PERSPECTIVES: NEUROSCIENCE

Single-Neuron Arithmetic

Stanislas Dehaene

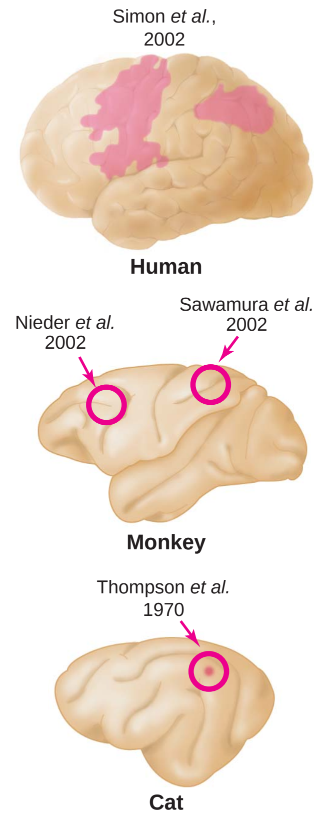
Space, time, and number are basic objects of human thought that are fundamental to mathematics. Yet, just like any other aspect of our mental life, these abstract concepts must somehow be encoded in the biology of neurons and synapses. Although the representation of space has occupied much of neuroscience research, the neuronal bases of the sense of time and number have received much less attention. This is set to change with the study by Nieder *et al*. (*1*) published on page 1708 of this issue. These investigators report the discovery of number-encoding neurons in the lateral prefrontal cortex of the macaque brain (see the figure). Together with an earlier report of number-responsive neurons in monkey parietal cortex (*2*) and a long-forgotten similar study in cats in the 1970s (*3*), this work opens up the exciting possibility of studying the cerebral bases of elementary arithmetic at the single-cell level.

Nieder *et al*. showed macaque monkeys a sequence of two visual displays, each comprising up to five dots. They trained the monkeys to decide whether the two displays contained the same number of items. Once the monkeys achieved a significant success rate (between 70 and 100%, depending on the numbers), electrodes were inserted into the lateral prefrontal cortex. The researchers then discovered that one-third of the neurons in this region acted as "number detectors": They fired maximally in response to a specific preferred number. For instance, one neuron might respond maximally to displays of four items, somewhat less to displays of three or five items, and none at all to displays of one or two items.

Ever since the infamous "Clever Hans" episode, in which scientists mistakenly suggested that a horse had exceptional abilities in arithmetic, reports of numerical abilities in animals have been met with skepticism. Can we be sure that the monkeys in the Nieder *et al*. study attended to number rather than to other features of the display, such as size or location of the dots? During training, the monkeys only saw displays in which the items were of the same average size. Thus, they could have learned to respond to physical dimensions other than number, such as the area occupied by the dots. However, Nieder and colleagues convincingly demonstrate that the monkeys did in fact rely on number, because they responded correctly to a wide variety of new displays in which the cues were not confounded. It did not matter whether the displays were equalized according to perimeter, area, shape, linear arrangement, or density: The monkeys attended only to number. And so did their prefrontal cortex neurons: The tuning curves of these neurons appeared to depend solely on number, and not on other irrelevant features of the display.

Not only do these findings confirm that monkeys can represent number, they also prove that the monkeys' numerical talents could not be attributed solely to the many months of training. Their ability to generalize when presented with a wide variety of new displays indicates that the monkeys were bringing to the task more knowledge of numerical invariance than the training alone could provide. This meshes well with other reports of numerical discrimination in untrained monkeys (*4*) and young human infants (*5*). Obviously, a number sense is part of the native endowment of many species, not just ours.

Still, an important goal for future research will be to clarify the extent to which training affected the neuronal encoding of number, and to determine how abstract this code is. A previous study by Sawamura *et al*. (*2*) reported number-tuned neurons in monkeys trained to perform a sequential motor task, which required them to keep track of how many times they had performed a given motor action. Would the neurons of the Nieder *et al*. monkeys fire during this motor task, or during other similar tasks with sequential rather than simultaneous presentation of a quantity of items? Would they respond to numbers presented in other modalities, for example, tactile or auditory? Would the neuronal encoding of number extend to numbers beyond the training range of up to five items, as observed in a previous behavioral study (*6*)? And does this neuronal encoding contribute to simple computations such as 2 + 1, which are possible even for untrained monkeys (*4*)?



Numerical neurons. Cerebral networks that may underlie the sense of number in mammals (*11*). The brain areas that are activated when we compute a simple subtraction, such as 11 – 5, may encompass areas homologous to those in the monkey and cat brain, where neurons tuned to a specific number have now been recorded.

Another central question is how the numerical dimension of the displays is extracted. Nieder *et al*. did not directly address this issue, but their data place tight constraints on theories of the number detection mechanism. A classic view proposes that the numbers 1, 2, and 3 can be recognized because they form simple shapes of a dot, a line, or a triangle. This theory can be rejected, however, because the neurons recognized numbers up to 5, even when the dots were all aligned. Even the broader idea that the small numbers 1, 2, and 3 are special, perhaps because they are perceived by a distinct object-file system (*7*), also receives no support from the present data. There was no sign of a discontinuity around three items. Rather, the neuronal tuning curves got continuously wider in direct proportion to the number that they represented (Weber's law).

That the monkeys' representation of number gets increasingly fuzzy for larger and larger numbers is compatible with so-called accumulator models. In those models, approximate number is estimated by accumulating noisy estimates of the presence of individual objects. But not just any accumulator model will do. A strong constraint is imposed by the remarkably short latency of the neurons. Many neurons fired selectively a constant 120 ms after display onset, whatever the number on the screen. This is incompatible with the idea that monkeys enumerate the items serially, as postulated in most models (*8*).

In the end, the data fit remarkably well with a parallel accumulator model that

The author is at INSERM Unit 562 Cognitive Neuroimaging, Service Hospitalier Frederic Joliot, CEA/DRM/DSV, 91401 Orsay Cedex, France. E-mail: dehaene@shfj.cea.fr

Jean-Pierre Changeux and I proposed some 10 years ago (*9*). The model, which was implemented as a working neural network simulation, supposes that number is extracted by pooling activation of neural maps of the locations of salient objects, computed preattentively in the parietal lobe. The model correctly predicts the fixed firing latency of the neurons and the linear increase of their tuning curves as the numbers get larger. It even helps make sense of fine details, such as the fact that the tuning curves assume a symmetrical Gaussian shape only when plotted on a logarithmic scale, not a linear scale of number; this is predicted if the internal "number line" is compressed and logarithmic, a coding scheme that may be optimal given the increasing imprecision associated with larger numbers.

The model predicts that numerical information is first computed in parietal cortex, and only then is it transmitted to prefrontal cortex neurons. Currently, however, the respective contributions of parietal and prefrontal cortices cannot be assessed from the existing data. There is even some inconsistency, with Sawamura *et al*. observing 31% numerical neurons in parietal cortex and 14% in prefrontal cortex, and Nieder *et al.* reporting the reverse. To resolve this discrepancy and to map out the entire circuit for number detection, more extensive electrophysiological surveys will be required, perhaps combined with functional imaging and reversible lesion experiments.

On a broader scale, the finding of a parietofrontal circuit for number in the monkey fits well with neuroimaging studies that reveal a homologous network in humans performing simple arithmetic tasks (*10*) (see the figure). The new findings in numerical neuroscience compel us to accept that our mathematics, sometimes heralded as the pinnacle of human activity, is really made possible by conceptual foundations laid down long ago by evolution and rooted in our primate brain (*11*). We are clearly not the only species with a knack for numbers.

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PERSPECTIVES: CHEMICAL SYNTHESIS

Raising the Bar for the "Perfect Reaction"

John F. Hartwig

Amines pervade our body and the world around us. They are found on the termini and side chains of amino acids, are components of common pharmaceuticals, and are behind the stench of rotting fish. They link the monomer units in most carpeting, help foam our shampoo, and soften our clothes. Fifteen to 20 billion kilograms of ammonia are produced per year, and amines are produced from ammonia in similarly staggering amounts (*1*). On page 1676 of this issue, Seayad *et al.* (*2*) report on a synthetic method that may ultimately make the production of amine cleaner and more efficient.

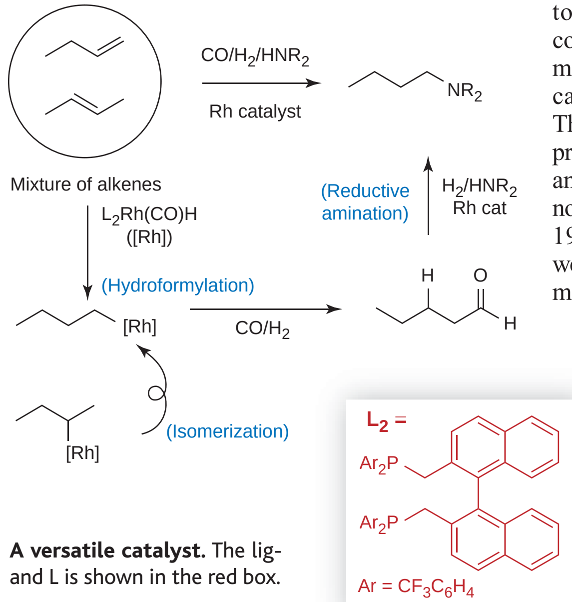
Amines are derivatives of ammonia that contain three single bonds between nitrogen and carbon or hydrogen. There are several classic methods to prepare amines, but most of them are inappropriate for large-scale production. For example, the reactions of amines with alkyl halides are taught in introductory organic chemistry courses. But the large amounts of halide by-product, the need for blocking groups to address poor selectivity, and the cost of the alkyl halide reagent make this method unsuitable for commodity chemical production.

Instead, amines are generally produced from alcohols with a solid-acid catalyst by elimination of water (*3*). The alcohols in these reactions are often produced from alkene hydrocarbons, which contain a reactive carbon-carbon double bond. A synthetic route to amines directly from alkenes would eliminate the need for the alcohol intermediate, thereby avoiding the cost and energy consumption of the separation and purification of the alcohol. This is what Seayad *et al.* report. The yields are not yet 100%, but the reaction transcends the criteria typically assigned to the "perfect reaction."

A perfect reaction is generally thought to occur with inexpensive reagents, run with fast rates, form 100% yield of product, require no added heat, and generate no waste (*4–5*). Because impure reactants usually form even less pure products, synthetic chemists are usually taught to start with clean reagents. The remarkable feature of the reaction reported by Seayad *et al.* is that predominantly a single terminal amine is made from a mixture of alkenes.

Most new reaction processes build on a long history of related reactions. The history that led to amine synthesis from an isomeric mixtures of alkenes began in 1938, when Otto Roelen discovered that cobalt compounds could catalyze the formation of aldehydes from hydrogen, carbon monoxide, and an alkene. The aldehyde was a side product of a process for generating hydrocarbons and alcohols. Roelen's discovery is now called hydroformylation. In the 1960s, soluble rhodium catalysts were discovered that operate under milder conditions than the cobalt catalysts. Today, 5 to 10 million tons of aldehydes and alcohols are produced annually by this reaction worldwide (*1*).

The link between hydroformylation and the amine synthesis of Seayad *et al.* is reductive amination. In a reductive amination, an aldehyde reacts



A versatile catalyst. The ligand L is shown in the red box.

The author is in the Department of Chemistry, Yale University, New Haven, CT 06422, USA. E-mail: john.hartwig@yale.edu