The Priming Method: Imaging Unconscious Repetition Priming Reveals an Abstract Representation of Number in the Parietal Lobes

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Most of the current brain imaging methods are limited by the low spatial resolution of neuroimaging techniques and remain unable to measure activity at the scale of single neurons or small columns of neurons, which are the coding elements of the nervous system. In this work we have adapted the priming method, an emerging research strategy that can overcome some of these spatial limitations, to investigate the coding of numerical quantities in the human brain. This approach combines the logic of psychological priming experiments with the recently discovered neurophysiological phenomenon called repetition suppression (RS). In each trial, while subjects perform a constant task, a subliminal prime is presented prior to each target. By varying the relationship between prime and target, one can detect which brain areas present RS specifically for any given level of prime–target repetition. We first expose the general logic, potential and limitations of the priming method and then illustrate it by demonstrating that a region of parietal cortex is coding for numbers at the quantity level, independently of other stimulus attributes, and that this region processes both consciously and unconsciously perceived stimuli.

Introduction

One goal of brain imaging experiments is to provide us with a precise description of the neural codes used during cognitive processing. However, the ultimate coding elements of the nervous system (synapses, neurons and columns) remain below the spatial resolution of current non-invasive brain imaging techniques. In the present paper we examine an emerging research strategy, the priming method, which can provide novel information about neural coding in the human brain. We then adapt this method to investigate the coding of numerical quantities and show that a parietal cortex region is coding for numbers at the quantity level, independently of other stimulus attributes, and that this region processes both consciously and unconsciously perceived stimuli.

Several strategies have been developed to decode the patterns of brain activity recorded during PET, fMRI or electrophysiological recordings, from the subtraction method, which suffers from the well-known problem of 'pure insertion' (Friston *et al.*, 1996), to more sophisticated parametric or correlational methods (Price *et al.*, 1994; Dehaene, 1996) derived from Sternberg's additive factor method (Sternberg, 1969). The latter is particularly applicable to event-related fMRI experiments that offer a trial level of analysis comparable to mental chronometry experiments (Buckner *et al.*, 1996). Further demonstration that neural activity in a brain area is related to a given experimental factor, independently of other factors, is provided by the conjunction method (Price and Friston, 1997), which can use a factorial design to isolate brain areas showing a reliable difference in several elementary contrasts, without significant differences across these comparisons.

All of these methods, however, are limited by the low spatial resolution of current brain imaging techniques. While they can distinguish in some cases a macro-level of neural coding [e.g. the specialization of the fusiform face area (FFA) (Kanwisher *et al.*, 1997)], they cannot easily resolve the micro-level of coding which may, for instance, represent different objects within the same category (e.g. different faces in the FFA), although encouraging progress has been made in using fMRI to map iso-orientation columns in the primary visual cortex of the anesthetized cat (Kim *et al.*, 2000).

An alternative research strategy which overcomes some of these limitations has emerged in the last 3 years. This approach combines the logic of psychological priming experiments with the recently discovered neurophysiological phenomenon called repetition suppression (RS). Behavioral priming is a basic tool of experimental psychology which can be used to investigate the coding of mental representations occurring between stimulus presentation and behavioral response. In a typical priming experiment a subject is exposed, in each trial, to a first stimulus (the 'prime'), then to a second stimulus (the 'target'), while performing a constant task on the target stimulus. The relation between prime and target is experimentally manipulated. By identifying a behavioral priming effect elicited exclusively by specific prime–target pairs, one may demonstrate the existence of mental representations coding information at the level which is repeated on such prime–target pairs. In that sense, priming may be considered as a method for probing the format in which mental representations are encoded.

From a neurophysiological point of view, RS, a recently discovered phenomenon, provides a possible neural correlate of priming. RS was first described by Desimone and Miller in single cell recordings in the monkey infero-temporal cortex (Miller *et al.*, 1991; Desimone, 1996). They showed that when the same visual stimulus was repeated, the neuronal activity evoked in some of the cells was reduced. Importantly, they demonstrated that repeating the same object, but changing some stimulation parameter such as its retinal location or its size, still led to a similar reduction in activity (Lueschow *et al.*, 1994). Their proposed interpretation was that these cells belonged to a neural network representing information at an object-based coding level. Subsequently, several brain imaging priming experiments in humans, in which a subject is exposed to a prime then to a target stimulus, reported a decrease in neural activity in many different brain regions, such as occipito-temporal, insular, parietal, prefrontal cortices and thalamus and basal ganglia structures (Squire *et al.*, 1992; Schacter *et al.*, 1996; Schacter & Buckner, 1998). RS may thus appear as a general cerebral phenomenon related to neural coding specificity.

Examining the conditions of RS using functional brain imaging provides a general method to explore the neural code in humans. The general logic is: first, to isolate a brain area in which repetition of the same exact task conditions leads to RS; second, to then vary the nature of the prime–target relation in

order to identify which coding variations are relevant and which are not relevant to obtain the effect. Many issues in cognitive neuroscience may be addressed with a priming design exploring the nature of the neural code whose repetition causes RS in a given brain region. Considering the field of language, for instance, one could imagine a design in which prime–target relations explore such various levels of repetition as early visual or auditory similarities, phonological, graphemic, semantic or articulatory repetitions. Such a design might reveal which cerebral networks show RS in response to each level of repetition. The priming method also presents the interesting ability to identify the 'microcode' of a brain area and may even help decipher the tuning curves of neurons by measuring the intensity of RS when varying the similarity between prime and target stimuli. This last point, however, would presuppose that RS is a graded rather than an all-or-none phenomenon and that the same metric of stimulus similarity underlies the tuning curve of the neuron and the RS phenomenon, two hypotheses that deserve further investigations at the physiological level.

Several previous studies illustrate the value of the priming method, but also underline various important methodological issues. Grill-Spector and colleagues first used the priming method to investigate object recognition processes. Capitalizing on previous work on the role of lateral occipital cortex (LOC) in visual object recognition (Grill-Spector *et al.*, 1998a,b), they explored the invariance of the neural code in this area using an experimental design based on the fMRI equivalent of RS, named fMRI adaptation (Grill-Spector *et al.*, 1999). In a first experiment they presented subjects with blocks of 32 pictures with a variable number of image repetitions (from 0 to 32) and found a reliable decrease in neural activity in LOC when the number of image repetitions increased. They then examined the invariance of this RS phenomenon in the face of variations in object size and position. This led them to distinguish two sub-regions in LOC, a posterior area that showed little or no RS in blocks where images were presented with a variable size or position and a more anterior area where RS persisted across large variations of these parameters. This suggested the presence of a view-invariant representation of visual objects in the anterior LOC, in agreement with electrophysiological observations in monkeys (Lueschow *et al.*, 1994; Ito *et al.*, 1995). However, the use of a block design left the door open to alternative interpretations. Notably, the subject's attention could have varied across experimental blocks, with more attention being given to blocks in which the stimuli were more varied. Thus attentional amplification, rather than RS, could explain the greater activation in non-repeated compared with repeated blocks.

The priming method is greatly improved by adopting an event-related design, in which repeated and non-repeated trials are randomly intermixed. Indeed, Buckner *et al.* obtained RS in infero-temporal cortex using event-related fMRI (Buckner *et al.*, 1998), although they did not investigate the neural code by using various degrees of object repetition. More recently, Kourtzi and Kanwisher used an event-related fMRI paradigm and were able to observe RS in LOC regions independently of the visual format used to present objects drawings (Kourtzi and Kanwisher, 2000).

Thompson-Schill *et al.* used event-related fMRI and a priming-based design to investigate the role of left inferior frontal cortex in word generation tasks (Thompson-Schill *et al.*, 1999). They tested two alternative hypotheses that associate this region either with semantic information retrieval or with selection of a correct answer. Subjects were presented with a word and either had to generate a verb related to this word (e.g. salad/eat) or a color related to this word (e.g. salad/green). During the experiment some of the words were repeated either in the same task (word repetition and task repetition, e.g. salad/verb–salad/verb) or with a switch of task (salad/verb–salad/color). If inferior frontal cortex is associated with semantic retrieval, one should observe repetition suppression whenever the same word is repeated, regardless of the task. Alternatively, if it is associated with response selection, RS should be observed only when the same word is repeated in the same task, since this is the only condition that causes the same response to be selected. The results unambiguously supported this second possibility. RS was observed in inferior frontal cortex in the same word, same task trials, while in the same word, different task trials, not only was there no reduction, but frontal activity was even greater than during a baseline unprimed condition. Interestingly, another region in left temporal cortex presented a pattern of RS compatible with the semantic retrieval hypothesis, showing RS to word repetition independently of the task context.

This study illustrates the power of the priming method, by showing that what counts as a repetition can differ across brain regions, thus clarifying what is being represented: word meanings in left temporal cortex and selection of a task-appropriate response in left inferior frontal cortex. Still, a possible limitation of this study lies in the fact that subjects could have become aware of the presence of word repetitions and could have developed strategies to take advantage of them. The reduction in frontal activation might then be interpreted as a change in the strategy adopted by subjects between the trials in which a word is seen for the first time and trials in which it is seen again and the previous response can simply be retrieved. Indeed, the finding that inferior frontal activation can completely disappear after several repetitions of the same word list in the word generation task suggests a strategical change rather than a mere RS effect (Raichle *et al.*, 1994).

This general problem of potential strategical and attentional changes elicited by the awareness of repetition is strengthened by a recent study by James *et al.* (James *et al.*, 2000). In this work the authors were able to precisely determine the temporal dynamics of RS with fMRI using a task of recognizing scrambled visual stimuli. In particular, they showed that while the overall BOLD response was smaller for primed than for unprimed trials, BOLD signal curves were shifted leftwards in time for primed objects relative to unprimed objects. This may suggest that priming is accompanied by an acceleration of neural processing, perhaps linked to increased synaptic efficiency and finer neuronal tuning. The main finding of this study, however, was that decreases in the BOLD signal mainly affected the post-recognition phase of stimulus processing. This result reminds thus that top-down effects independent of local processing may contaminate most previous studies. Ideally, experimental designs based on the priming method should prevent subjects from becoming aware of the presence of repeated versus non-repeated trials. We demonstrate below that this can be achieved by using a subliminal priming paradigm in which primes are masked and, therefore, the distinction between repeated and non-repeated trials is not consciously perceptible.

In summary, the above methodological remarks lead us to define the desirable features of a priming paradigm in which a decrease in the BOLD response, if observed, can only be attributed to RS and therefore to properties of the local neural code.

- Every experimental trial consists of presentation of both a prime and a target.
- Primes are masked and are not consciously perceived.

- Subjects perform a constant task on the target throughout the experiment.
- The relationship between prime and target is varied randomly in each trial, thus preventing subjects from shifting their strategy or their attention in advance.
- In matched subsets of trials, the same primes and the same targets are used, only their relationship being varied. This can be achieved by using a factorial two-by-two design in which the same stimuli s_1 and s_2 serve both as primes and as targets, thus defining four prime–target pairs, two repeated ones s_1–s_1 and s_2–s_2 and two non-repeated ones s_1–s_2 and s_2–s_1. This design prevents any differential activation to the individual stimuli s_1 and s_2 from contaminating the results.

Experimental Application: Coding of Numerical Quantity in Human Parietal Cortex

The objective of this study was to use the priming method to investigate the coding of numerical quantity in the parietal lobe. Functional imaging techniques have revealed that this region is active during number processing and calculation (Appolonio *et al.*, 1994; Chochon *et al.*, 1999; Dehaene *et al.*, 1999; Pinel *et al.*, 1999; Pesenti *et al.*, 2000). It is thought to play a crucial role in the mental representation of numerical quantity (Dehaene and Cohen, 1995; Dehaene *et al.*, 1998a). Indeed, lesions to that area can cause a severe deficit in understanding the quantity meaning of numbers (Cipolotti *et al.*, 1991; Dehaene and Cohen, 1997; Delazer and Benke, 1997) and tasks that emphasize quantity manipulation cause greater activation in this area than tasks that require only rote verbal calculation (Dehaene *et al.*, 1999). However, the 'microcode' that intraparietal neurons use to represent a given numerical quantity has not been directly investigated. Here we show how the priming method can reveal this quantity coding and demonstrate, albeit indirectly, that different populations of intraparietal neurons encode different numbers.

Our experimental approach is based on a recently described masked priming paradigm using numbers as stimuli (Dehaene *et al.*, 1998c). Briefly, subjects pressed a right or left key to decide whether a visually presented number (called the 'target') was larger or smaller than 5. Unbeknownst to them, another number (called the 'prime') was presented for 43 ms just before the target, surrounded by masks that made it invisible (see Fig. 1). Converging behavioral and brain imaging results showed that the primes were unconsciously processed through a series of perceptual, semantic and motor stages. First, analysis of response times (RTs) revealed a significant response priming effect characterized by faster reaction times in trials in which the prime and the target stimuli fell on the same side of 5 than in incongruent trials. Secondly, primes induced a covert activation of primary motor cortex corresponding to the hand that should have been used, had subjects responded overtly to the primes. The presence of this motor activation suggested that the numerical primes had been processed at a semantic level and had been categorized as quantities larger or smaller than 5. This unconscious semantic stage, however, was not directly visualized. We now present new analyses, based on the priming method, which permit us to directly image unconscious semantic processing and the quantity code.

The logic of these analyses is simple. In some trials the prime and target numbers were the same, even though they might be presented in different notations (e.g. prime SIX, target 6). In other trials the prime and target numbers differed (e.g. prime NINE, target 6). According to the hypotheses of the priming method, brain regions that encode numerical quantities should show a RS effect on repeated quantity trials relative to different quantity trials.
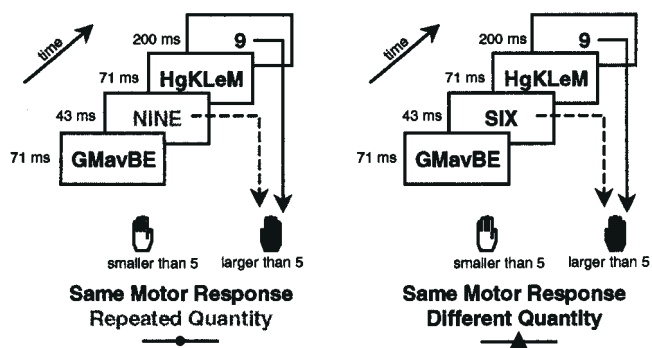
Materials and Methods

Procedure
We report here a new analysis of previously published experimental data (Dehaene *et al.*, 1998c). All experiments were approved by the French ethical committee for biomedical research and subjects gave informed consent. The stimulus set consisted of 64 pairs of prime and target numbers 1, 4, 6 and 9, each in either Arabic or spelled out format. As a result of this design, half of the trials were congruent (prime and target on the same side of 5) and the other half were incongruent (prime and target on opposite sides of 5). Furthermore, within the congruent trials, half were repeated trials in which the prime and target were identical numbers (possibly in different notation) and half were congruent, non-repeated trials in which the prime and target differed. The new analysis focuses exclusively on a comparison of the latter two trial types. Note that, because this comparison is based only on congruent trials, it is orthogonal to and unconfounded by the motor priming effect that we reported earlier (Dehaene *et al.*, 1998c).

Subjects performed the number comparison task twice in counter-balanced order. In one block the instruction was to press the right-hand key for targets greater than 5 and the left-hand key for targets smaller than 5. In another block the opposite instruction was used. Within each block subjects received initial training (ERP experiment, 16 trials; fMRI experiment 25 trials) before the experimental session (ERP experiment, 256 trials; fMRI experiment, 64 trials).

ERP Experiment
Twelve right-handed subjects (six males, mean age 25 years) undertook the trials. We presented a total of 512 trials at a 3 s rate on a standard PC-compatible SVGA screen (EGA mode, 70 Hz refresh rate). Half of the trials (256) were congruent (both prime and target numbers fell on the same side of 5). Of these, 128 comprised repeated numbers and the other 128 were unrepeated numbers. The electroencephalogram was digitized at 125 Hz from 128 scalp electrodes referenced to the vertex (Tucker, 1993), for a 2048 ms period starting 400 ms before onset of the first mask. We rejected trials with incorrect responses, voltages exceeding ±70 μV, transients exceeding ±50 μV, electro-oculogram activity exceeding ±70 μV or response times outside a 250–1000 ms interval. The remaining trials were averaged in synchrony with stimulus onset, digitally transformed to an average reference, bandpass filtered (0.5–20 Hz) and corrected for baseline over a 400 ms window before stimulus onset. Experimental conditions were compared by sample-by-sample two-tailed t-tests, with a criterion of at least five consecutive temporal samples showing a significant difference at $P = 0.05$ over at least 10 electrodes. An ANOVA was also performed on signal averaged across 10 contiguous left parietal electrodes (left cluster, electrodes 58–60, 64–67 and 70–72 from the Electrical Geodesic system) and across the 10 symmetrical right contiguous parietal electrodes (right cluster, electrodes 77, 78, 84–86,

Figure 1. Schematic depiction of the two trial types analyzed here (actual stimuli appear white on a black background). See Dehaene *et al.* for detailed methods (Dehaene *et al.*, 1998c).

90–92, 96 and 97), on a temporal window from 287 to 367 ms after target onset.

fMRI Experiment

Nine subjects were tested (seven males, mean age 26 years). We used an event-related design (Buckner *et al.*, 1996). We presented a list of 128 randomly intermixed stimuli through mirror glasses and an active matrix video projector (EGA mode, 70 Hz refresh rate), with a 14 s inter-stimulus interval. In each trial stimulus onset was synchronized with the acquisition of the first slice in a series of seven volumes of 18 slices each. We used a gradient echo echo-planar imaging sequence sensitive to brain oxygen level-dependent contrast (18 contiguous slices, 6 mm thickness, repetition time/echo time 2000/40 ms, in-plane resolution 3×4 mm^2, 64×64 matrix) on a 3 T whole-body system (Bruker). High resolution anatomical images (three-dimensional gradient echo inversion-recovery sequence, inversion time 700 ms, repetition time 1600 ms, field of view 192×256 mm^2, matrix $256 \times 128 \times 256$, slice thickness 1 mm) were also acquired.

Analysis was done with SPM96 software. Images were corrected for subject motion and slice acquisition delays, normalized to Talairach coordinates using a linear transform calculated on the anatomical images, smoothed (FWHM 15 mm) and averaged to define 24 types of events consisting of combinations of two prime and two target notations (numerical or alphabetical), two response sides (left or right) and three possible relations between primes and targets (repeated quantity, same response but different quantity or different response). Images from nine subjects were analyzed together. The signal in each voxel was modeled by SPM96 software as a linear combination, for each subject and each event type, of a standard hemodynamic response function and its temporal derivative, thus allowing for different delays across brain regions.

Results

Behavior

Response times measures collected during ERP recordings were submitted to ANOVA with notation change (same or different) and repetition (repeated or congruent non-repeated) as factors. Subjects were significantly faster on repeated trials than on congruent non-repeated trials [496 versus 508 ms, effect size 12 ms, $F(1,11) = 12.48$, $P < 0.004$]. Crucially, this effect was unaffected by whether or not the prime and target numbers were presented in the same notation (interaction $F < 1$). This indicates that, for equal motor responses, repetition of the same numerical quantity causes an additional acceleration of the comparison process. A similar numerical repetition effect was observed in the behavioral data collected during the fMRI experiment [527 versus 544 ms, effect size 17 ms, $F(1,8) = 6.17$, $P = 0.04$], again without interaction with notation change ($F < 1$).

fMRI

We predicted that repetition of the same quantity would cause reduced activation, relative to non-repeated trials, in a brain area thought to encode the quantity meaning of numbers, the intra-parietal sulcus. This prediction was fully confirmed by fMRI (see Fig. 2). We searched the whole brain for such a RS effect (voxelwise $P < 0.001$ uncorrected for multiple comparisons, cluster extent threshold $P = 0.05$ corrected for multiple comparisons across the brain volume). The only brain regions showing RS were located in the left and right intraparietal sulci (right, Talairach coordinates 36, –44, 44, $Z = 5.21$; left, –44, –56, 56, $Z = 4.17$). These coordinates are within a few millimeters of those reported in previous studies of number processing (Chochon *et al.*, 1999; Dehaene *et al.*, 1999; Pinel *et al.*, 1999; Pesenti *et al.*, 2000).
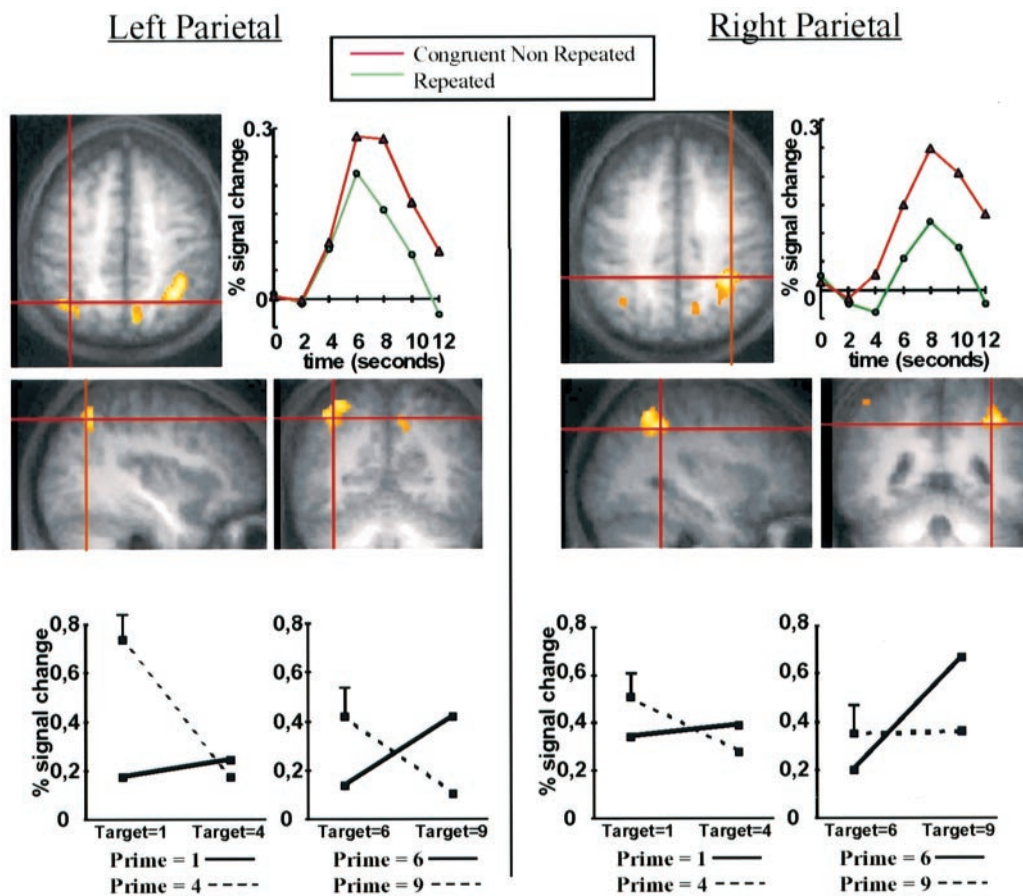
SPM results were confirmed by complementary analyses. For each parietal cluster the BOLD signal averaged across all voxels was submitted to a 2 (repeated/congruent non-repeated) × 2 (same notation/different notation) × 7 (time points) ANOVA with subjects as random factor. RS was tested as the interaction between the time and the repetition factors and was confirmed in both the left [$F(6,48) = 3.46$, $P = 0.006$] and right parietal [$F(6,48) = 8.49$, $P < 10^{-4}$] clusters (multivariate ANOVA tests taking into account the violation of sphericity hypothesis due to repeated measures in time yielded equally significant results). In these regions RS was unaffected by notation change (time × repetition × notation change interaction F values < 1.3). This confirmed that the priming effect was conceptual rather than perceptual.

Given that subjects responded faster in the repeated than in the congruent non-repeated condition, one could object that our parietal cortex effect reflects a task difficulty component unrelated to the coding of numbers. Indeed, subjects were faster when they were primed, suggesting that their task was easier, and several studies have reported a correlation between task difficulty and parietal lobe activity (Winstein *et al.*, 1997). This alternative hypothesis, however, can be refuted by showing that our observed activations are not affected by other factors that have an equally strong impact on response times, for instance the response priming effect. In our original work (Dehaene *et al.*, 1998c) we reported an acceleration of response times in congruent non-repeated trials relative to incongruent trials in which the prime and the target elicit different responses (e.g. prime ONE, target SIX). This behavioral effect was similar in size to the repetition effect reported here (size effect 18 ms, $P = 0.001$). According to the 'task difficulty' hypothesis, we should still observe a significant difference in parietal cortex signal between congruent non-repeated and incongruent trials. In contrast, under the hypothesis of abstract coding for numbers in this region of parietal cortex no difference is predicted between these two kinds of trials because neither of them contains a repetition of the same number. We thus ran a similar ANOVA on the baseline-corrected BOLD signal separately for each parietal cluster with the factors congruity (congruent non-repeated/incongruent) and time (seven time points). Results clearly supported the abstract number coding hypothesis by showing similar responses to incongruent and congruent non-repeated trials in both left [$F(6,48) = 0.98$, $P > 0.5$] and right [$F(6,48) = 1.5$, $P = 0.2$] parietal clusters.

We then contrasted the results for the priming method with those that could have been obtained with a more direct subtraction method. Our experimental design incorporated two 2 × 2 designs. In one subset of trials both the prime and the target were independently drawn from the numbers 1 and 4 and in another they were drawn from the numbers 6 and 9. Each of these 2 × 2 designs can be analyzed separately for the main effect of the target and for the influence of prime–target repetition. The impact of the target number can be measured, for example by comparing the BOLD signal with trials in which the target equals 1 and with trials in which the target equals 4. This strategy corresponds to the direct subtraction method. Independently, the impact of prime–target repetition can be measured, for example by comparing the 1–1 and 4–4 trials to the 1–4 and 4–1 trials. This corresponds to the interaction term of the 2 × 2 design. Thus, we can directly compare the sensitivity of the subtraction method and the priming method on the same data set.

The dependent variable was the BOLD signal differences between the baseline (time points 0 and 2 s) and activated states (time points 6 and 8 s), averaged separately for voxels belonging
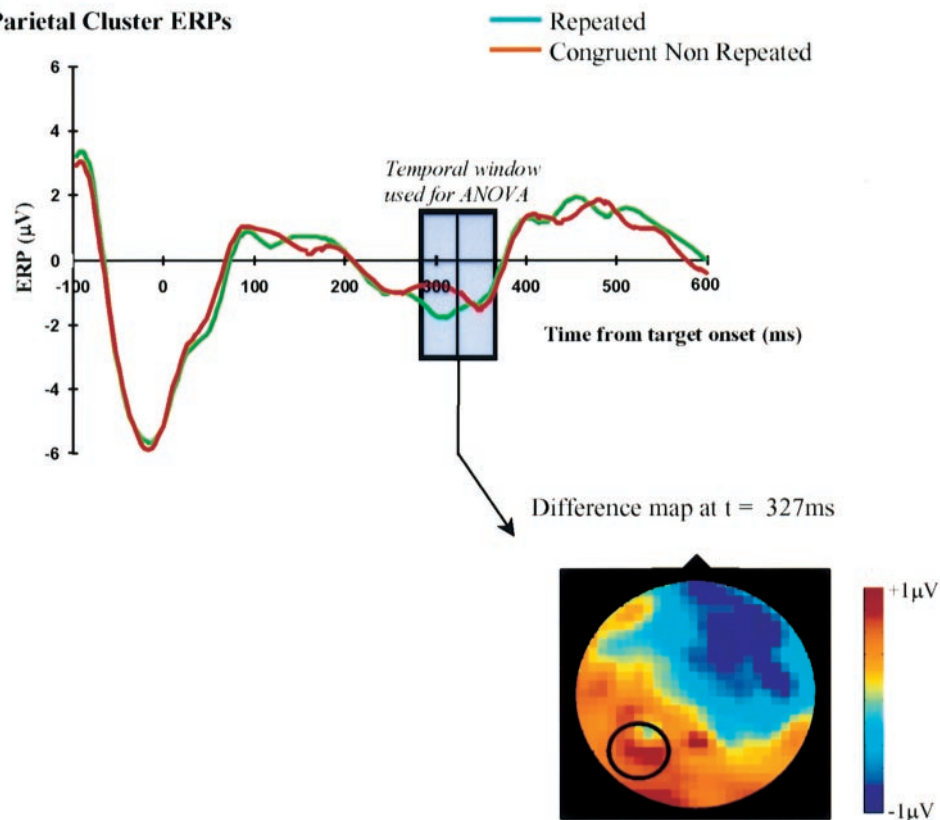
Figure 2. FMRI correlates of numerical repetition priming. Repetition suppression was observed in two brain regions shown here in axial, coronal and saggital section (top). Curves show the averaged time course of the BOLD signal in left and right parietal clusters separately for repeated (green curves) and congruent non-repeated (red curves) across the 14 s of an fMRI trial. Bottom graphs show the percent signal change in the various combinations of primes and targets, revealing a repetition suppression effect in the form of a prime × target interaction in each separate 2 × 2 design.

to the left and right intraparietal clusters. For the right parietal cluster the direct subtraction method did not reveal any significant target effects. The BOLD response did not differ for target 1 versus 4 [$F(1,8) = 1.70$, $P = 0.23$] nor for target 6 versus 9 [$F(1,8) = 0.59$, $P = 0.46$]. Nevertheless, the priming method revealed a RS effect when comparing trials in which prime and target were repeated with those in which they were not ['1,4' trials, $F(1,8) = 7.56$, $P = 0.013$; '6,9' trials, $F(1,8) = 10.13$, $P = 0.005$]. In the left parietal cluster direct subtraction did not reveal any difference in activation to targets 1 and 4 [$F(1,8) = 0.83$, $P = 0.39$], but revealed a significantly greater activation to target 9 than to target 6 [$F(1,8) = 6.79$, $P = 0.03$]. The priming method revealed a marginal RS effect in the '1,4' trials [$F(1,8) = 2.56$, $P = 0.07$] and a significant effect in the '6,9' trials [$F(1,8) = 3.51$, $P = 0.05$]. Taken together, these results suggest that the priming method may be more sensitive than the direct subtraction method in revealing the encoding of numerical quantity in parietal cortex. In the right parietal region, while the direct subtraction method was blind to microcode differences between the stimuli, the priming method revealed RS effects that indirectly imply that the quantities 1, 4, 6 and 9 must be coded by different neural assemblies. In the left parietal region the same pattern of result was observed for the '1,4' design, while for the '6,9' design both a significant target effect and a priming effect were observed.

ERPs

ERPs were used to specify the time course of the numerical repetition priming effect. We focused on ERP differences occurring in left and right parietal regions between repeated and congruent non-repeated trials during a temporal window of 200–400 ms after target onset, during which previous studies have revealed semantic processing of visually presented numbers (Dehaene, 1996; Kiefer & Dehaene, 1997; Dehaene et al., 1999). Sample-by-sample t-tests revealed a significant priming effect occurring on top of a posterior bilateral negativity peaking around 300 ms after target onset. Voltages were more negative for repeated than for congruent non-repeated trials, as can be seen in the subtraction voltage map (Fig. 3). We then defined two parietal clusters of 10 contiguous electrodes centered on the parieto-occipito-temporal junction in each hemisphere. ERPs averaged across a 80 ms temporal window (from 287 to 367 ms after target onset) were submitted to ANOVA with repetition, notation change and hemisphere as factors. There was a significant main effect of repetition [$F(1,11) = 5.15$, two-tailed $P = 0.04$] corresponding to more negative voltage values for repeated than for congruent non-repeated trials. No other main effect was significant (all F values < 1.1). Crucially, there was again no interaction between repetition priming and notation change ($F < 1$). Finally, we observed a non-significant trend towards an interaction between repetition and hemisphere

Figure 3. ERP correlates of the numerical repetition effect. The time course of grand averaged voltages for repeated (green curve) and congruent non-repeated trials (red curve), averaged across 10 left parietal electrodes, shows a significant difference at ~300 ms after target onset. The voltage map shows the topography of the difference between congruent non-repeated and repeated trials at 327 ms after target onset.

$[F(1,11) = 2.62, P = 0.13]$, suggesting a larger repetition effect under left parietal electrodes than under right parietal electrodes.

Discussion

In this paper we have examined an emerging brain imaging research strategy combining the logic of psychological priming experiments with the RS phenomenon. In this section we first discuss our experimental results, which illustrate the use of this method to probe the cerebral bases of number representations. We then turn to some general issues concerning the method and its applications in cognitive neuroscience.

Unconscious Coding of Numerical Quantity in the Parietal Lobes

The objective of this experimental study was to use the priming method to investigate the coding of numerical quantity in the parietal lobe. We capitalized on a repetition priming effect which was initially observed behaviorally. Subjects compared a target number with number 5 with significantly greater speed when it was immediately preceded by a subliminal presentation of the same number than when it was preceded by a different number. This repetition effect was independent of both prime and target notations, suggesting that it occurred at an abstract level of representation.

We then used fMRI to probe the whole brain for regions showing RS as a correlate of this numerical repetition effect. Only the left and right intraparietal regions demonstrated a reduced activation on repeated compared with non-repeated

trials, again independent of the notation used. Our design allowed us to compare the power of the priming method with that of the classical direct subtraction method. Direct subtraction could not reliably detect signal differences in most cases. Only a small effect was observed in the left parietal region, consisting of a greater activation for number 9 than for number 6. This may correspond to the number size effect reported in a recent study (Stanescu-Cosson *et al.*, 2001) on exact calculation which revealed greater BOLD activations for numerical problems involving large numbers (from 5 to 9) than for those using small numbers (from 1 to 5) in a very close region of the left intraparietal sulcus (–36, –44, 44). It may suggest that large quantities are coded by neural populations with coarser firing properties than small quantities (Weber's law).

Contrasting with this weak sensitivity of the direct subtraction method, RS effects were reliably observed in both left and right parietal regions and with both small and large numbers. The observed decrease in the BOLD signal to ~50% of its value on non-repeated trials fits with cellular recordings obtained in the infero-temporal cortex of the monkey, where firing rates on repeated trials may drop to 40% of their initial value (Li *et al.*, 1993).

Correlating the behavioral repetition priming effect with activation of the bilateral intraparietal sulci allows us to narrow down the origins of this effect. On the sole basis of the present behavioral data, the finding of a notation-independent repetition priming effect suggest that the prime and target numbers have been converted into a common code, but does not resolve whether this code is lexical, phonological or semantic. Narrow-

ing down this effect to the intraparietal sulci, however, strongly suggests that a semantic quantity code is involved. Previous brain imaging studies have revealed that the bilateral intraparietal sulci are typically not engaged during phonological or lexical tasks with non-numerical stimuli, but are activated whenever subjects are engaged in an active manipulation of numbers, for instance when calculating or comparing two numbers (Appolonio *et al.*, 1994; Chochon *et al.*, 1999; Dehaene *et al.*, 1999; Pinel *et al.*, 1999; Pesenti *et al.*, 2000; Stanescu-Cosson *et al.*, 2000). Furthermore, patients with left parietal lesions develop acalculia, a specific impairment in number manipulations which often cannot be attributed to phonological or lexical impairments, but rather suggests a deficit in the mental representation of quantities (Cipolotti *et al.*, 1991; Dehaene and Cohen, 1997; Delazer and Benke, 1997). These findings support a model in which the intraparietal sulci are thought to hold an abstract representation of numerical quantities in the form of distributions of activation on a mental number line (Dehaene and Cohen, 1995). Indeed, recent follow-up studies of the behavioral priming effect support the claim that the priming effect observed here arises at the semantic quantity level, because the amount of priming depends on the numerical distance between the prime and the target numbers (Koechlin *et al.*, 1999; Reynvoet and Brysbaert, 1999) and because priming generalizes to novel quantities that are never presented as targets (Naccache and Dehaene, 2001).

Compared with previous brain imaging studies of calculation, which merely show more parietal activity during a quantity processing task than during a control task, the present study provides finer grained evidence for a micro-coding of quantities in intraparietal cortex. Observing a differential effect of, say, primes 1 and 4 on the subsequent processing of target 1 logically implies that the numbers 1 and 4 were coded by partially distinct neural assemblies. Given that the direct subtraction method failed to revealed global activation differences to numbers 1 and 4, these assemblies are probably intermingled within the same parietal voxels. Yet the observation of a notation-independent RS effect warrants the inference that such assemblies exist.

Repetition priming was also observed in recordings of event-related potentials. Interpretation of ERP results is complicated by the fact that their polarity cannot be predicted. Differences in dipole orientation cause inversion of voltage polarities recorded at different locations on the skull surface, preventing us from predicting, in the general case, whether the voltages should be more negative or more positive on repeated compared with non-repeated trials (Rugg *et al.*, 1995). Furthermore, the voltages recorded at any given time under each electrode reflect the sum of many neural events occurring in several cortical regions, not all of which are expected to show RS. Hence, it cannot even be predicted that ERP RS effects should be characterized by a reduction in the absolute values of voltages. Indeed, in the ERP literature on repetition priming most studies report that stimulus repetition elicits decreased voltages in a 200–400 ms time window following stimulus onset (Badgaiyan and Posner, 1997; Radeau *et al.*, 1998), but some report increased voltages, for instance when repeating drawings of objects (Rugg *et al.*, 1995) or words at the same spatial location (Otten *et al.*, 1993; Swick, 1998). For these reasons, we used ERP measurements solely to assess the time course of the RS effect whose localization was evidenced by fMRI. The results indicated that repeating the same numerical quantity, again independently of notation, began to have an impact on brain activity by 287 ms after target onset. This latency is compatible with previously published ERP measures of the onset of semantic processing of numbers, as measured by the first point in time when ERPs begin to be influenced by parameters such as the distance between numbers [~230 ms (Dehaene, 1996)], the size of the numbers involved [~330 ms (Kiefer and Dehaene, 1997)] or whether or not the task emphasizes quantity processing [~280 ms (Dehaene *et al.*, 1999; Stanescu-Cosson *et al.*, 2000].

In addition to contributing to our understanding of number coding, the results also bear upon our understanding of unconscious processing. In this experiment prime awareness was assessed through several tests [for details see Dehaene *et al.* (Dehaene *et al.*, 1998c)]. First, none of the subjects spontaneously reported the presence of the primes during debriefing. Moreover, once informed about the precise structure of the trials and engaged in tasks focusing their attention on the primes, they still remained unable to reliably report their presence or absence nor to discriminate them from nonsense strings. Analyses based on signal detection theory, separating d' measures from shifts in the response criterion β, showed that subjects could not consciously perceive the primes. Finally, in order to verify that the priming effect was not due solely to a small number of trials in which the primes were consciously perceived, we showed that the effect affected the entire distribution of response times. Those controls have been replicated in a recent behavioral extension of the priming effect (Naccache and Dehaene, 2001).

Taken together, these results strongly suggest that the primes were genuinely processed unconsciously and, therefore, that the present experiment is relevant to the controversial issue of unconscious semantic processing. Recent studies have suggested that unconscious access to semantic information is possible (Greenwald, 1996; Luck *et al.*, 1996; Dehaene *et al.*, 1998c), but non-semantic interpretations of the same data have also been proposed (Neumann, 1990; Abrams and Greenwald, 2000) [for a discussion see Naccache and Dehaene (Naccache and Dehaene, 2001)]. In this context the present findings provide direct evidence that an area thought to be involved in semantic level processing of numbers, the intraparietal region, can be affected by subliminal primes. The data suggest that the same brain circuits that are at work during conscious number processing can also be involved in the processing of subliminal information, as proposed for instance in the global workspace model of conscious processing (Baars, 1989; Dehaene *et al.*, 1998b; Dehaene and Naccache, 2001).

Potential of the Priming Method

In this work we have reviewed and used a new research strategy for brain imaging experiments, taking advantage of the RS phenomenon, that can go beyond the limits of traditional imaging paradigms. In the design proposed here each experimental trial consists of the presentation of both a prime and a target, while subjects perform a constant task on the target only. By varying the relationship between prime and target, one can detect which brain areas present RS specifically for any given level of prime–target repetition. This method may be more sensitive than classical methods based on subtraction and may reveal the neuronal microcodes that differentiate populations of neurons within the same voxel.

The potential and limits of the priming method depend on the validity of its two key hypotheses. A first hypothesis is that priming effects can be observed at many if not all stages of cognitive processing. In support of this hypothesis, a wide variety of behavioral priming effects have been reported in the psychological literature, in domains as different as visual object identification (Cooper *et al.*, 1992), orthographical and phonological processing (Evett and Humphreys, 1981; Humphreys *et al.*, 1982; Ferrand and Grainger, 1992, 1994; Bijeljac-Babic *et al.*,

1997; Ferrand *et al.*, 1998), semantic word processing (Neely, 1991), stimulus–response associations (Neumann and Klotz, 1994) or mental visual imagery (Stadler and McDaniel, 1990; McDermott and Roediger, 1994). Moreover, one should keep in mind that RS effects might be observed on brain activation measures in the absence of significant behavioral effects. Indeed, response times usually reflect the net outcome of several processing stages that may have counterbalancing effects, while brain imaging can potentially give access to each stage separately.

A second assumption behind the priming method is that RS is a general property of cerebral networks. At present, RS has been observed in several occipito-temporal, temporal and frontal regions and with stimuli presented in various modalities and tasks (Buckner *et al.*, 1998; Grill-Spector *et al.*, 1998a, 1999; Wiggs and Martin, 1998; Bagdaiyan *et al.*, 1999; Thompson-Schill *et al.*, 1999; Gauthier *et al.*, 2000; Henson *et al.*, 2000; James *et al.*, 2000). From the cellular point of view, Wiggs and Martin proposed a theoretical mechanism for RS based on the progressive tuning of neuronal responses in response to a repeated stimulus (Wiggs and Martin, 1998). This mechanism, if correct, does not *a priori* imply any particular constraint on the type of neuronal network involved. However, as demonstrated by Buckner and co-workers for primary visual retinotopic brain regions and output motor areas, it seems that RS may not be found in primary sensory-motor cortices (Buckner *et al.*, 1998).

More generally, it should be stressed that the physiological mechanisms underlying RS remain largely unknown. In a recent study, Poldrack and Gabrieli have shown that almost all brain areas exhibiting significant learning-related changes in a mirror reading task also exhibited RS (Poldrack and Gabrieli, 2001), suggesting that skill learning and priming share a common neural substrate. However, as long as the critical parameters determining the occurrence or absence of RS in a given area remain uncertain, any experimental strategy based on RS will have to be used and interpreted with caution. For instance, the precise relationship linking RS to stimulus preference remains a major unsolved issue even at the single neuron level. Learning-induced shifts in stimulus preference may account for occasional observations of repetition enhancement rather than RS as a correlate of repetition priming. Which effect is observed may vary depending on the strength of the counterbalancing effects of learning and of RS. Indeed, in a recent fMRI study of repetition priming Henson *et al.* found an interaction between stimulus familiarity and stimulus repetition in the right fusiform gyrus for faces and symbols (Henson *et al.*, 2000). This effect reflected the existence of RS for familiar stimuli as opposed to repetition enhancement for unfamiliar repeated stimuli. As proposed by these authors, this response enhancement may reflect the elaboration of a new representation and thus interfere with RS effects through a reshaping of neuronal tuning curves between repetitions. It should be noted, however, that Henson *et al.*'s reliance on conscious stimulus repetition leaves open the possibility of a contamination by conscious strategical processing, such as increased attention to the unfamiliar stimuli. Thus, a replication of this experiment with unconscious repetitions of familiar and unfamiliar stimuli seems desirable.

In closing, we note that the observation of repetition enhancement rather than suppression does not in itself limit the use of the priming method. Enhancement effects, like suppression effects, can be submitted to priming-based experiments in order to study the level of coding at which they are occurring. In their explorations of behavior psychologists and ethologists have long used transfer of learning as a criterion to identify the level of abstraction of knowledge acquired during training. The priming method offers an equally general means of identifying the neural correlates of such abstract transfers.

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