurons). A principal component analysis was used to condense the population activity in a three-dimensional (3D) subspace. Red and blue lines show the time course of average multidimensional dynamical trajectories during 'greater-than' and 'fewer-than' trials, respectively, with separated trajectories during the rule delay. Even if single neurons adaptively switch tuning properties throughout an ongoing task, the entire population robustly differentiates between numerical rules. Numbers indicate trial epochs depicted in part **a**. **e** | Numerical rule areas in the monkey brain. Frontolateral view of a macaque brain showing areas in red that contain a relatively high proportion of number rule neurons. **f** | Frontolateral view of a human brain showing areas consistently activated by calculations in functional imaging studies. IPS, intraparietal sulcus; lPFC, lateral PFC; mPFC, medial PFC. Parts **b** and **c** are republished with permission of the Society for Neuroscience, from: Representation of abstract quantitative rules applied to spatial and numerical magnitudes in primate prefrontal cortex. Eiselt, A.K. & Nieder, A. *J. Neurosci.* **33** (17), 2013; permission conveyed through Copyright Clearance Center, Inc. Part **d** is based on data from REF. 160 and is provided courtesy of T. Ott. Part **f** is reproduced with permission from REF. 82, Elsevier.

activity in addition to posterior parietal activity is readily observed when individuals perform arithmetic operations (for example, addition or subtraction)[82,161,162] (FIG. 5f), particularly at young ages (around 10 years of age)[163].

Consistent with the general role of the PFC in executive functions, the deficits that occur with numbers and calculation following frontal lesions are complex. Luria[164] suggested that the difficulty patients with frontal lobe lesions experience in carrying out arithmetical operations stems from a disturbance of intellectual activity — a general problem of solving a complex problem — rather than primary acalculia. Cognitive estimation requires quantitative reasoning, and cognitive estimation deficits in various quantitative domains (size, weight, numerosity and time) have frequently been reported for patients with frontal lesions[165–168]. As semantic number representations tend to be spared in such patients, these estimation deficits are attributed to executive deficits that disrupt the translation of number representations to structured output. As a most peculiar deficit, 'task-switching acalculia' was reported in a patient with stroke who had brain lesions in the left ventral and dorsolateral frontal lobe[169]. Interestingly, the patient's calculation ability per se was not affected, but he showed a specific deficit in switching between different operations in simple calculations; for example, from multiplication to addition or subtraction, and vice versa. This 'task-switching acalculia' is consistent with the idea that frontal lesions lead to weak top-down control that is caused by an inability to switch between mathematical rules.

Conclusions

The combined evidence from neurological, developmental, imaging and neurophysiological studies points towards a dedicated, putatively homologous number network in the primate brain that processes number and other abstract magnitudes[112,170–174]. The reviewed studies highlight striking similarities between numerical representations in both non-human and human primates. First, number neurons exist in comparable brain regions of the lPFC and IPS, with the IPS being the first region to process number information in the neural number network. Second, number neurons in both groups are tuned to preferred numbers. Third, number neurons encode numerosity abstractly across modalities and sensory-motor domains. Fourth, experimental (in monkeys) or acquired (in humans) lesions in these cortical areas are detrimental to number processing. Fifth, active processing of numbers is not required for number neurons to exist and to respond to number.

Collectively, these similarities suggest that the parieto-frontal network for nonverbal numerical information constitutes an evolutionary pre-adaptation for semantic number representations and mathematics in humans. Of course, this does not mean that symbolic and non-symbolic number representations need to be identical[175–177]. Even so, symbolic mathematical operations may co-opt or 'recycle' prefrontal and posterior parietal circuits[178] to vastly enrich and enhance our symbolic mathematical skills.

Comparisons of the response properties of number neurons in different brain areas help to clarify the respective contributions of the PPC and PFC in number processing. They show that neurons in the PFC operate at a more abstract level than do PPC neurons. By abstracting number and disposing of specific sensory information during encoding and memorizing sets, the brain expands its computational power. It reduces the complexity of neuronal signals that can then be processed more rapidly and more easily. In particular, this provides an advantage during learning, for example, when linking numerosities with arbitrary shapes as a first step towards learning number symbols[40,45,49,50]. Number neurons also support the learning and application of task rules, so that neurons selective to quantitative rules provide easy readout signals for rule-based decisions and action selection. Because numbers are abstract categories and their processing relies on derived principles, they constitute ideal stimuli to probe sophisticated executive control functions of the association cortices.

1. Wiese, H. *Numbers, Language, and the Human Mind.* (Cambridge Univ. Press, 2003).
2. Nieder, A. Counting on neurons: the neurobiology of numerical competence. *Nat. Rev. Neurosci.* **6**, 177–190 (2005).
3. Whalen, J., Gallistel, C. R. & Gelman, R. Nonverbal counting in humans: the psychophysics of number representations. *Psychol. Sci.* **10**, 130–137 (1999).
4. Merten, K. & Nieder, A. Compressed scaling of abstract numerosity representations in adult humans and monkeys. *J. Cogn. Neurosci.* **21**, 333–346 (2009).
5. Gordon, P. Numerical cognition without words: evidence from Amazonia. *Science* **306**, 496–499 (2004).
6. Pica, P., Lemer, C., Izard, V. & Dehaene, S. Exact and approximate arithmetic in an Amazonian indigene group. *Science* **306**, 499–503 (2004).
7. Siegler, R. S. & Opfer, J. E. The development of numerical estimation: evidence for multiple representations of numerical quantity. *Psychol. Sci.* **14**, 237–243 (2003).
8. Feigenson, L., Dehaene, S. & Spelke, E. Core systems of number. *Trends Cogn. Sci.* **8**, 307–314 (2004).
9. Dacke, M. & Srinivasan, M. V. Evidence for counting in insects. *Anim. Cogn.* **11**, 683–689 (2008).
10. Gross, H. J. *et al.* Number-based visual generalisation in the honeybee. *PLoS ONE* **4**, e4263 (2009).
11. Agrillo, C., Piffer, L. & Bisazza, A. Number versus continuous quantity in numerosity judgments by fish. *Cognition* **119**, 281–287 (2011).
12. Bisazza, A., Tagliapietra, C., Bertolucci, C., Foà, A. & Agrillo, C. Non-visual numerical discrimination in a blind cavefish (*Phreatichthys andruzzii*). *J. Exp. Biol.* **217**, 1902–1909 (2014).
13. Uller, C., Jaeger, R., Guidry, G. & Martin, C. Salamanders (*Plethodon cinereus*) go for more: rudiments of number in an amphibian. *Anim. Cogn.* **6**, 105–112 (2003).
14. Krusche, P., Uller, C. & Dicke, U. Quantity discrimination in salamanders. *J. Exp. Biol.* **213**, 1822–1828 (2010).
15. Koehler, O. Can pigeons "count"? *Zeitschrift Tierpsychol.* **1**, 39–48 (in German) (1937).
16. Emmerton, J. in *Avian Visual Cognition* (ed. Cook, R. G.) [online], http://www.pigeon.psy.tufts.edu/avc/emmerton/ (Comparative Cognition Press, 2001).
17. McComb, K., Packer, C. & Pusey, A. Roaring and numerical assessment in contests between groups of female lions, *Panthera leo. Animal Behav.* **47**, 379–387 (1994).
18. Brannon, E. M. & Terrace, H. S. Ordering of the numerosities 1 to 9 by monkeys. *Science* **282**, 746–749 (1998).
    Using painstakingly controlled visual stimuli and elegant protocols, this seminal behavioural study showed that monkeys grasp the cardinal and ordinal meaning of numbers.
19. Cantlon, J. F. & Brannon, E. M. How much does number matter to a monkey (*Macaca mulatta*)? *J. Exp. Psychol. Anim. Behav. Process* **33**, 32–41 (2007).
20. Jordan, K. E., Maclean, E. L. & Brannon, E. M. Monkeys match and tally quantities across senses. *Cognition* **108**, 617–625 (2008).
21. Beran, M. J. Quantity judgments of auditory and visual stimuli by chimpanzees (*Pan troglodytes*). *J. Exp. Psychol. Anim. Behav. Process* **38**, 23–29 (2012).
22. Wilson, M. L., Kahlenberg, S. M., Wells, M. & Wrangham, R. W. Ecological and social factors affect the occurrence and outcomes of intergroup encounters in chimpanzees. *Anim. Behav.* **83**, 277–291 (2012).
23. Kaufman, E. L. & Lord, M. W. The discrimination of visual number. *Am. J. Psychol.* **62**, 498–525 (1949).
24. Anobile, G., Cicchini, G. M. & Burr, D. C. Number as a primary perceptual attribute: a review. *Perception* **45**, 5–31 (2016).
25. Dehaene, S., Molko, N., Cohen, L. & Wilson, A. J. Arithmetic and the brain. *Curr. Opin. Neurobiol.* **14**, 218–224 (2004).
26. Nieder, A. & Dehaene, S. Representation of number in the brain. *Annu. Rev. Neurosci.* **32**, 185–208 (2009).
27. Nieder, A., Freedman, D. J. & Miller, E. K. Representation of the quantity of visual items in the primate prefrontal cortex. *Science* **297**, 1708–1711 (2002).
    This was the first report of neurons in the PFC responding to the number of visual items monkeys were trained to discriminate.
28. Nieder, A. & Miller, E. K. Coding of cognitive magnitude: compressed scaling of numerical information in the primate prefrontal cortex. *Neuron* **37**, 149–157 (2003).
29. Nieder, A. & Miller, E. K. A parieto-frontal network for visual numerical information in the monkey. *Proc. Natl Acad. Sci. USA* **101**, 7457–7462 (2004).
30. Tudusciuc, O. & Nieder, A. Contributions of primate prefrontal and posterior parietal cortices to length and numerosity representation. *J. Neurophysiol.* **101**, 2984–2994 (2009).
31. Nieder, A. & Merten, K. A labeled-line code for small and large numerosities in the monkey prefrontal cortex. *J. Neurosci.* **27**, 5986–5993 (2007).
32. Okuyama, S., Kuki, T. & Mushiake, H. Representation of the numerosity 'zero' in the parietal cortex of the monkey. *Sci. Rep.* **5**, 10059 (2015).
33. Ramirez-Cardenas, A., Moskaleva, M. & Nieder, A. Neuronal representation of numerosity zero in the primate parieto-frontal number network. *Curr Biol.* http://dx.doi.org/10.1016/j.cub.2016.03.052 (2016).
34. Nieder, A., Diester, I. & Tudusciuc, O. Temporal and spatial enumeration processes in the primate parietal cortex. *Science* **313**, 1431–1435 (2006).
35. Castelli, F., Glaser, D. E. & Butterworth, B. Discrete and analogue quantity processing in the parietal lobe: a functional MRI study. *Proc. Natl Acad. Sci. USA* **103**, 4693–4698 (2006).
36. Sawamura, H., Shima, K. & Tanji, J. Numerical representation for action in the parietal cortex of the monkey. *Nature* **415**, 918–922 (2002).
    This was the first report of neurons in the parietal lobe responding to the number of hand movements that monkeys were trained to perform.
37. Sawamura, H., Shima, K. & Tanji, J. Deficits in action selection based on numerical information after inactivation of the posterior parietal cortex in monkeys. *J. Neurophysiol.* **104**, 902–910 (2010).
    Transient pharmacological inactivation of neuronal activity in parietal area 5 prevented monkeys from performing the correct number of movements, while sparing general motor functions and action selection. This demonstrates that the activity of number neurons is causally related to number estimation.
38. Nieder, A. Supramodal numerosity selectivity of neurons in primate prefrontal and posterior parietal cortices. *Proc. Natl Acad. Sci. USA* **109**, 11860–11865 (2012).
    Neurons in the PFC encode the same number of visual or auditory events in behaving monkeys.
39. Piazza, M., Mechelli, A., Price, C. J. & Butterworth, B. Exact and approximate judgements of visual and auditory numerosity: an fMRI study. *Brain Res.* **1106**, 177–188 (2006).
40. Ansari, D., Garcia, N., Lucas, E., Hamon, K. & Dhital, B. Neural correlates of symbolic number processing in children and adults. *Neuroreport.* **16**, 1769–1773 (2005).
41. Ansari, D. & Dhital, B. Age-related changes in the activation of the intraparietal sulcus during nonsymbolic magnitude processing: an event-related functional magnetic resonance imaging study. *J. Cogn. Neurosci.* **18**, 1820–1828 (2006).
42. Eger, E., Sterzer, P., Russ, M. O., Giraud, A. L. & Kleinschmidt, A. A supramodal number representation in human intraparietal cortex. *Neuron* **37**, 719–725 (2003).
43. Cohen Kadosh, R. & Walsh, V. Numerical representation in the parietal lobes: abstract or not abstract? *Behav. Brain Sci.* **32**, 313–328 (2009).
44. Nieder, A. The number domain — can we count on parietal cortex? *Neuron* **44**, 407–409 (2004).
45. Diester, I. & Nieder, A. Semantic associations between signs and numerical categories in the prefrontal cortex. *PLoS Biol.* **5**, e294 (2007).
46. Park, J., DeWind, N. K., Woldorff, M. G. & Brannon, E. M. Rapid and direct encoding of numerosity in the visual stream. *Cereb. Cortex* **26**, 748–763 (2016).
47. Leibovich, T., Vogel, S. E., Henik, A. & Ansari, D. Asymmetric processing of numerical and nonnumerical magnitudes in the brain: an fMRI study. *J. Cogn. Neurosci.* **28**, 166–176 (2016).
48. Dehaene, S. Varieties of numerical abilities. *Cognition* **44**, 1–42 (1992).
49. Ansari, D. Effects of development and enculturation on number representation in the brain. *Nat. Rev. Neurosci.* **9**, 278–291 (2008).
50. Piazza, M. Neurocognitive start-up tools for symbolic number representations. *Trends Cogn. Sci.* **14**, 542–551 (2010).
51. Freedman, D. J., Riesenhuber, M., Poggio, T. & Miller, E. K. Categorical representation of visual stimuli in the primate prefrontal cortex. *Science* **291**, 312–316 (2001).
52. Roy, J. E., Riesenhuber, M., Poggio, T. & Miller, E. K. Prefrontal cortex activity during flexible categorization. *J. Neurosci.* **30**, 8519–8528 (2010).
53. Viswanathan, P. & Nieder, A. Neuronal correlates of a visual "sense of number" in primate parietal and prefrontal cortices. *Proc. Natl Acad. Sci. USA* **110**, 11187–11192 (2013).
    Visual number neurons were spontaneously present in monkeys that had never been trained to judge numerosity, arguing that the primate brain is hard-wired to assess numerical quantity.
54. Burr, D. & Ross, J. A visual sense of number. *Curr. Biol.* **18**, 425–428 (2008).
55. Ross, J. & Burr, D. C. Vision senses number directly. *J. Vis.* **10**, 10.1–10.8 (2010).
56. Arrighi, R., Togoli, I. & Burr, D. C. A generalized sense of number. *Proc. Biol. Sci.* **281**, 20141791 (2014).
    Impressive psychophysical experiments reporting the generalization of number adaptation across modalities and spatio-temporal formats, suggesting a perceptual system to encode an abstract sense of number.
57. Roitman, J. D., Brannon, E. M. & Platt, M. L. Monotonic coding of numerosity in macaque lateral intraparietal area. *PLoS Biol.* **5**, e208 (2007).
58. Colby, C. L., Duhamel, J. R. & Goldberg, M. E. Ventral intraparietal area of the macaque: anatomic location and visual response properties. *J. Neurophysiol.* **69**, 902–914 (1993).

59. Wang, L., Uhrig, L., Jarraya, B. & Dehaene, S. Representation of numerical and sequential patterns in macaque and human brains. *Curr. Biol.* **25**, 1966–1974 (2015).

60. Barbas, H. & Mesulam, M. M. Cortical afferent input to the principalis region of the rhesus monkey. *Neuroscience* **15**, 619–637 (1985).

61. Petrides, M. & Pandya, D. N. Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *J. Comp. Neurol.* **228**, 105–116 (1984).

62. Cavada, C. & Goldman-Rakic, P. S. Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *J. Comp. Neurol.* **287**, 422–445 (1989).

63. Lewis, J. W. & Van Essen, D. C. Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *J. Comp. Neurol.* **428**, 112–137 (2000).

64. Quintana, J., Fuster, J. M. & Yajeya, J. Effects of cooling parietal cortex on prefrontal units in delay tasks. *Brain Res.* **503**, 100–110 (1989).

65. Chafee, M. V. & Goldman-Rakic, P. S. Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *J. Neurophysiol.* **83**, 1550–1566 (2000).

66. Miller, E. K. & Cohen, J. D. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* **24**, 167–202 (2001).

67. Vallentin, D. & Nieder, A. Representations of visual proportions in the primate posterior parietal and prefrontal cortices. *Eur. J. Neurosci.* **32**, 1380–1387 (2010).

68. Berger, H. Über Rechenstörungen bei Herderkrankungen des Großhirns. *Archiv. Psychiatrie Nervenkrankheiten* **78**, 238–263 (in German) (1926).

69. Hécaen, H., Angelergues, R. & Houillier, S. Les variêtes cliniques de acalculies au cours de lesions retrorolandiques: approche statistique du problème. *Revue Neurol.* **105**, 85–103 (in French) (1961).

70. Lemer, C., Dehaene, S., Spelke, E. & Cohen, L. Approximate quantities and exact number words: dissociable systems. *Neuropsychologia* **41**, 1942–1958 (2003).

71. Lewandowsky, M. & Stadelmann, E. Über einen bemerkenswerten Fall von Hirnblutung und über Rechenstörungen bei Herderkrankung des Gehirns. *J. Psychol. Neurol.* **11**, 249–265 (in German) (1908).

72. Henschen, S. E. Über Sprach-, Musik-und Rechenmechanismen und ihre Lokalisation im Großhirn. *Zeitschrift Gesamte Neurol. Psychiatrie* **52**, 273–298 (in German) (1919).

73. Ashkenazi, S., Henik, A., Ifergane, G. & Shelef, I. Basic numerical processing in left intraparietal sulcus (IPS) acalculia. *Cortex* **44**, 439–448 (2008).

74. Cohen, L. & Dehaene, S. in *The Behavioral and Cognitive Neurology of Stroke.* 2nd edn (ed. Godefroy, O.) 101–113 (Cambridge University Press, 2013).

75. Cipolotti, L. & van Harskamp, N. *Handbook of Neuropsychology.* 2nd edn Vol. 3 (ed. Berndt, R.S.) 305–334 (Elsevier Science, 2001).

76. Cappelletti, M. *The Oxford Handbook of Numerical Cognition* (ed. Cohen Kadosh, R. & Dowker, A.) 808–836 (Oxford University Press, 2015).

77. Butterworth, B., Varma, S. & Laurillard, D. Dyscalculia: from brain to education. *Science* **332**, 1049–1053 (2011).

78. Isaacs, E. B., Edmonds, C. J., Lucas, A. & Gadian, D. G. Calculation difficulties in children of very low birthweight: a neural correlate. *Brain* **124**, 1701–1707 (2001).

79. Rotzer, S. *et al.* Optimized voxel-based morphometry in children with developmental dyscalculia. *Neuroimage* **39**, 417–422 (2008).

80. Piazza, M., Pinel, P., Le Bihan, D. & Dehaene, S. A magnitude code common to numerosities and number symbols in human intraparietal cortex. *Neuron* **53**, 293–305 (2007).

81. Harvey, B. M., Klein, B. P., Petridou, N. & Dumoulin, S. O. Topographic representation of numerosity in the human parietal cortex. *Science* **341**, 1123–1126 (2013).

82. Arsalidou, M. & Taylor, M. J. Is 2 + 2 = 4? Meta-analyses of brain areas needed for numbers and calculations. *Neuroimage* **54**, 2382–2393 (2011).

83. Nieder, A. Coding of abstract quantity by 'number neurons' of the primate brain. *J. Comp. Physiol. A Neuroethol. Sens. Neural Behav. Physiol.* **199**, 1–16 (2013).

84. Viswanathan, P. & Nieder, A. Differential impact of behavioral relevance on quantity coding in primate frontal and parietal neurons. *Curr. Biol.* **25**, 1259–1269 (2015).

85. Dehaene, S., Izard, V., Spelke, E. & Pica, P. Log or linear? Distinct intuitions of the number scale in Western and Amazonian indigene cultures. *Science* **320**, 1217–1220 (2008).

86. Pouget, A., Dayan, P. & Zemel, R. Information processing with population codes. *Nat. Rev. Neurosci.* **1**, 125–132 (2000).

87. Piazza, M., Izard, V., Pinel, P., Le Bihan, D. & Dehaene, S. Tuning curves for approximate numerosity in the human intraparietal sulcus. *Neuron* **44**, 547–555 (2004).
Using fMRI adaptation, the authors retrace logarithmically scaled number-tuning functions in the human parietal lobe.

88. Jacob, S. N. & Nieder, A. Tuning to non-symbolic proportions in the human frontoparietal cortex. *Eur. J. Neurosci.* **30**, 1432–1442 (2009).

89. Dehaene, S. & Changeux, J. P. Development of elementary numerical abilities: a neural model. *J. Cogn. Neurosci.* **5**, 390–407(1993).

90. Verguts, T. & Fias, W. Representation of number in animals and humans: a neural model. *J. Cogn. Neurosci.* **16**, 1493–1504 (2004).

91. Stoianov, I. & Zorzi, M. Emergence of a 'visual number sense' in hierarchical generative models. *Nat. Neurosci.* **15**, 194–196 (2012).

92. Meck, W. H. & Church, R. M. A mode control model of counting and timing processes. *J. Exp. Psychol. Anim. Behav. Process* **9**, 320–334 (1983).

93. Gallistel, C. R. & Gelman, R. Preverbal and verbal counting and computation. *Cognition* **44**, 43–74 (1992).

94. DeCharms, R. C. & Zador, A. Neural representation and the cortical code. *Annu. Rev. Neurosci.* **23**, 613–647 (2000).

95. Georgopoulos, A., Kalaska, J. & Caminiti, R. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J. Neurosci.* **2**, 1527–1537 (1982).

96. Salinas, E. & Abbot, L. Vector reconstruction from firing rate. *J. Comput. Neurosci.* **1**, 89–108 (1994).

97. Sanger, T. Probability density estimation for the interpretation of neural population codes. *J. Neurophysiol.* **76**, 2790–2793 (1996).

98. Deneve, S., Latham, P. E. & Pouget, A. Reading population codes: a neural implementation of ideal observers. *Nat. Neurosci.* **2**, 740–745 (1999).

99. Stokes, M. G. 'Activity-silent' working memory in prefrontal cortex: a dynamic coding framework. *Trends Cogn. Sci.* **19**, 394–405 (2015).

100. Crowe, D. A., Averbeck, B. B. & Chafee, M. V. Rapid sequences of population activity patterns dynamically encode task-critical spatial information in parietal cortex. *J. Neurosci.* **30**, 11640–11653 (2010).

101. Meyers, E. M., Freedman, D. J., Kreiman, G., Miller, E. K. & Poggio, T. Dynamic population coding of category information in inferior temporal and prefrontal cortex. *J. Neurophysiol.* **100**, 1407–1419 (2008).

102. Stokes, M. G. *et al.* Dynamic coding for cognitive control in prefrontal cortex. *Neuron* **78**, 364–375 (2013).
Population activity of PFC neurons experiences dynamic neuronal state transitions during the course of a cognitive task, indicating that neural tuning profiles adapt to accommodate changes in behavioural context.

103. Averbeck, B. B., Latham, P. E. & Pouget, A. Neural correlations, population coding and computation. *Nat. Rev. Neurosci.* **7**, 358–366 (2006).

104. Kohonen, T. *Self-Organizing Maps* (Springer-Verlag Berlin Heidelberg, 1997).

105. Tudusciuc, O. & Nieder, A. Neuronal population coding of continuous and discrete quantity in the primate posterior parietal cortex. *Proc. Natl Acad. Sci. USA* **104**, 14513–14518 (2007).

106. Genovesio, A., Tsujimoto, S. & Wise, S. P. Prefrontal cortex activity during the discrimination of relative distance. *J. Neurosci.* **31**, 3968–3980 (2011).

107. Leon, M. I. & Shadlen, M. N. Representation of time by neurons in the posterior parietal cortex of the macaque. *Neuron* **38**, 317–327 (2003).

108. Mita, A., Mushiake, H., Shima, K., Matsuzaka, Y. & Tanji, J. Interval time coding by neurons in the presupplementary and supplementary motor areas. *Nat. Neurosci.* **12**, 502–507 (2009).

109. Eiselt, A. K. & Nieder, A. Single-cell coding of sensory, spatial and numerical magnitudes in primate prefrontal, premotor and cingulate motor cortices. *Exp. Brain Res.* **234**, 241–254 (2016).

110. Pinel, P., Piazza, M., Le Bihan, D. & Dehaene, S. Distributed and overlapping cerebral representations of number, size, and luminance during comparative judgments. *Neuron* **41**, 983–993 (2004).

111. Kaufmann, L. *et al.* A developmental fMRI study of nonsymbolic numerical and spatial processing. *Cortex* **44**, 376–385 (2008).

112. Walsh, V. A theory of magnitude: common cortical metrics of time, space and quantity. *Trends Cogn. Sci.* **7**, 483–488 (2003).

113. Markram, H. *et al.* Interneurons of the neocortical inhibitory system. *Nat. Rev. Neurosci.* **5**, 793–807 (2004).

114. Wonders, C. P. & Anderson, S. A. The origin and specification of cortical interneurons. *Nat. Rev. Neurosci.* **7**, 687–696 (2006).

115. Wilson, F. A., O'Scalaidhe, S. P. & Goldman-Rakic, P. S. Functional synergism between putative γ-aminobutyrate-containing neurons and pyramidal neurons in prefrontal cortex. *Proc. Natl Acad. Sci. USA* **91**, 4009–4013 (1994).

116. Rao, S. G., Williams, G. V. & Goldman-Rakic, P. S. Isodirectional tuning of adjacent interneurons and pyramidal cells during working memory: evidence for microcolumnar organization in PFC. *J. Neurophysiol.* **81**, 1903–1916 (1999).

117. Constantinidis, C. & Goldman-Rakic, P. S. Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. *J. Neurophysiol.* **88**, 3487–3497 (2002).

118. Johnston, K. & Everling, S. Task-relevant output signals are sent from monkey dorsolateral prefrontal cortex to the superior colliculus during a visuospatial working memory task. *J. Cogn. Neurosci.* **21**, 1023–1038 (2009).

119. Merchant, H., de Lafuente, V., Peña-Ortega, F. & Larriva-Sahd, J. Functional impact of interneuron inhibition in the cerebral cortex of behaving animals. *Prog. Neurobiol.* **99**, 163–178 (2012).

120. Epping, W. J. & Eggermont, J. J. Coherent neural activity in the auditory midbrain of the grassfrog. *J. Neurophysiol.* **57**, 1464–1483 (1987).

121. Diester, I. & Nieder, A. Complementary contributions of prefrontal neuron classes in abstract numerical categorization. *J. Neurosci.* **28**, 7737–7747 (2008).

122. Rao, S. G., Williams, G. V. & Goldman-Rakic, P. S. Destruction and creation of spatial tuning by disinhibition: GABA$_A$ blockade of prefrontal cortical neurons engaged by working memory. *J. Neurosci.* **20**, 485–494 (2000).

123. Compte, A., Brunel, N., Goldman-Rakic, P. S. & Wang, X.-J. Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. *Cerebral Cortex* **10**, 910–923 (2000).

124. Durstewitz, D., Seamans, J. K. & Sejnowski, T. J. Neurocomputational models of working memory. *Nat. Neurosci.* **3**, S1184–S1191 (2000).

125. Selemon, L. D. & Goldman-Rakic, P. S. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. *J. Neurosci.* **8**, 4049– 4068 (1988).

126. Grieve, K. L., Acuña, C. & Cudeiro, J. The primate pulvinar nuclei: vision and action. *Trends Neurosci.* **23**, 35–39 (2000).

127. Goldman-Rakic, P. S. Topography of cognition: parallel distributed networks in primate association cortex. *Annu. Rev. Neurosci.* **11**, 137–156 (1988).

128. Baars, B. J. *A cognitive theory of consciousness.* (Cambridge Univ. Press, 1989).

129. Dehaene, S. & Changeux, J. P. Experimental and theoretical approaches to conscious processing. *Neuron* **70**, 200–227 (2011).

130. Fuster, J. M. & Alexander, G. E. Neuron activity related to short-term memory. *Science* **173**, 652–654 (1971).

131. Kubota, K. & Niki, H. Prefrontal cortical unit activity and delayed alternation performance in monkeys. *J. Neurophysiol.* **34**, 337–347 (1971).

132. Merten, K. & Nieder, A. Active encoding of decisions about stimulus absence in primate prefrontal cortex neurons. *Proc. Natl Acad. Sci. USA* **109**, 6289–6294 (2012).

133. Shadlen, M. N. & Gold, J. I. in *The Cognitive Neurosciences.* 3rd edn (ed. Gazzaniga, M. S.) 1229–1241 (MIT Press, 2004).

134. MacLeod, C. M. *Inhibition in cognition.* (eds Gorfein, D. S. & MacLeod, C. M.) 3–23 (American Psychological Association, 2007).

135. Jacob, S. N. & Nieder, A. Complementary roles for primate frontal and parietal cortex in guarding working memory from distractor stimuli. *Neuron* **83**, 226–237 (2014).
This single-cell study points to the PFC as a selection stage for goal-directed number processing that represents behaviourally relevant as well as transiently irrelevant numerical information, whereas distractor-resistant working memory representations seem to be maintained in parietal VIP.

136. Anderson, M. C. & Green, C. Suppressing unwanted memories by executive control. *Nature* **410**, 366–369 (2001).

137. McNab, F. & Klingberg, T. Prefrontal cortex and basal ganglia control access to working memory. *Nat. Neurosci.* **11**, 103–107 (2008).

138. Feredoes, E., Heinen, K., Weiskopf, N., Ruff, C. & Driver, J. Causal evidence for frontal involvement in memory target maintenance by posterior brain areas during distracter interference of visual working memory. *Proc. Natl Acad. Sci. USA* **108**, 17510–17515 (2011).

139. Suzuki, M. & Gottlieb, J. Distinct neural mechanisms of distractor suppression in the frontal and parietal lobe. *Nat. Neurosci.* **16**, 98–104 (2013).

140. Constantinidis, C. & Steinmetz, M. A. Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. *J. Neurophysiol.* **76**, 1352–1355 (1996).

141. Bisley, J. & Goldberg, M. Neural correlates of attention and distractibility in the lateral intraparietal area. *J. Neurophysiol.* **95**, 1696–1717 (2006).

142. Postle, B. R. Working memory as an emergent property of the mind and brain. *Neuroscience* **139**, 23–38 (2006).

143. Lara, A. H. & Wallis, J. D. The role of prefrontal cortex in working memory: a mini review. *Front. Syst. Neurosci.* **9**, 173 (2015).

144. Lennert, T. & Martinez-Trujillo, J. Strength of response suppression to distracter stimuli determines attentional-filtering performance in primate prefrontal neurons. *Neuron* **70**, 141–152 (2011).

145. Malmo, R. B. Interference factors in delayed response in monkeys after removal of frontal lobes. *J. Neurophysiol.* **5**, 295–308 (1942).

146. Chao, L. L. & Knight, R. T. Contribution of human prefrontal cortex to delay performance. *J. Cogn. Neurosci.* **10**, 167–177 (1998).

147. Cantlon, J. F. & Brannon, E. M. Semantic congruity affects numerical judgments similarly in monkeys and humans. *Proc. Natl Acad. Sci. USA* **102**, 16507–16511 (2005).

148. Bongard, S. & Nieder, A. Basic mathematical rules are encoded by primate prefrontal cortex neurons. *Proc. Natl Acad. Sci. USA* **107**, 2277–2282 (2010).
Populations of rule-selective neurons in the PFC of behaving monkeys signal abstract 'greater-than' or 'fewer-than' rules applied to numbers.

149. Okuyama, S., Iwata, J., Tanji, J. & Mushiake, H. Goal-oriented, flexible use of numerical operations by monkeys. *Anim. Cogn.* **16**, 509–518 (2013).

150. Vallentin, D., Bongard, S. & Nieder, A. Numerical rule coding in the prefrontal, premotor, and posterior parietal cortices of macaques. *J. Neurosci.* **32**, 6621–6630 (2012).

151. Eiselt, A. K. & Nieder, A. Representation of abstract quantitative rules applied to spatial and numerical magnitudes in primate prefrontal cortex. *J. Neurosci.* **33**, 7526–7534 (2013).

152. Wallis, J. D., Anderson, K. C. & Miller, E. K. Single neurons in prefrontal cortex encode abstract rules. *Nature* **411**, 953–956 (2001).

153. Genovesio, A., Brasted, P. J., Mitz, A. R. & Wise, S. P. Prefrontal cortex activity related to abstract response strategies. *Neuron* **47**, 307–320 (2005).

154. Mansouri, F. A., Buckley, M. J. & Tanaka, K. Mnemonic function of the dorsolateral prefrontal cortex in conflict-induced behavioral adjustment. *Science* **318**, 987–990 (2007).

155. Rigotti, M. *et al.* The importance of mixed selectivity in complex cognitive tasks. *Nature.* **497**, 585–590 (2013).

156. Dehaene, S. & Changeux, J. P. The Wisconsin Card Sorting Test: theoretical analysis and modeling in a neuronal network. *Cereb. Cortex* **1**, 62–79 (1991).

157. Duncan, J. The structure of cognition: attentional episodes in mind and brain. *Neuron* **80**, 35–50 (2013).

158. Seamans, J. K. & Yang, C. R. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog. Neurobiol.* **74**, 1–58 (2004).

159. Jacob, S. N., Ott, T. & Nieder, A. Dopamine regulates two classes of primate prefrontal neurons that represent sensory signals. *J. Neurosci.* **33**, 13724–13734 (2013).

160. Ott, T., Jacob, S. N. & Nieder, A. Dopamine receptors differentially enhance rule coding in primate prefrontal cortex neurons. *Neuron* **84**, 1317–1328 (2014).

161. Dehaene, S., Spelke, E., Pinel, P., Stanescu, R. & Tsivkin, S. Sources of mathematical thinking: behavioral and brain-imaging evidence. *Science* **284**, 970–974 (1999).

162. Gruber, O., Indefrey, P., Steinmetz, H. & Kleinschmidt, A. Dissociating neural correlates of cognitive components in mental calculation. *Cereb. Cortex* **11**, 350–359 (2001).

163. Rivera, S. M., Reiss, A. L., Eckert, M. A. & Menon, V. Developmental changes in mental arithmetic: evidence for increased functional specialization in the left inferior parietal cortex. *Cereb. Cortex* **15**, 1779–1790 (2005).

164. Luria, A. R. *Higher Cortical Functions in Man.* (Tavistock, 1966).

165. Shallice, T. & Evans, M. E. The involvement of the frontal lobes in cognitive estimation. *Cortex* **14**, 294–303 (1978).

166. Smith, M. L. & Milner, B. Differential effects of frontal-lobe lesions on cognitive estimation and spatial memory. *Neuropsychologia* **22**, 697–705 (1984).

167. Della Sala, S., MacPherson, S. E., Phillips, L. H., Sacco, L. & Spinnler, H. The role of semantic knowledge on the cognitive estimation task — evidence from Alzheimer's disease and healthy adult aging. *J. Neurol.* **251**, 156–164 (2004).

168. Revkin, S. K. *et al.* Verbal numerosity estimation deficit in the context of spared semantic representation of numbers: a neuropsychological study of a patient with frontal lesions. *Neuropsychologia* **46**, 2463–2475 (2008).

169. Domahs, F., Benke, T. & Delazer, M. A case of 'task-switching acalculia'. *Neurocase* **17**, 24–40 (2011).

170. Vallentin, D. & Nieder, A. Behavioural and prefrontal representation of spatial proportions in the monkey. *Curr. Biol.* **18**, 1420–1425 (2008).

171. Tudusciuc, O. & Nieder, A. Comparison of length judgments and the Müller-Lyer illusion in monkeys and humans. *Exp. Brain Res.* **207**, 221–231 (2010).

172. Dehaene, S. & Brannon, E. M. *Space, Time and Number in the Brain: Searching for the Foundations of Mathematical Thought* (Academic Press, 2011).

173. Jacob, S. N. & Vallentin, D. & Nieder, A. Relating magnitudes: the brain's code for proportions. *Trends Cogn. Sci.* **16**, 157–166 (2012).

174. Genovesio, A., Wise, S. P. & Passingham, R. E. Prefrontal-parietal function: from foraging to foresight. *Trends Cogn. Sci.* **18**, 72–81 (2014).

175. Bulthé, J., De Smedt, B. & Op de Beeck, H. P. Format-dependent representations of symbolic and non-symbolic numbers in the human cortex as revealed by multi-voxel pattern analyses. *Neuroimage* **87**, 311–322 (2014).

176. Bulthé, J., De Smedt, B. & Op de Beeck, H. P. Visual number beats abstract numerical magnitude: format-dependent representation of Arabic digits and dot patterns in human parietal cortex. *J. Cogn. Neurosci.* **27**, 1376–1387 (2015).

177. Lyons, I. M., Ansari, D. & Beilock, S. L. Qualitatively different coding of symbolic and nonsymbolic numbers in the human brain. *Hum. Brain Mapp.* **36**, 475–488 (2015).

178. Dehaene, S. & Cohen, L. Cultural recycling of cortical maps. *Neuron* **56**, 384–398 (2007).

179. Danzig, T. *Number — The Language of Science* (The Free Press, 1930).

180. Dehaene, S. *The Number Sense.* 2nd edn (Oxford University Press, 2011).

181. Evans, S. E. in *Evolutionary Developmental Biology of the Cerebral Cortex* (eds Bock, G. & Cardew, G.) 109–113 (Wiley, 2000).

182. Dugas-Ford, J., Rowell, J. J. & Ragsdale, C. W. Cell-type homologies and the origins of the neocortex. *Proc. Natl Acad. Sci. USA* **109**, 16974–16979 (2012).

183. Dugas-Ford, J. & Ragsdale, C. W. Levels of homology and the problem of neocortex. *Annu. Rev. Neurosci.* **38**, 351–368 (2015).

184. Jarvis, E. D. *et al.* Avian brains and a new understanding of vertebrate brain evolution. *Nat. Rev. Neurosci.* **6**, 151–159 (2005).

185. Butler, A., Reiner, A. & Karten, H. J. Evolution of the amniote pallium and the origins of mammalian neocortex. *Ann. NY Acad. Sci.* **1225**, 14–27 (2011).

186. Scarf, D., Hayne, H. & Colombo, M. Pigeons on par with primates in numerical competence. *Science* **334**, 1664 (2011).

187. Bogale, B. A., Kamata, N., Mioko, K. & Sugita, S. Quantity discrimination in jungle crows, *Corvus macrorhynchos. Anim. Behav.* **82**, 635–641 (2011).

188. Moll, F. W. & Nieder, A. The long and the short of it: rule-based relative length discrimination in carrion crows, *Corvus corone. Behav. Processes* **107**, 142–149 (2014).

189. Lyon, B. E. Egg recognition and counting reduce costs of avian conspecific brood parasitism. *Nature* **422**, 495–499 (2003).

190. Templeton, C. N., Greene, E. & Davis, K. Allometry of alarm calls: black-capped chickadees encode information about predator size. *Science* **308**, 1934–1937 (2005).

191. Hunt, S., Low, J. & Burns, K. C. Adaptive numerical competency in a food-hoarding songbird. *Proc. Roy. Soc. B* **275**, 2373–2379 (2008).

192. Ditz, H. M. & Nieder, A. Numerosity representations in crows obey the Weber–Fechner law. *Proc. R. Soc. B* **283**, 20160083 (2016).

193. Ditz, H. M. & Nieder, A. Neurons selective to the number of visual items in the corvid songbird endbrain. *Proc. Natl Acad. Sci. USA* **112**, 7827–7832 (2015).
This was the first study reporting number neurons in a non-mammalian species, and a species without a neocortex: the crow.

194. Divac, I., Mogensen, J. & Björklund, A. The prefrontal "cortex" in the pigeon. Biochemical evidence. *Brain Res.* **332**, 365–368 (1985).

195. Güntürkün, O. The avian "prefrontal cortex" and cognition. *Curr. Opin. Neurobiol.* **15**, 686–693 (2005).

196. Veit, L. & Nieder, A. Abstract rule neurons in the endbrain support intelligent behaviour in corvid songbirds. *Nat. Commun.* **4**, 2878 (2013).