

INTERACTIONS BETWEEN NUMBER AND SPACE IN PARIETAL CORTEX

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Abstract | Since the time of Pythagoras, numerical and spatial representations have been inextricably linked. We suggest that the relationship between the two is deeply rooted in the brain's organization for these capacities. Many behavioural and patient studies have shown that numerical–spatial interactions run far deeper than simply cultural constructions, and, instead, influence behaviour at several levels. By combining two previously independent lines of research, neuroimaging studies of numerical cognition in humans, and physiological studies of spatial cognition in monkeys, we propose that these numerical–spatial interactions arise from common parietal circuits for attention to external space and internal representations of numbers.

INTRAPARIETAL SULCUS (IPS). A long, deep fissure that cuts through the parietal lobe, dividing the superior and inferior parietal lobules. This sulcus is present in both humans and non-human primates, and accumulating data indicate that its organization might be partially conserved in evolution.

LATERAL INTRAPARIETAL (LIP). A region of the lateral bank of the IPS that is involved in visual representations of space in an eye-centred coordinate frame. This region is crucial for attention, intention to make saccadic eye movements and spatial updating.

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The history of mathematics is traversed by a deep connection between numbers and space. From the most elementary aspects of mathematics, such as the notion of measurement, all the way up to the concepts of the real number line, Cartesian coordinates, the complex plane and even the proof of Fermat's Last Theorem, metaphors by which numbers are made to correspond to spatial positions permeate mathematical thinking^{1–3}. The evolution of these culturally-defined representations of numbers has been crucial to the development of mathematics. In this review, we discuss the neural mechanisms that might underpin these cultural achievements. We begin by reviewing recent behavioural and patient data that show that certain aspects of numerical understanding depend on spatial representations. We then turn to neuroimaging data in humans, which indicate that the deep connection between numbers and space might be mediated by the neural circuitry in the parietal lobe. Drawing on recent work in monkey physiology and neuroimaging studies that established tentative monkey–human homologies, we then present a refined hypothesis about the specific neural regions in the INTRAPARIETAL SULCUS (IPS) that might be involved in these numerical and spatial processes, including the LATERAL INTRAPARIETAL (LIP) and VENTRAL INTRAPARIETAL (VIP) regions.

So far, these two lines of research have been largely independent, as most studies of numerical cognition have been conducted in humans using functional imaging, whereas most studies of spatial processing have been conducted in monkeys using single-unit electrophysiology. However, this division is breaking down, as single-unit data has revealed 'number neurons' in the IPS, and many recent neuroimaging studies in humans have focused on establishing human–monkey homologies in the parietal lobe. We conclude by combining data from these complementary lines of research to suggest several testable predictions that concern the anatomical localization and neural mechanisms of numerical–spatial interactions.

Behavioural studies

Many behavioural protocols have shown a close connection between numbers and space, in which small numbers are represented on the left side of space, and large numbers on the right. In this section, we consider three important questions that have guided research in this area. First, how automatic is this association between numbers and space? Second, what level of spatial representation is involved? And, third, what role do cultural factors play in the orientation of these numerical–spatial associations?

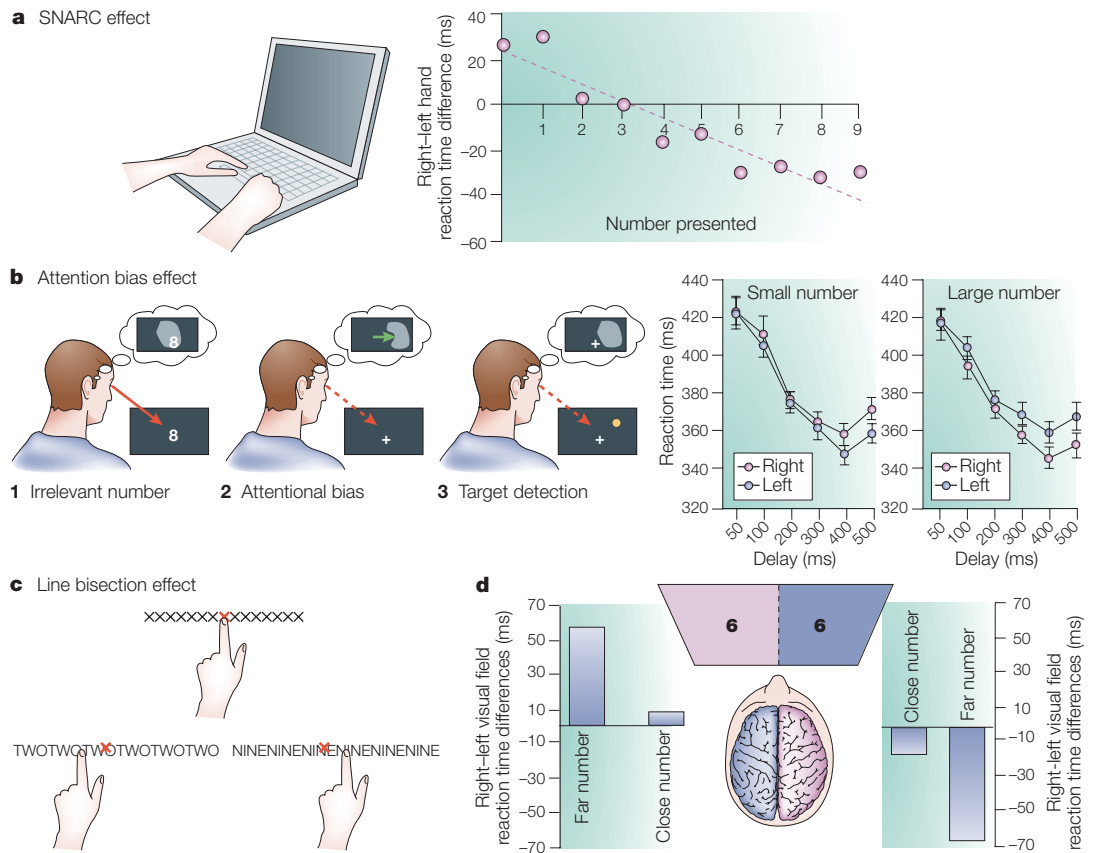


Figure 1 | Behavioural studies showing numerical-spatial interactions. a | The spatial-numerical association of response codes (SNARC) effect. Participants are asked to judge whether a number is even or odd. Responses to larger numbers are faster on the right side of space whereas those for smaller numbers are faster on the left side. The graph represents the response-time difference between right-hand and left-hand key presses. Values greater than 0 indicate a left-hand advantage, whereas values less than 0 indicate a right-hand advantage. **b** | In the attention bias effect, presentation of a non-informative digit at fixation leads to an automatic shift of attention to the left or right, which results in faster subsequent responses to visual targets. The graphs indicate detection of a visual target on the left or right side of space as a function of whether the cue was a small or large number. Blue symbols indicate left-sided targets, which induce a faster response after the presentation of small numbers, whereas pink symbols represent right-sided targets, which induce a faster response after the presentation of large numbers. **c** | The line bisection effect. When asked to point to the midpoint of a line (red x), participants are approximately accurate when the line is composed of 'x's. However, when the line is composed of the words two or nine, pointing deviates leftwards or rightwards from the midpoint. **d** | When a number is presented in one visual field during a number comparison task, an interaction between numerical distance and visual field is observed. Numbers that are smaller than the standard (left graph) show an advantage for left visual field/right hemisphere presentation, whereas numbers that are larger than the standard (right graph) show an advantage for right visual field/left hemisphere presentation. This effect is further modulated by numerical distance. Numbers that are close to the standard show only small advantages with lateralized presentation. Panel **a** modified, with permission, from REF. 4 © (1993) American Psychological Association; panel **b** modified, with permission, from REF. 10 © (2003) Macmillan Magazines Ltd; panel **c** modified, with permission, from REF. 11 © (2005) Elsevier Science; panel **d** modified, with permission, from REF. 23 © (2004) Elsevier Science.

VENTRAL INTRAPARIETAL (VIP). A region in the ventral portion of the IPS that is responsive to motion in visual, auditory and tactile modalities with head-centred receptive fields. Recent studies indicate that number-selective neurons are located in or near this region.

SPATIAL-NUMERICAL ASSOCIATION OF RESPONSE CODES EFFECT (SNARC effect). The finding that subjects respond more quickly to larger numbers if the response is on the right side of space, and to the left for smaller numbers, which indicates automatic spatial-numerical associations.

The simplest demonstration of a connection between numbers and space is the SPATIAL-NUMERICAL ASSOCIATION OF RESPONSE CODES (SNARC) EFFECT⁴. When subjects are asked to classify numbers as even or odd (parity judgement), the responses to larger numbers are quicker when responses are made on the right side of space, whereas responses to smaller numbers are quicker when the responses are made on the left (FIG. 1a). This association of numbers and space occurs despite the fact that the task itself has nothing to do with numerical magnitude. Indeed, the SNARC effect can occur with non-numerical tasks, such as judging phonemic content of number words⁵, or even in tasks in which the digit itself is completely irrelevant to the task^{6,7}.

In one series of experiments, participants were asked to perform an orientation-discrimination task on a triangle or line superimposed on a digit, and to respond with the left or right hand. In this task, a SNARC effect was observed^{6,7}, which showed that numerical magnitude is processed automatically. This effect was reduced or absent when participants were asked to report the colours of the digits or to identify a shape (circle or square) superimposed on the digits. The authors suggest that this reduction in the SNARC effect is attributable to the reduced amount of overlap between neural circuits for number and colour or shape compared with those for number and orientation. Although plausible, recent data indicate

that the parietal lobe is also involved in colour and form tasks^{8,9} and so this interpretation remains open to further tests.

Even the simple presentation of a digit automatically draws attention to either the left or right visual field (LVF/RVF) according to the relative size of the number¹⁰. Fisher *et al.* presented single digit numbers (1, 2, 8 or 9) at fixation, followed by a target in either the LVF or RVF, which participants responded to as quickly as they could (detection reaction time). The presentation of the number preferentially influenced the direction of the allocation of attention, and, therefore, the detection reaction time (FIG. 1b). The presentation of digits 1 and 2 automatically directed attention to the LVF and so facilitated the response to stimuli in the LVF, whereas the opposite was true for 8 and 9, even though the digit was non-informative and completely irrelevant to the detection task.

In a third demonstration of automatic numerical–spatial interactions, line bisection can be biased when the lines are composed of numbers^{11,12}. When asked to indicate the midpoint of a line composed of ‘x’s, participants are, on average, accurate. However, when asked to indicate the midpoint of a line composed of either the digit 9 or the French word ‘neuf’ (nine) participants deviate to the right. When the line is composed of the digit 2 or the word ‘deux’ (two) participants deviate to the left (FIG. 1c). The suggestion is that the numbers automatically bias attention to the left or the right, and, therefore, that the bisection of the lines deviates in the same direction.

A second issue that is relevant to this review is the determination of the coordinate frame in which the SNARC effect arises. For example, it is known that the SNARC effect occurs even when the hands are crossed⁴, which indicates that the effect depends on eye- or world-centred coordinates, rather than hand-centred coordinates. Similar data from cross-modal visual–tactile attentional studies show that the delivery of non-informative tactile stimuli to either hand improves detection thresholds on the same side of space even when the hands are crossed¹³. This indicates that similar mechanisms might underlie both the spatial representation in the SNARC effect and in cross-modal spatial cuing. Neuroimaging studies of these cross-modal cuing effects consistently find parietal lobe activation^{14,15}, and a recent patient study indicated that the parietal cortex has a crucial role in mediating these effects¹⁶.

Furthermore, the SNARC effect arises when individuals are asked to perform the parity judgement by pointing¹⁷ or by making a saccade, instead of a manual response¹⁸. It must also be remembered that non-informative digits can bias covert visuospatial attention¹⁰. Finally, a recent study has shown that the size of grip aperture also has a SNARC-like effect, in which small numbers are responded to more quickly by closing the hand, and large numbers by opening the hand¹⁹. Taken together, these results indicate that numerical–spatial interactions occur in effector-independent, stable spatial-coordinate frames (that is, at a level of spatial

representation that is shared by the programming of a hand, eye or attention movement). However, so far, no study has sufficiently shown whether these reference frames are eye- or world-centred.

Another related question concerns the stage of processing at which spatial–numerical interactions arise; do they occur during stimulus comprehension, response selection or response execution? A recent study using a dual-task paradigm showed that the presentation of a stimulus digit is not necessary for the SNARC effect to emerge. When participants were asked to verbally respond ‘one’ or ‘two’ to different stimuli, the automatic activation of numerical information interfered with responding to the orientation of an arrow (backward compatibility effect)²⁰. This study indicates that spatial–numerical interactions occur at a task- and modality-independent level. Another recent study showed that the SNARC effect is not simply due to spatial stimulus–response compatibility (Simon effect), because it has a different time course and does not interact with the Simon effect²¹. Event-related potential (ERP) evidence also points to an intermediate level of processing as the neural basis of the SNARC effect. The SNARC effect best correlates with the response-locked (as opposed to stimulus-locked) ERPs, and begins to emerge at a response selection stage, before response preparation or execution²².

Indeed, interference between numerical and spatial information can arise even from spatial congruity of the stimulus, rather than the response²³ (FIG. 1d). The classic ‘numerical-distance effect’ in a number comparison task is the finding that responses are increasingly faster with increasing distance between the compared numbers^{24,25}. However, when numbers are presented to the left (LVF) or right (RVF) of fixation, a distance-dependent effect of target location is observed: numbers smaller than the standard show an advantage for LVF presentation, whereas numbers larger than the standard show an advantage for RVF presentation. This effect is highly reminiscent of the SNARC effect (compare FIGS 1a and 1d). Taken together, these results indicate that numerical–spatial interactions arise at a central level, independent of input modality or output effector, and that they depend on spatial compatibility in both the input and output processes.

Although these associations are automatic, and depend on abstract representations of number and space, the direction of the effect — small numbers left, large numbers right — might be determined by cultural factors. Spatial–numerical interactions might have been progressively shaped by cultural conventions, such as the orientation of writing or the conventional orientation of mathematical graph axes. American children do not show a SNARC effect until age nine²⁶, which is compatible with this cultural-shaping hypothesis. Furthermore, the SNARC effect tends to be reversed in adult Iranian individuals, who write from right-to-left⁴. Studies of cultural influences on the SNARC effect remain scarce, and are difficult because mathematical conventions are now essentially universal. For instance, Japanese participants respond faster to small numbers

with a lower response button and large numbers with an upper response button²⁷, despite the fact that Japanese people write either left-to-right (as for Western individuals) or top-to-bottom (which would predict the converse SNARC effect). It is possible that this is due to graphing conventions (in which small = bottom left).

Moreover, the SNARC effect seems to be subject to contextual influences. In one experiment²⁸, participants were presented with a magnitude task (judging whether a number was larger or smaller than 5) after being primed with an image of either a ruler or a clock. After being primed with a ruler, the standard SNARC effect was observed: participants responded to smaller numbers more quickly when the responses were made on the left side of space, and responded to larger numbers more quickly when responses were made on the right (small-left, large-right). However, after being primed with a clock-face, participants showed a reverse SNARC effect (small-right, large-left), which is consistent with the representation of time on the clock face.

In this context, it is particularly interesting to note that not only numbers, but other culturally learned sequences, such as month names or days of the week, can also induce SNARC effects^{29,30}. These findings also raise the issue of whether it is the ordinal or cardinal semantic content of numbers that is crucial for the SNARC effect, a question that remains to be investigated.

Finally, we note that, although most subjects are unaware of spatial–numerical interactions, a small group of people experience vivid images of spatially extended ‘number forms’ when they process numbers (BOX 1). In the future, studies of this particular form of synaesthesia for numbers, using rigorous psychophysical and neuroimaging protocols, might further illuminate our understanding of the connections between numbers and space^{31,32}.

In summary, various protocols indicate that numbers automatically elicit task-, modality- and effector-independent spatial representations, even when these spatial representations are not strictly relevant to the task. Although cognitive and cultural factors clearly have a part in the orientation of these effects, the existence of numerical–spatial interference is robust. Below, we relate these effects to monkey physiology and human neuroimaging studies of parietal regions that are involved in the appropriate representation of numbers and space.

Neuropsychological studies

Another source of evidence for numerical–spatial interactions comes from joint deficits of space and number that are frequently observed in patients with lesions of the parietal lobes. Classic evidence for this comes from studies of patients with Gerstmann’s syndrome, which often involves dyscalculia and spatial problems, such as left–right confusion and finger agnosia^{33–36}, and is classically associated with lesions to the left angular gyrus. Recently, a case of pure Gerstmann’s syndrome due to a small lesion beneath the left angular gyrus was identified³⁵. After substantial testing of all the elements of Gerstmann’s syndrome, the

authors suggested that the common deficit linking the symptoms in this patient was a deficit in visuospatial manipulations, which is consistent with our hypothesis of numerical–spatial interaction in the parietal lobe. However, interpretation of such symptom–association data remains complicated because it could be due to the mere anatomical proximity of functionally-distinct systems. Indeed, many studies have questioned the unity of Gerstmann’s syndrome by showing that its defining features can be dissociated in both patient³⁴ and intracranial-stimulation studies³⁶.

Another classic study that indicates a connection between number and space is the work of Spalding and Zangwill³⁷ on a patient who experienced number-form synaesthesia before he suffered a gunshot wound, which entered near the right angular gyrus and lodged near the left temporal–parietal junction. Five years after injury he still complained of spatial problems and showed considerable difficulty with calculation tasks. In addition, the patient complained that his synaesthetic number form, as well as his spatial forms for months, days of the week and letters of the alphabet, were no longer distinct.

Recent studies^{38,39} that investigated distortions in number processing in patients with hemi-spatial neglect due to brain damage in the right hemisphere also support a fundamental connection between number and space. Participants with neglect tend to ignore the contralesional (usually left) portion of space, particularly when contralesional stimuli compete with ipsilesional stimuli. Furthermore, neglect can extend to imagined representations of space (representational neglect)⁴⁰ (FIG. 2a). In a classic test of neglect, in which patients are asked to bisect a line, they neglect the left portion of the line, and so place the perceived midpoint of the line to the right of centre⁴¹. In a recent study³⁸, patients with neglect were asked to state the midpoint number of various numerical intervals (for example, to give the numerical midpoint of 3 and 12). Remarkably, they responded with numbers that deviated to the right, that is, towards larger values, despite the fact that both the problem input and the subject’s response were given in a non-spatial spoken form. However, with very small lines, and with small numerical intervals, a ‘cross-over’ effect was observed, in which patients deviated to the left in line bisection, and towards smaller numbers in numerical interval bisection. This numerical bias reflects a purely representational form of neglect⁴⁰, and indicates that numerical bisection involves an internal stage of representation on a spatially oriented ‘number line’. Patients with brain damage in the right hemisphere but no neglect do not show this pattern³⁸. A second study showed that these representational deficits extend to the clock and ruler tasks described above³⁹ (FIG. 2b). Wearing leftward-adapting prisms tends to obviate both spatial^{42,43} and representational neglect⁴⁴, including numerical neglect⁴⁵, which further indicates that the neural mechanisms that underlie spatial abilities are crucial for certain numerical tasks.

Box 1 | **Number forms**

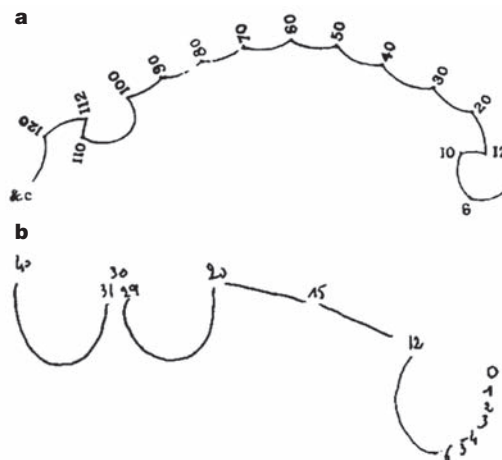
In 1880, *Nature* published two articles by Sir Francis Galton entitled ‘Visualised numerals’ in which he reported a peculiar phenomenon: to otherwise normal people, numbers seemed to occupy very precise locations in space, forming two- or three-dimensional objects of different shapes and orientations^{146,147}.

More than 120 years later, we identified a French individual who was unaware that the phenomenon existed in others, yet reported a number form similar to one of Galton’s subjects. Galton’s subject’s number form is shown in panel a. This number form shows cultural influences, as the first section (1–12) clearly resembles the face of a clock. Beyond 12, note the repeated volutes for successive decades. Panel b shows the number form reported by our French subject (M.P., P.P. and S.D., unpublished observations), which also shows a clock-like organization for 1–12, and repeating volutes beyond that.

Such reports³² indicate that number forms are not mere figments of the imagination, but a constrained experiential phenomenon, which is probably subject to both neurobiological and cultural influences. Indeed, number forms often represent number as a continuous line, subject to compression for larger numbers, similar to the ‘number line’ representation that can be inferred from chronometric and neuroimaging data in people who do not report having an explicit number form. Some individuals even report that they see days, months or other temporal sequences as having a spatial layout¹⁴⁸ similar to spatial number forms, consistent with the presence of a spatial–numerical association of response codes (SNARC) effect for these stimuli^{29,30}. Introspective reports indicate that the number forms are mentally represented as visual objects and can be subjected to visuospatial transformations like rotation or zooming. Such individuals report that they can observe their forms from different perspectives, sometimes situating themselves directly on the forms, and that they can zoom in and out on different segments of these forms^{32,147}. Self-reports also indicate that the number forms spontaneously arise at a young age.

Number forms might be considered to be a type of synaesthesia, which is a relatively rare condition (at least 1 in 2,000) in which stimulation of one sensory modality causes experiences in a second, unstimulated modality (for reviews, see REFS 148,149). For instance, colour is frequently and automatically associated with sounds or visual graphemes. Imaging studies have shown that colour-selective regions of the cortex are active when synaesthetes experience colours, whether they are induced by tones^{150,151} or by graphemes¹⁵². Other recent data show increased activity in the mirror neuron system of an individual who experiences ‘seen’ touches on others as ‘felt’ touches on the corresponding body part¹⁵³.

The extent to which number–form synaesthesia depends on the same mechanisms as the numerical–spatial interactions described in non-synaesthetic observers remains an open question. However, it seems plausible that number–form synaesthesia arises from similar brain mechanisms of genetically-mediated cross-activation, in this case, between spatial and numerical representations in the parietal lobe. We propose that there might be an early predisposition for seeing such forms, possibly due to the existence of exuberant random connections between the cortical representations of numbers and space in these individuals^{1,148}. However, the existence of recurrent themes more than a century after Galton’s original report indicates that culture also has some influence on the shaping of number forms in synaesthesia. Future research on number–form synaesthesia should use both rigorous psychophysical and brain imaging methods to explore such properties as automaticity, spatial frames of reference and cultural influences to reveal the underlying brain mechanisms. Panel a reproduced, with permission, from REF. 146 © (1880) Macmillan Magazines Ltd.



Joint deficits of space and number can also be induced by repetitive transcranial magnetic stimulation (rTMS) in healthy individuals. Performance on both a visuospatial search task and a numerical comparison task can be disrupted by rTMS over the left angular gyrus, but not by rTMS over the left supramarginal gyrus or corresponding sites in the right hemisphere⁴⁶ (FIG. 2c). Importantly, these results, like those discussed above in connection with the SNARC effect and lateralized presentation (see FIGS 1a and 1d), show clear hemispheric and visual field asymmetries. In patients with right hemisphere lesions, it is the smaller numbers that are associated with faster responses to the left side

of space. Conversely, in the case of the rTMS study, stimulation over the left angular gyrus led to impaired performance on larger numbers, which are associated with faster responses on the right side of space. Therefore, the lesion data and the reaction time data both indicate a left-to-right orientation for the mental number line.

In general, these results indicate that numerical manipulations crucially depend on intact spatial representations, and that the neural mechanisms of numerical–spatial interactions might be the same as those that subservise spatial cognition in the intact brain. One caveat is that both lesions and rTMS are likely to

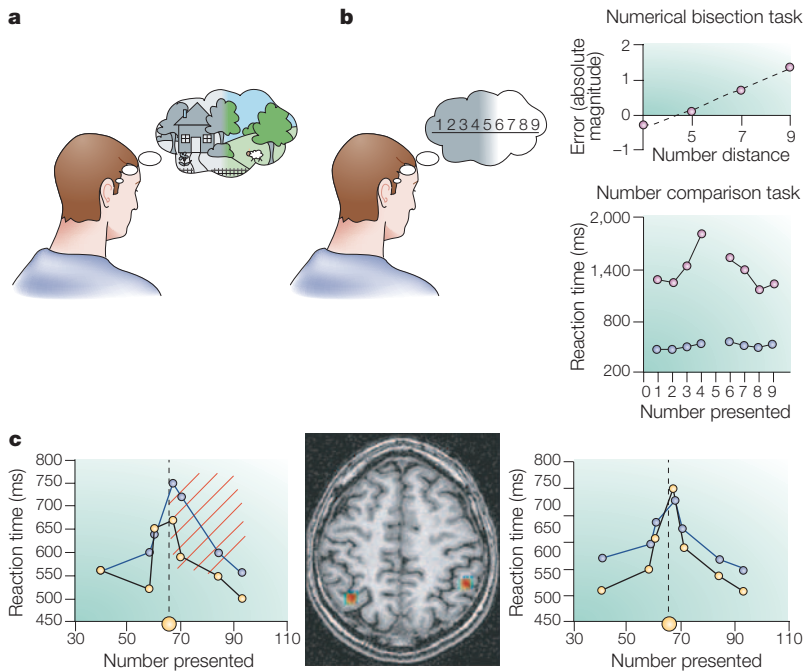


Figure 2 | Lesion evidence for interference between numbers and space. **a** | Patients with right parieto-temporal lesions often neglect the left side of space, including that in internal mental images. When asked to report all the objects in their mental image, they tend to omit those on the left side of space. **b** | Neglect patients also show severe deficits in numerical comparison and bisection tasks. The image (right) represents a metaphor of neglect on the mental number line. The first graph shows the deviation on a numerical bisection task, in which subjects are asked to give the number closest to the middle of various numerical intervals, as a function of interval size. For most intervals, patients with neglect deviate towards larger values (those greater than 0), whereas for the smallest numerical interval, patients deviate towards smaller values, which is consistent with the 'cross-over' effect that is also observed in spatial line bisection. The second graph shows the reaction times taken to decide whether a number is less than or greater than 5. For target number 4, which is reported to be left of the midpoint, reaction times are differentially slowed, which indicates a difficulty in shifting attention to the left. **c** | Participants with a 'virtual lesion' caused by repetitive transcranial magnetic stimulation (rTMS) show interference in both numerical comparison and visuospatial tasks. In particular, when rTMS is applied to the left angular gyrus (left graph; blue symbols), at a site selected because its stimulation interferes with visual search, number comparison performance is slowed compared with the no stimulation condition (yellow symbols), particularly when responding to a number greater than the standard (red hashed region indicates significant difference). A symmetrical, although nonsignificant, deficit was observed for numbers smaller than the standard when stimulation was applied to the right angular gyrus (right graph). The brain image shows the sites of stimulation by transcranial magnetic stimulation. Panel **b** modified, with permission, from REF. 38 © (2002) Macmillan Magazines Ltd and REF. 39 © (2004) Masson; panel **c** modified, with permission, from REF. 46 © (2001) Elsevier Science.

affect several cortical regions and could, therefore, cause many independent impairments. This indicates the need for more fine-grained analysis of the neural substrates of these functions, which would be possible if patients with small focal lesions were tested.

The parietal basis of number processing

The past 10 years have seen an explosion of interest in the neural basis of basic mathematical processes such as subitizing, addition, subtraction and multiplication^{1,47}. One of the main suggestions from this line of research is that the neural circuitry that is crucial for abstract representations of quantity is housed in the parietal lobe, in regions that overlap with the neural circuitry involved in spatial representations.

The triple-code model of number processing⁴⁸ proposes that numbers can be mentally represented in a visual system, a verbal system and a non-verbal quantity representation, which depend on different neural substrates. The visual system, in which numbers can be encoded as strings of Arabic numerals, probably depends on ventral occipito-temporal structures. The verbal system, in which numerals are represented lexically, phonologically and syntactically, probably depends on left frontal and temporal language areas, much like other types of words. Most important for our purposes here is the quantity system, which provides a semantic representation of the size and distance relations between numbers, is thought to be located in the parietal cortex, and might be crucial for mediating the observed interactions between numerical and spatial representations.

Functional MRI (fMRI) has been used to test this model and to precisely localize the non-verbal quantity system. The results indicate that numerical tasks typically involve a distributed network of areas, including the frontal cortex and the left and right parietal lobes⁴⁹⁻⁵⁶. Here we focus on the role of the parietal cortex in these tasks. In some experiments, participants are asked to compare two numbers and decide which is larger^{50,51}. An identical behavioural distance effect is observed, regardless of whether the numbers are presented as digits or as words. fMRI indicates that the activation of the left and right intraparietal sulci (IPS) shows a tight correlation with the behavioural-distance effect. The activation signal in this region also shows an inverse relationship to the distance between the numbers being compared. On the basis of this and other fMRI experiments of arithmetical tasks, such as comparison, calculation⁵³, approximation⁴⁹ or even the mere detection of digits⁵⁴, a recent meta-analysis indicated that the bilateral horizontal segment of the IPS (HIPS) might have a particular role in the quantity representation⁵⁷. In some cases, the activation extends to dorsal parietal sites that are thought to be involved in spatial attention orientation.

Crucially, it should be noted that the quantity system in the parietal lobe might be part of a broader network of areas that are involved in non-numerical magnitude representation^{51,58}. Pinel *et al.* recently measured parietal activation in response to three tasks: luminance comparison, size comparison and numerical magnitude comparison^{50,51}. Because all three tasks show a distance effect, it was possible to match task difficulty by varying the discriminability of the stimuli for each individual. fMRI revealed a network of areas that were activated in each of the three tasks, with the IPS showing partial specificity, but also considerable overlap, among the three dimensions. Interestingly, the amount of overlap predicted the presence of cross-dimensional interference. In particular, number and size activations overlapped within the HIPS, and those dimensions interfered in behavioural response time measures.

To further investigate the neural basis of the quantity system, Simon *et al.*⁵⁹ used fMRI to examine the topographical relationship of calculation-related activation to other spatial and language areas in the human parietal lobe. They found that manual tasks (grasping and pointing) activated a large overlapping region in the anterior parietal cortex, with the greatest extent of activation seen for grasping, which activated an additional anterior parietal region bilaterally (possibly coinciding with the ANTERIOR INTRAPARIETAL area (AIP), see below). Posterior to this was a region that was selectively activated by calculation alone (specifically in the IPS). The posterior parietal cortex was activated by all visuospatial tasks (grasping, pointing, saccades and spatial attention), which is consistent with previous data⁶⁰. Finally, calculation and phoneme detection jointly activated a portion of the IPS lying underneath the left angular gyrus. Overall, these results indicate that calculation activates the fundus of the IPS, a region closely surrounded by a geometrically reproducible array of areas that are involved in manual, visuospatial and verbal tasks.

As described above, not only numbers, but also other ordered sequences, such as days of the week and months of the year, are able to induce the SNARC effect^{29,30}. Another region that might be of interest for mediating these behavioural effects is the left angular gyrus⁵⁷, which might be connected with basic numerical representations in the IPS, and is also involved in verbal processing⁵⁹. Given that cardinal and ordinal information can be dissociated in patients with angular gyrus lesions⁶¹ it is possible that, in addition to numerical representations in the IPS, linguistically-learned sequences in the angular gyrus might be important for understanding the origin of these numerical–spatial interactions. In this respect, it might be interesting to test patients who show such dissociations in the SNARC task and other similar tasks to determine the extent to which numerical–spatial associations depend on cardinal and ordinal information.

Number-sensitive neurons

Several animal species spontaneously keep track of numerosity^{62–64}, and can be trained to use symbolic representations of numbers in a variety of tasks^{65–67}. Furthermore, physiological recordings have shown that there are neurons in the parietal cortex of cats⁶⁸ and macaque monkeys^{69,70} that respond selectively to numbers (for a recent review, see REF. 71). Human infants also respond to numerosity⁷². These results indicate that there might be an evolutionary necessity to keep track of the number of objects and events in the environment, and that, at least at a rudimentary level, the ability to estimate numerosity might be present in many non-human animals and in pre-verbal human infants. It is thought that the adult competence for arithmetic arises from this fundamental ‘number sense’⁷³.

Recently, Andreas Nieder and Earl Miller^{70,74,75} recorded from single neurons in awake monkeys that

had been trained to perform a visual number match-to-sample task. Many neurons were tuned to a preferred numerosity; some responded preferentially to sets of one object, others to two objects, and so on, up to five objects. The tuning was coarse, and became increasingly imprecise as numerosity increased. Importantly, these neurons were originally observed in the dorso-lateral prefrontal cortex, but, more recently, another population of neurons with a shorter latency has been found in the parietal lobe^{69,70}. These neurons, although broadly distributed, were mostly clustered in the depths of the IPS, a location that is a plausible homologue of the human HIPS area, which is active during many number tasks⁴⁷. However, it is worth noting that at most 18% of neurons in this region were tuned to numerosity. The intermixing of neurons from many unrelated types might explain a recent failure to observe human IPS activation in response to numerosity stimuli relative to colour or shape tasks using fMRI⁷⁶.

Recently, an adaptation method was used to investigate whether such numerosity tuning also exists in humans⁷⁷, and so to link human fMRI responses to those obtained with monkeys. During fMRI, we repeatedly presented sets of a fixed number of dots (for example, 16 dots). The purpose was to ‘adapt’ the neural population coding for this value, leading putative human number neurons to progressively reduce their firing rate, as observed in electrophysiological experiments with macaques⁷⁸. We then presented occasional deviant numbers that ranged from half to twice the adapted number. fMRI revealed that only two regions, the left and right IPS, responded to the change in numerosity by increasing their activation in relation to the ratio between the adapted number and the deviant one, regardless of the direction of the change (more or less dots).

These human fMRI and monkey electrophysiological data yielded similar tuning profiles, which suggests that humans and macaques have similar populations of intraparietal number-sensitive neurons. In both the single-unit recording studies and the human fMRI study, responses closely match predicted responses from computational models^{79,80}. Specifically, the firing rates assume a Gaussian distribution only if plotted on a logarithmic scale. This logarithmic compression is commonly seen in human numerical tasks⁸¹, and is reflected in the frequency of use of number words in many of the world’s languages⁸². Therefore, even the detailed properties of numerical abilities can be related to the responses of neurons in the parietal cortex.

Physiological studies of spatial cognition

In addition, recent work in both electrophysiology and neuroimaging has begun to converge on specific cortical regions as the possible neural basis for the spatial representations that interfere with number processing. Spatial cognition depends on a network of frontal, parietal and hippocampal regions. In this review, we concentrate on parietal regions for two main reasons: specificity and proximity. First,

ANTERIOR INTRAPARIETAL (AIP). A region in the anterior portion of the IPS that is involved in fine grasping behaviours. Neurons in this area respond to both visual and tactile stimuli, with receptive fields that move with the hand.

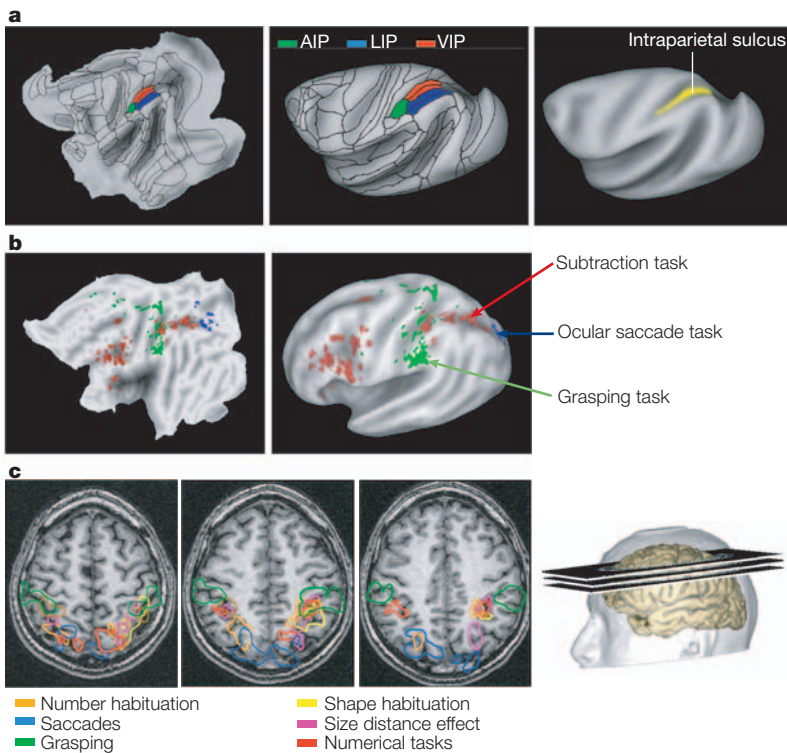


Figure 3 | Location of numerical processing relative to the regions of the intraparietal sulcus involved in space and grasping. **a** | Monkey anterior intraparietal (AIP), lateral intraparietal (LIP) and ventral intraparietal (VIP) regions based on the partitioning scheme of Lewis and Van Essen⁸⁴ on the flattened cortex (left) and inflated brain (centre). Black lines indicate boundaries between regions. Yellow line (right) indicates the fundus of the intraparietal sulcus (IPS). Produced using the Sums Database. **b** | Putative human homologues of the monkey regions described in **(a)**⁵⁹. Colours indicate areas activated during performance of different tasks. Human reaching regions might correspond to monkey area AIP, whereas human saccade regions might correspond to monkey area LIP, which shows that the overall organization of the monkey IPS is conserved in the human. On the basis of these anatomical and functional landmarks, brain activation during arithmetic in the human roughly overlies area VIP in the monkey (see main text for more details). Monkey and human brain renderings were produced using Caret software^{154,155} and the Sums Database. **c** | Horizontal slices that show, in more detail, the same posterior–anterior parietal organization across tasks in humans as described above. Placement of slices is shown on the right. As shown in **(b)**, the regions involved in grasping lie in the most anterior area, and regions involved in saccades lie in the most posterior area⁵⁹. Between these regions are many areas that are involved in visuospatial and numerical tasks⁵⁷. Although tentative, it seems that there is greater overlap for these tasks in the right hemisphere than in the left, most strikingly in the right anterior IPS. Note the proximity of the posterior areas involved in saccade tasks and numerical tasks. Each coloured outline represents the extent of activation in each study. See colour code for tasks used in each study. Number and shape habituation data taken from REF. 77; size distance effect data from REF. 51.

CAUDAL INTRAPARIETAL (CIP). A region at the posterior end of the IPS that is involved in the analysis of three-dimensional shapes. Signals from area CIP are sent to area AIP, where they are integrated to plan the grasping of three-dimensional objects.

although frontal regions are involved in both spatial and numerical tasks, such overlap seems nonspecific and is found in a broad variety of tasks⁸³. By way of comparison, parietal activations are related to a more restricted set of cognitive processes. Second, the close proximity of spatial and numerical representations in the parietal lobe increases the probability that there are neural interactions that might mediate the behavioural interactions described above. Hippocampal and parahippocampal regions, although clearly involved in spatial cognition, are not known to contain numerical representations that might support such behavioural interactions.

On the basis of architectonic⁸⁴, connectivity^{85,86} and physiological criteria^{87,88}, the macaque IPS has been divided into several subregions that represent space in various frames of reference. Although a consensus is emerging, considerable debate remains about the precise boundaries and extent of these regions, which depend on whether anatomical, connectivity or functional criteria are used.

Many neurons in macaque area LIP represent target position in an eye-centred frame of reference⁸⁹ and are highly active during memory-guided saccades^{90,91}. That is, when the eyes are directed to different locations in the visual field, the position of the best visual stimulus moves the same amount. Furthermore, these neurons are involved in spatial updating, even before an eye movement is made^{89,92}.

Regions medial to area LIP seem to be more involved in coding the location of an intended reach (parietal reach region; PRR)^{93,94}, although still in an eye-centred coordinate frame⁹⁵, which indicates that it could have a role in reach guidance and hand–eye coordination. Whether these responses relate to the specific intention to perform an action or to attention to a spatial location is still being debated^{87,88}.

Area VIP, on the other hand, represents targets in a head-centred frame of reference, or with receptive fields that are partially shifting or gain-modulated by eye position^{96,97}. That is, when the eyes are moved around in the visual field, the best stimulus location either remains fixed relative to the position of the head (head-centred) or shifts part-way between the position relative to the eyes and that relative to the head (partially-shifting receptive fields). In addition, unlike area LIP, which responds only to stimuli in the visual modality, many VIP neurons have joint tactile and visual motion-determined receptive fields⁹⁷, and are strongly driven by optic flow fields^{98,99}. Finally, area LIP codes for far space, whereas area VIP codes for near (and even ‘ultra-near’) space^{91,96,100}.

Area AIP represents space in hand-centred coordinates, and is crucial for fine grasping^{101,102}. Neurons in this area are bimodal (visual–tactile)^{101,103,104}, so that when the hand moves, the visual receptive field remains in a fixed position relative to the hand. Neurons in this area, in combination with the CAUDAL INTRAPARIETAL (CIP) area, which extracts three-dimensional shape, are crucial for correctly reaching and grasping three-dimensional objects^{105,106} and tools^{107–109}.

Neuroimaging studies of spatial cognition

Recent neuroimaging studies have identified putative human homologues of macaque IPS regions¹¹⁰ (FIG. 3). Such homologues are highly tentative, both because the parietal (and frontal) cortex is differentially expanded in humans compared with similar regions in macaques¹¹¹, especially in the region of the inferior parietal lobule and mid-IPS⁵⁹, and because direct comparisons between monkey and human fMRI responses to the same stimuli have revealed important differences^{112,113}. Nevertheless, the overall pattern of posterior-to-anterior organization, with a systematic

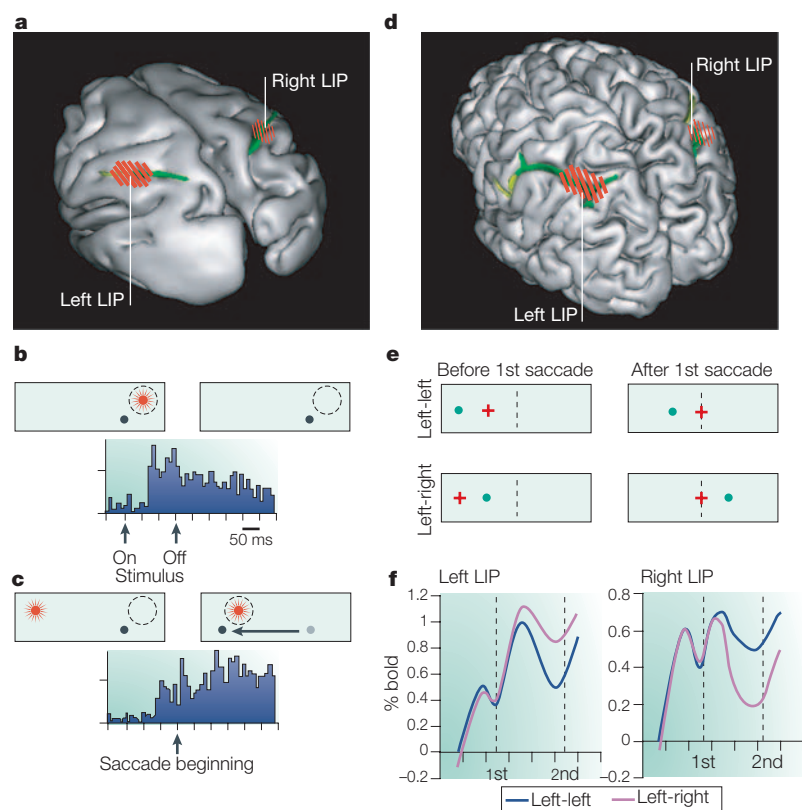


Figure 4 | Spatial updating in the lateral intraparietal area. In monkeys^{89,92} and humans^{124,125}, the spatial updating of attention to a target location leads to increased activation even when there is no physical stimulus. **a** | Approximate location of macaque lateral intraparietal (LIP) area is indicated by the red hashed region. The posterior intraparietal sulcus (IPS) is indicated in green. Brain rendering and automatic sulcus identification were performed using BrainVisa/Anatomist software. **b** | In this experiment, monkeys were shown a target (red star) and a reference point (black dot) (top left panel). Single-unit physiological studies show that neural activity continued even after the stimulus had been turned off, which indicates that the monkeys were able to remember the location of the target in relation to the reference point (top right panel). **c** | Crucially, when the monkey makes an eye movement that will bring a target into the neuron's receptive field (dashed circle in the top left panel), neural activity increases, even prior to the onset of the saccade. Initially, there is no stimulus in the neuron's receptive field, and, correspondingly, neural activity is low in area LIP. However, just before making a saccade that brings the stimulus location within the receptive field, neural activity increases, which shows that the memory of the target has been updated to reflect the new position in eye-centred coordinates. **d** | Approximate location of human area LIP is indicated by the red hashed region, with the posterior IPS indicated in green. The anterior IPS is indicated in yellow. **e** | In a double saccade paradigm, participants see a red cross, then a brief green target. Participants first make a saccade to the position of the red cross, and then, only after a delay, to the remembered location of the green target. Crucially, on half the trials, when participants make the first eye movement to the red cross, the target changes sides, for example, from the left to the right side of fixation (left-right trial). Therefore, participants must re-map the position of the target in eye-centred coordinates. **f** | The presentation of the initial target to the left of fixation leads to increased activity in right area LIP. When the remembered saccade target remains to the left of fixation (left-left trial), activity in right area LIP remains high. However, when the remembered saccade target shifts to the right of fixation (left-right trial), activity in right area LIP decreases, and activity in left area LIP correspondingly increases, which shows spatial re-mapping. Panels **b** and **c** modified, with permission, from REF. 92 © (1992) American Association for the Advancement of Science; panels **e** and **f** modified, with permission, from REF. 124 © (2003) Society for Neuroscience.

transformation from sensory to effector-specific properties, presents a striking parallel with that observed in previous studies of monkey physiology¹¹⁴. Three of these putative homologues — areas LIP, VIP and AIP — are of particular relevance here, although other potential homologues have been identified^{115–117}.

Area LIP. Sereno *et al.*¹¹⁸ have identified a region of the posterior IPS that is thought to be homologous to monkey area LIP. This region is active when humans make saccades to targets in different locations in space. By presenting the targets in a fixed order, around the perimeter of an imaginary circle, it is possible to demonstrate that this region shows retinotopic responses in the human similar to those seen in the monkey¹¹⁹.

In addition, recent studies have shown that this region responds in an effector-independent manner^{120,121}. For example, Astafiev *et al.* report that the anterior IPS is jointly active for attending, pointing and making saccades to peripheral targets¹²⁰ (for converging data, see REF. 59). Using a surface-based warping procedure, they then aligned human anatomical landmarks with macaque anatomical landmarks. The activity in this study overlapped considerably with anatomically-defined LIP in the warped macaque atlas, which indicates homology between macaque area LIP and this region in humans. Interestingly, this effector independence differs from the distinction between area LIP and PRR described in macaques^{93,94}. This might be due to the lower resolution of fMRI, to species differences (for example, increased hand-eye coordination in humans) or to the fact that fMRI and single-unit physiology tap into different physiological mechanisms (that is, local field potential versus spikes)^{122,123}. Future studies will need to investigate this issue in more detail.

Another parallel between macaque and human area LIP is the involvement of these areas in spatial updating^{124,125}. In a recent study¹²⁴, participants were asked to perform a double-saccade task (FIG. 4). Each trial started with participants fixating a central cross and two peripheral targets (a cross and a spot). Participants performed a saccade to the peripheral cross, and then prepared a second saccade to the final target (the spot). However, on half the trials, after the first saccade the spot reappeared on the opposite side of the cross from its initial position. Using event-related fMRI, it was possible to show that when the position of the target moved, the neural activity in area LIP also shifted, to represent the new spatial location of the target in eye-centred coordinates.

Area VIP. As it is known that monkey area VIP responds well to motion in any sensory modality, regions of the human IPS that respond multimodally to motion might be plausible homologues of monkey area VIP. Following this logic, Bremner *et al.* tested for regions that were conjointly activated by visual, tactile and auditory motion¹²⁶. Only one such region was identified in the fundus of the IPS, anterior to area LIP, consistent with the known organization in the monkey. However, given the increased area of the mid-IPS that is described above, this is perhaps the most tentative homology, and further studies will be required to confirm this proposed connection.

Area AIP. Neurons in monkey area AIP respond in a hand-centred manner and are involved in fine grasping, but not necessarily in the transport phase of the

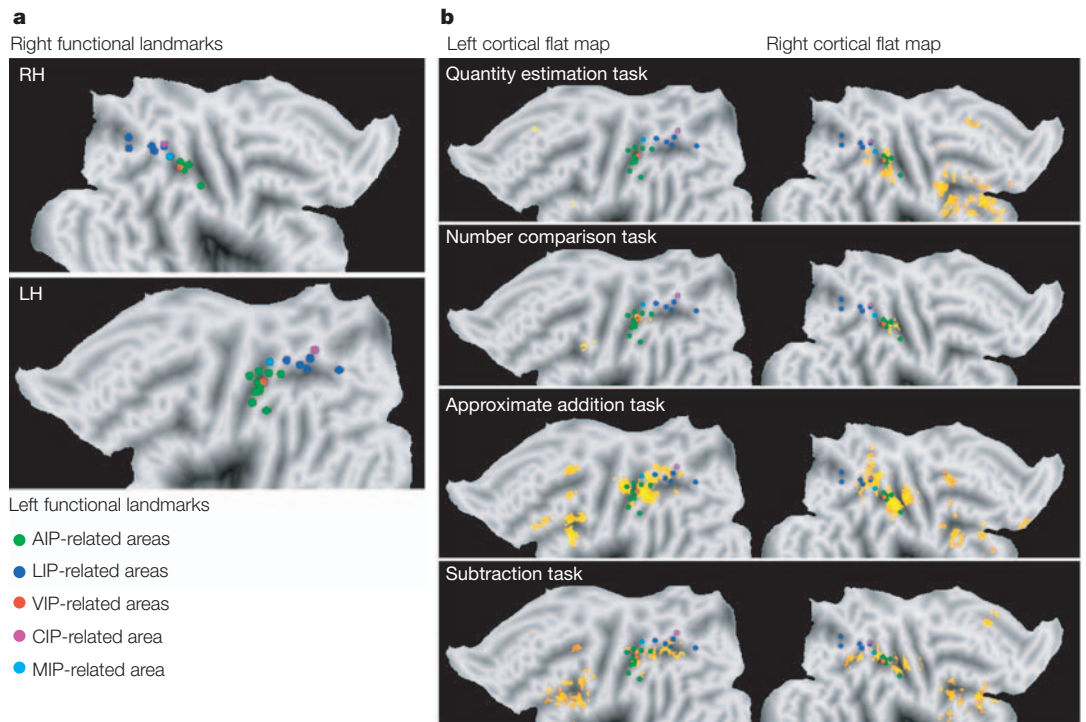


Figure 5 | Numerical tasks and intraparietal regions. **a** | Flattened human left (LH) and right (RH) hemispheres showing the peaks of various studies aimed at identifying human homologues of macaque regions. The regions shown are the lateral intraparietal (LIP) area^{59,118,121,124} (dark blue), the ventral intraparietal (VIP) area¹²⁶ (red), the anterior intraparietal (AIP) area^{59,106,127–133} (green), the medial intraparietal (MIP) area¹¹⁵ (turquoise) and the caudal intraparietal (CIP) area¹¹⁶ (purple). Brain renderings were produced using Caret software. **b** | Overlaid onto these maps is the activation shown in four different types of numerical study — addition⁵⁷, subtraction⁵³, estimation⁵² and comparison⁵¹. Estimation and comparison activated fairly circumscribed regions, roughly overlapping with the human homologue of area VIP, which is consistent with macaque physiology data. In the left hemisphere, numerical activations tend to overlap more with area VIP, whereas in the right hemisphere, numerical activations tend to extend more anteriorly towards area AIP, which indicates possible hemispheric asymmetries in these tasks. However, addition and subtraction activated larger networks, extending posteriorly towards area LIP. Although tentative, these results are consistent with our hypothesis that numerical operations might also depend on VIP–LIP circuitry and interactions.

action. Several studies have used these properties to try to identify a human homologue of area AIP^{116,127}. Others have used different properties, such as mental rotation¹²⁸, bimodal responses¹²⁹ and responses to tools¹³⁰. In the first study of this type, regions of the IPS that were activated when individuals grasped objects were identified¹³¹. Interestingly, the region identified overlapped almost completely with a region that was damaged in a patient who showed a selective impairment in fine-grasping behaviour¹³¹. Other studies identified a region of the anterior IPS that responded more strongly to grasping than to reaching¹²⁷ or to finger pointing⁵⁹. Other studies have shown that this region is activated by action observation^{132,133}. As expected from monkey maps, activations in these putatively homologous regions to area AIP are consistently located anteriorly to the activations identified in the putative human homologues of areas LIP and VIP.

Numerical tasks and IPS regions. Crucially, the HIPS region that has been shown to be consistently activated in arithmetical tasks in humans roughly coincides with the putative human area VIP. Such a co-localization is

consistent with the localization of monkey numerosity-tuned neurons in the fundus of the IPS, close to the anatomically-defined monkey area VIP (FIG. 5). We speculate that overlap between comparison processes and spatial networks in the IPS might account for the behavioural interactions between representations of number and space (for a similar proposal, see REF. 134). At present, however, this overlap remains only tentative, given that these regions have been defined only on the basis of average foci of brain activation in a normalized template space. Future studies should concentrate on higher resolution studies in which human homologues of areas LIP, VIP and AIP can be identified in individual subjects. Once these regions have been identified on an individual subject basis, the activation seen in relation to number processing can be compared with these predefined regions of interest.

Area LIP and the mental number line

On the basis of the above, we speculate that shifts of attention along the mental number line might be mediated by shifts of attention in area LIP in the same manner that shifts of attention in the external world are

mediated by area LIP. This hypothesis might explain many of the behavioural and patient data reviewed above. First, the finding that the SNARC effect is present even when the hands are crossed⁴ is consistent with the stable, eye-centred spatial representation in area LIP, and with data indicating that multisensory (tactile–visual) attentional effects show similar re-mapping in space, including the activation of posterior IPS regions. Second, this hypothesis would explain why the SNARC effect generalizes over multiple effectors^{4,17,18}. As reviewed above, human imaging studies indicate that area LIP contains an effector-independent representation of space; in addition, numerical signals might propagate from area VIP to both area LIP and PRR, and area LIP neurons might modulate PRR neurons, as has previously been proposed⁹⁵.

Finally, this hypothesis can explain the results of the Fischer studies^{10,12}, in which presentation of numbers led to automatic shifts of attention to the left or to the right. We propose that all of these effects arise from a common neural mechanism, namely the flow of some activation from a quantity representation in area VIP to interconnected area LIP neurons involved in programming overt and covert shifts to the contralateral side of space⁶⁰. Although there is currently no direct evidence for such information flow, it seems plausible on the basis of the presence of dense bidirectional connections between areas VIP and LIP⁸⁵.

Similarly, in patients with hemispatial neglect, we suggest that area LIP is damaged or functionally disconnected, leading to a joint failure to attend to the left side of space and the left side of the number line. It is clear that neglect is not a unitary syndrome¹³⁵, with some authors pinning its neural substrate to the superior temporal gyrus (STG)¹³⁶, and others placing it in the parietal lobe¹³⁷. One recent proposal¹³⁸ suggests that neglect is composed of two deficits, a spatial one, which depends on posterior parietal cortex (PPC) structures (including the IPS), and a memory one, which depends on the superior temporal sulcus. TMS studies have shown that the PPC (but not the STG) is involved in searching for conjunctions of colour and orientation, whereas the STG (but not the PPC) is involved in a difficult feature search¹³⁹. In light of this debate, it is interesting that transient inactivation of monkey area LIP leads to neglect-like phenomena^{140,141}. We propose that damage to this region is responsible not only for the observed deficits in shifts of attention to external space, but also for shifts of attention along internal representations of the mental number line.

One important issue here is the role that cultural learning might have in the development of neural connectivity in the region of the angular gyrus, area VIP and area LIP. Given that even two weeks of tool use leads to the development of additional connections between the temporal–parietal junction and area AIP in macaques¹⁴², it is interesting to consider the effects that a lifetime of training with numerical symbols and their transformations might have on connectivity between the angular gyrus, area VIP and area LIP. Perhaps this cultural learning induces or reinforces connections

that are present even in non-human primates, but that have not served these functions until the acquisition of a culturally developed system of arithmetic. However, it might also be that such circuits do not exist in non-human primates, given the increased size of this region in humans¹¹¹, and that such functions can be shown only in linguistically competent humans. Future studies will be required to explore these effects in more depth.

Grasping, space and number

Although we have focused on the potential role of area LIP in the interaction between number, space and attention, a complimentary story might be told about the role of finger knowledge² in the development of numerical representations, based on the proximity of number-selective regions (putative area VIP) and grasp related regions (putative area AIP) in the IPS⁵⁹. One intriguing piece of data that is consistent with this account is the grasp aperture study described above¹⁹, in which responses were faster to small numbers with small grip apertures and faster to large numbers with large grip apertures. It is also possible that this close connection between motor behaviour and numerical tasks can explain the results of a recent study that found response selection-related activations in number comparison¹⁴³. These two accounts should not be seen as contradictory, but rather complimentary. Future research will need to take into consideration not only the predominantly spatial role of area LIP, but also the predominantly motor role of area AIP, and the role of intermediate IPS areas like area VIP and the MEDIAL INTRAPARIETAL (MIP) area in visuomotor transformation, to better understand the origins of numerical–spatial interactions.

Predictions and conclusions

On the basis of our prediction of VIP–LIP interactions during number processing, we propose specific, testable hypotheses about the effects that we would expect to find with regard to numerical and spatial interactions. First, we predict that shifts of attention along the number line would make use of the same area LIP–VIP neural circuitry that is involved in the development of multisensory, world-centred representations of space^{144,145}. This implies that the same computational transformations that support spatial updating are crucial for arithmetic operations that create shifts in the locus of activation along an internal number line (FIGS 4 and 5). Indeed, the problem of computing a world-centred spatial representation by combining two separate population codes for eye and retinal location is formally identical to that of computing an approximate addition or subtraction by combining two population codes for numerosity^{144,145}. Therefore, the parietal mechanisms that are thought to support spatial transformations might also be ideally suited to supporting arithmetic transformations.

Future studies can test this prediction by comparing patterns of blood oxygen level dependent (BOLD) signal change in human spatial updating protocols and in numerical tasks. First, we would predict that

MEDIAL INTRAPARIETAL (MIP). A region in the medial bank of the IPS that is involved in visuomotor transformations. Along with area V6A, this region comprises the PRR, which is active in tasks that require reaching to specific locations.

when human participants compute additions or subtractions on numerical symbols, they should shift their attention to the left for subtraction problems, and to the right for addition problems, leading to increased activation of contralateral area LIP. Second, we predict that behavioural protocols in which attention is shifted to the left should interfere with addition, whereas rightward attentional shifts should interfere with subtraction. Third, in number-form synaesthetes, presentation of, or thinking about, numerical quantities and their transformations should lead to greater activation of area LIP than in non-synaesthetes, given their strong numerical-spatial associations. Fourth, once 'number' neurons can be recorded in animals during the performance of simple addition and subtraction tasks, we predict that

it should be possible to observe numerical equivalents of the partially shifting receptive fields and gain fields observed in the spatial domain.

All of these predictions seem to be easily testable, and would further strengthen the claim of an intimate link between number and space. In the more distant future, it might become possible to study whether more advanced mathematical concepts that also relate numbers and space, such as Cartesian coordinates or the complex plane, rely on similar parietal brain circuitry. Our hypothesis is that those concepts, although they appear by cultural invention, were selected as useful mental tools because they fit well in the pre-existing architecture of our primate cerebral representations. In a nutshell, our brain organization both shapes and is shaped by the cultures in which we live.

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Competing interests statement

The authors declare no competing financial interests.

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