

# Double Dissociation of Format-Dependent and Number-Specific Neurons in Human Parietal Cortex

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**Based on neuroimaging methods, it is a commonly held view that numerical representation in the human parietal lobes is format independent. We used a transcranial magnetic stimulation adaptation paradigm to examine the existence of functionally segregated overlapping populations of neurons for different numerical formats and to reveal how numerical information is encoded and represented. Based on 2 experiments, we found that right parietal lobe stimulation showed a dissociation between digits and verbal numbers, whereas the left parietal lobe showed a double dissociation between the different numerical formats. Further analysis and modeling also excluded pre- or postrepresentational components as the source of the current effects. These results demonstrate that both parietal lobes are equipped with format-dependent neurons that encode quantity.**

**Keywords:** brain stimulation, neuronal specialization, numerical cognition, parietal lobes, representation

## Introduction

The question of how we represent numbers, the basic component for more sophisticated numerical and arithmetical skills, is a matter of central concern for researchers from various disciplines such as neuroscience, psychology, philosophy, education, linguistics, and anthropology (Wiese 2003; Gordon 2004; Cohen Kadosh and Walsh 2009; Nieder and Dehaene, 2009).

Numbers can come in many forms; we can represent the same quantity, as a word (ONE), a digit (1), in Roman numerals (I), nonsymbolically as on a dice (●), with our fingers, in a temporal series (e.g., a drum beat) or with other words (eins, uno) or symbols with agreed meanings (♪) that carry semantic and numerical meaning. The question of how we represent numbers and whether there is a unitary cognitive and neuronal basis for all forms of numerical representation is therefore an important problem. In this paper, we examined the commonly held view that numbers are represented in an abstract fashion in the intraparietal sulcus (Dehaene et al. 1998; Eger et al. 2003; Cohen Kadosh and Walsh 2009; Nieder and Dehaene, 2009), a core area for numerical representation. This is a critical testing ground for models of numerical cognition (Verguts and Fias 2004), education (Ansari 2008), and remediation from dyscalculia (Wilson et al. 2006; von Aster and Shalev 2007). Previous studies have used functional magnetic resonance imaging (fMRI) to examine the numerical representation for numbers as a function of modality or notation in the human intraparietal sulcus (IPS) (Eger et al. 2003; Cohen Kadosh, Cohen Kadosh, Kaas, et al. 2007; Piazza et al. 2007; Jacob and Nieder 2009; Cantlon et al. 2009). In the current study, we

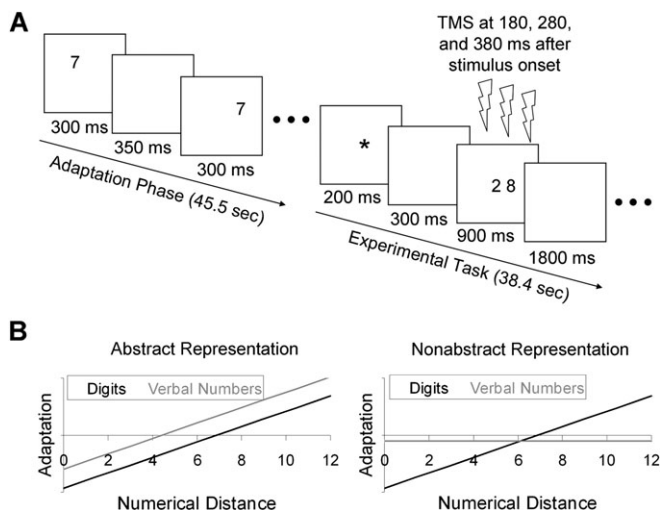
combined transcranial magnetic stimulation (TMS) with an adaptation paradigm (TMSA) (Silvanto et al. 2008). This combination enables improved functional resolution by differential stimulation of distinct but spatially overlapping neural populations within a stimulated region (Silvanto et al. 2008). The paradigm is based on findings that the effects of TMS are determined by the initial neural activation state, with attributes encoded by the less active/excitable neural populations within the stimulated region being more susceptible to the effects of TMS. Thus, by using adaptation to manipulate neural activation states prior to the application of TMS, one can control which neural populations are preferentially activated by TMS (Silvanto et al. 2008). For example, following color adaptation, it was found that phosphenes induced from the early visual cortex selectively took on the color qualities of the adapting stimulus (Silvanto et al. 2007). This behavioral facilitation of the adapted neural populations by TMSA suggests that, at the behavioral level, the effects of TMS are akin to microstimulation of the adapted neural populations (Silvanto and Muggleton 2008a). This state dependency can be used to reveal receptive field properties of the stimulated region: if TMS applied over a given area facilitates the detection of the adapted attribute, this indicates that neurons in that area were adapted by and, thus, to some degree tuned to the adapting stimulus.

By using TMSA, we tested whether, in the human IPS, number-sensitive neurons code numbers in an abstract, that is, format-independent fashion (Dehaene et al. 1998) or rather in a format-dependent fashion (Cohen Kadosh and Walsh 2009; Fig. 1). Moreover, single-cell neurophysiology studies in monkeys have revealed neurons with preferences for specific nonsymbolic numbers (e.g., an array of 4 dots) in the IPS, and a decrease in sensitivity as the numerical proximity to this number decreases (Nieder et al. 2002; Diester and Nieder 2007). Therefore, we used the improved functional resolution of TMSA to examine whether in the human IPS there are neurons with greater preference for a specific symbolic numerical quantity, such as the digit 7, but not the number word “SEVEN.”

## Materials and Methods

### Subjects

Seven native English speakers (20–27 years, mean age = 22.71 years, standard deviation [SD] = 2.37, 6 females, all right handed) took part in Experiment 1 and 6 participants (20–28 years, mean age = 24.33 years, SD = 2.35, all females, all right handed) took part in Experiment 2. None reported any neurological illnesses or mathematical learning difficulties. Subjects received monetary compensation for their participation. The study was approved by the local ethics committee and all gave informed consent.



**Figure 1.** Illustration of the experimental paradigm and prediction of the 2 competing hypotheses. (A) After an adaptation phase, the subject participated in a same-different task while receiving TMS to the vertex, left IPS, or right IPS. During the baseline task, the # sign appeared, and TMS was not delivered. The adapted number was in digit form in Experiment 1 and verbal number form in Experiment 2. (B) According to the abstract representation hypothesis, numerical representation is subserved by format-independent neuronal populations; therefore, the effect of TMSA should be greater on processing of adapted quantity irrespective of format (e.g., 7, SEVEN), and this effect should decrease according to the distance of numbers of the mental number line (Restle 1970), thus, yielding a positive beta value between adaptation and numerical distance irrespective of the numerical notation. In contrast, the nonabstract representation hypothesis (Cohen Kadosh and Walsh 2009) posits that numerical information is implemented by format-dependent neuronal populations and, therefore, predicts that the TMSA effect will modulate specifically the quantity processing of the adapted format, thus, yielding a positive beta value between adaptation and numerical distance only to the numerical format that has been adapted. For example, if digits are adapted, then the TMSA effect should decrease according to the distance of the numbers of the mental number line, only for digits but not for verbal numbers). This effect should decrease according to the distance of numbers of the mental number line and should be absent for the nonadapted format.

### Stimuli and Procedure

To adapt number-tuned neurons, the digit 7 (Experiment 1) or the verbal number “SEVEN” or “TWO” (Experiment 2) was presented to subjects at different locations, fonts, and sizes for 45.5 s on a monitor. In the adaptation phase, the number being adapted to appeared for 300 ms with 350-ms interstimulus interval (ISI). The number was presented 70 times during each adaptation period (Fig. 1A).

Following this adaptation phase, the subjects performed 12 trials of a physical same-different task on pairs of digits or verbal numbers that contained the numbers 1, 2, 7, and 8 (Van Opstal et al. 2008). The numbers 1, 2, 7, and 8 were selected as they are well controlled for differences in perceptual similarity (Verguts and Van Opstal 2005). In this task, a fixation appeared for 200 ms, followed by a blank screen for 300 ms. The stimulus then appeared for 900 ms. The ISI was 1800 ms. We used a physical same-different task as it provides an examination of the default mental representation, independent of subjects’ strategies that are used during intentional tasks (Tzelgov and Ganor-Stern 2004; Fischer and Rottmann 2005; Shaki and Fischer 2008; Cohen Kadosh and Walsh 2009). All stimuli appeared in white on a black background.

Ten blocks of adaptation-task pairs were presented for each stimulation site (left IPS, right IPS, vertex). In order to estimate the effect of the TMSA, the same procedure was applied without TMS although the subjects were adapted to the # symbol in the place of numbers (baseline task).

The order of the session (left TMS, right TMS, vertex, and baseline), as well as the buttons used for same and different decisions (the buttons P and Q on QWERTY keyboard), was counterbalanced across subjects.

### TMS Apparatus and Stimulation Parameters

During the task, we delivered biphasic TMS pulses through a figure-eight coil and Magstim Super Rapid machine at 180, 280, and 380 ms

after trial onset (Fig. 1). This timing was chosen for 2 reasons. First, the most effective timing to deliver a disruptive TMS pulse has been suggested to occur before the peak of the event-related potential (ERP) component that relates to the mental operation of interest (Walsh and Cowey 2000; Cohen Kadosh, Cohen Kadosh, Kaas, et al. 2007). Therefore, the timing of the TMS pulses (180, 280, and 380 ms after stimulus presentation) were chosen based on previous ERP studies that found modulation of the P2p and P3b during numerical processing (Dehaene 1996; Turconi et al. 2004; Cohen Kadosh, Cohen Kadosh, Linden, et al. 2007; Libertus et al. 2007; Szucs et al. 2007). Second, this timing makes it unlikely that we would induce a perceptually related effect (cf., timings of parietal cortex TMS on perception [Ashbridge et al. 1997; Kalla et al. 2008]).

Prior to the experiment, a  $T_1$ -weighted structural image (1 mm<sup>3</sup> resolution) was acquired to allow neuronavigation of the TMS coil to the coordinates of interest in each individual IPS by usingBrainsight software (Magstim, UK). TMS pulses were delivered at 60% of maximum stimulator output (maximum stimulator output equals ~2 Tesla). The site of IPS stimulation was localized based on coordinates from a meta-analysis of fMRI studies of numerical representation (Cohen Kadosh et al. 2008). To increase sensitivity and to compensate for the large individual difference in the IPS anatomy (Zilles et al. 2003; Sack et al. 2009) when the foci fell on a gyrus, the foci were moved to the nearest portion of the IPS. The vertex was localized according to the EEG 10-20 system.

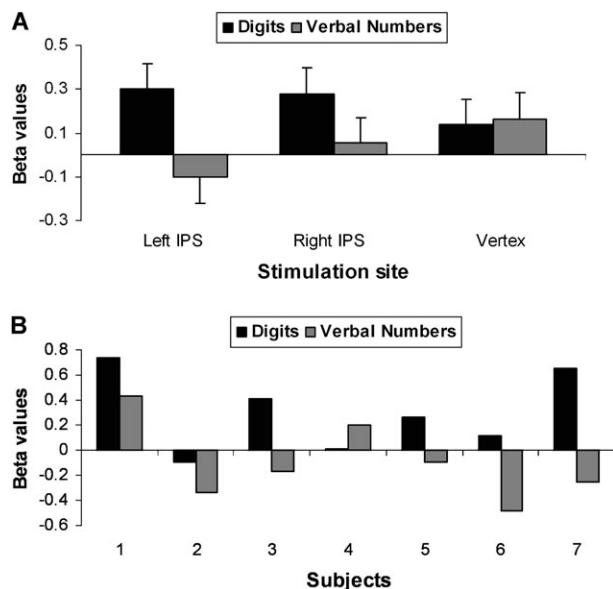
## Results

### Experiment 1

To evaluate the adaptation level, and eliminate any nonspecific adaptation effect (e.g., size effect [Moyer and Landauer 1967] or linguistic frequency [Landauer and Dumais 1997]) for individual pairs, we subtracted the reaction times (RTs) and error rates for each pair in the TMSA conditions from its respective pair in the baseline conditions. Whenever error rates were analyzed, the arcsine transformation was used to approximate normal distributions. To assess the effect of TMSA on the mental number line, each pair received a distance value according to the sum of deviations from the adapted number (also known as numerical distance). For example, when the adapted number was 7, the pair 7–8, received the value 1 (the sum of  $|7-8|+|7-7|$  in absolute value), whereas the pair 1–2 received the value 11 ( $|7-1|+|7-2|$ ). We then conducted a simple regression analysis between these values and the adaptation RT. We examined, using a regression analysis, whether the results were consistent across subjects (Lorch and Myers 1990). In the first step, for each individual participant, a simple regression analysis was computed. In the second step, 2-tailed  $t$ -tests were performed to test whether the beta values of the group deviated significantly from zero. Following TMSA to the left IPS, digits differed significantly from verbal numbers and zero (digit vs. verbal numbers  $t(6) = 3.07$ ,  $P = 0.01$ ; digits vs. zero,  $t(6) = 2.51$ ,  $P = 0.02$ ; verbal number vs. zero,  $t(6) = -0.83$ ,  $P = 0.44$ ). After TMS to the right IPS, digits did not differ significantly from verbal numbers ( $t(6) = 1.39$ ,  $P = 0.21$ ). However, digits ( $t(6) = 3.45$ ,  $P = 0.01$ ) but not verbal numbers ( $t(6) = 0.43$ ,  $P = 0.67$ ) differed significantly from zero. Digits and verbal numbers did not differ from each other with vertex TMS and did not differ from zero (all  $P$  values  $> 0.1$ ) (Fig. 2). When error rates were considered, none of the effects mentioned above were significant (all  $P$  values  $> 0.2$ ).

### Experiment 2

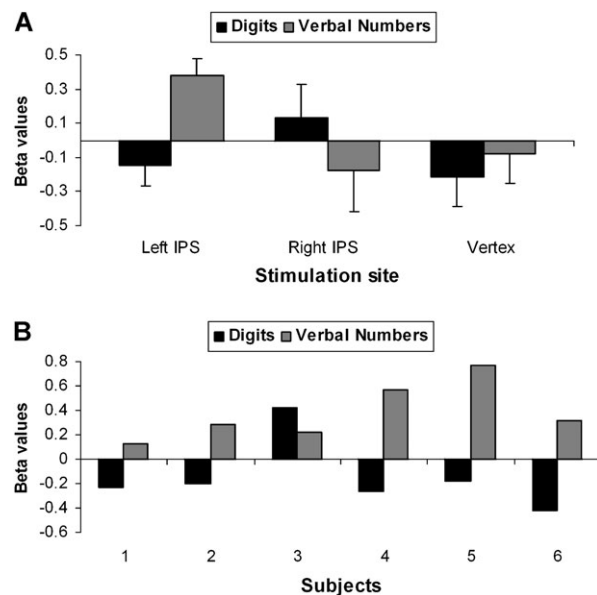
To generalize the results to other stimuli and to examine the case of a possible double dissociation between digits and verbal



**Figure 2.** A dissociation between digits and verbal numbers in the left and right IPS in Experiment 1. (A) Only stimulation of the left IPS yielded significant differences between the numerical formats and only digits significantly differed from zero. For the right IPS stimulation, the differences between the numerical formats were not significant, but the mean beta values for right IPS when digits were presented differed significantly from zero. Vertex stimulation did not yield any difference between the formats or difference from zero when the mean beta values of both numerical formats was compared with zero. (B) The beta values for the different formats for each subject after stimulation of the left IPS. Digits differed significantly from zero and from verbal numbers. Error bars depict 1 standard error of the mean.

numbers in the left IPS, we conducted a second experiment, in which the subjects were adapted to verbal numbers rather than digits. The analysis for Experiment 2 followed the same steps as for Experiment 1. The adaptation effect was not significant for RT (all  $P$  values  $> 0.2$ ). However, the effects were clearly observed for errors; as numerical distance increased errors increased. Following left IPS TMS, digits significantly differed from verbal numbers and zero (verbal numbers vs. digits  $t(5) = 2.9$ ,  $P = 0.01$ ; verbal numbers vs. zero,  $t(5) = 3.27$ ,  $P = 0.01$ ; digits vs. zero,  $t(5) = -1.17$ ,  $P = 0.3$ ). This effect was consistent across the adapted values, and all the subjects showed the same trend. In the right IPS, vertex numerical formats did not differ significantly from each other (all  $P$  values  $> 0.4$ ) and did not differ from zero (all  $P$  values  $> 0.2$ ) (Fig. 3).

TMSA affected different indices of information processing. In Experiment 1, the effect was observed for RT, whereas in Experiment 2 it was present for accuracy. These results can be caused by differences in the required amount of accumulated evidence before a response is activated (Pachella 1974). Fast responses will lead to error rate effects, whereas slow responses will lead to RT effects (Pachella 1974). To assess if and how these results related to one another, we used a diffusion model (Wagenmakers et al. 2007). This approach is very similar to classical signal detection theory in its aim, scope, and method. Based on accuracy, mean RT, and RT variance, the model yields 3 different parameters: 1) *drift rate*, which combines respond speed and response accuracy to quantify subject ability and can be interpreted as an index for the signal-to-noise ratio (the equivalent of  $d'$  prime in the signal detection theory framework) of the information processing system (Wagenmakers et al. 2007), 2) *boundary separation*, which indicates response conserva-



**Figure 3.** Results from Experiment 2 completed a double dissociation between digits and verbal numbers in the left IPS by mirroring the TMSA result in Experiment 1 (Fig. 2). (A) Only the TMS to the left IPS yielded a significant difference between the beta values of digits and verbal numbers and a significant difference from zero for the verbal numbers. Stimulation of the right IPS and vertex did not yield a significant difference between the numerical formats or a significant difference from zero. (B) All participants showed a positive beta value between adaptation and numerical distance for verbal numbers after stimulation of the left IPS. In this experiment, verbal numbers differed significantly from zero and from digits. Error bars depict 1 standard error of the mean.

tiveness (the equivalent of beta in the signal detection theory framework), and 3) *mean of nondecision time*. Thus, this model allows one to examine whether the results in Experiments 1 and 2 were derived from a common mechanism that affected the signal-to-noise ratio of the numerical representation (drift rate) but not other non-numerical processes (boundary separation or nondecision time). The results from the diffusion model supported this view. In Experiment 1, TMSA to the left IPS, but also the right IPS, led to increased drift rate (a better signal-to-noise ratio) as numerical distance from the adapted digit decreased. This beta value differed from the beta value for verbal numbers and from zero (all  $P$  values  $< 0.03$ ). In Experiment 2, TMSA to the left IPS revealed a beta value between drift rate and numerical distance for verbal numbers. This beta value differed from zero and from the beta value for digits (all  $P$  values  $< 0.005$ ). Neither boundary separation nor mean nondecision time was modulated by the numerical distance in any of the experiments (all  $P$  values  $> 0.1$ ).

The double dissociation between Experiment 1 (TMSA to the left IPS affect digits but not verbal numbers) and Experiment 2 (TMSA to the left IPS affect verbal numbers but not digits) was statistically confirmed by subjecting the drift rate data from the left IPS in both experiments to a 2-way analysis of variance with the format (digits, verbal numbers) as the within-subject factor and Experiment (Experiment 1, Experiment 2) as the between-subject factor. The only significant effect was the 2-way interaction between format and experiment,  $F(1,11) = 17.23$ ,  $P = 0.001$ , thus, confirming a double dissociation between the different numerical formats in the left IPS.

We also analyzed the results without subtracting the RTs and accuracy for each pair in the TMSA conditions from its



respective pairs in the baseline conditions. This analysis yielded the same results as with the subtraction analysis. We described this analysis in detail in the Supplementary Results section.

We controlled for perceptual adaptation in several ways (see Materials and Methods), but we nevertheless assessed whether the effects were due to perceptual adaptation. The exclusion of the pairs that contained the adapted number from the analysis did not change the results (all  $P$  values  $< 0.05$ ).

## Discussion

TMSA selectively affected information processing of numbers in a format-specific manner in the IPS, an area that is believed to hold the putative abstract representation (Dehaene et al. 1998; Eger et al. 2003; Cohen Kadosh, Cohen Kadosh, Kaas, et al. 2007; Piazza et al. 2007; Cohen Kadosh and Walsh 2009; Cantlon et al. 2009). This was reflected by a dissociation between digit and verbal numbers in the right IPS and a double dissociation between the different formats in the left IPS. These effects specifically affected the mental number line (Restle 1970); when neurons were adapted for numerical value, processing of numerical information was made easier by TMS, the closer the numbers were to the adapted number. However, this effect was specific for the format in which it was adapted.

The current results therefore support the idea that numerical representation is notation dependent and the computation of the numerical information is not necessarily abstract (Cohen Kadosh and Walsh 2009). The current study also shows that both the left and the right IPS are equipped with notation-dependent numerical representations.

Results from computational models, neuroimaging in adults and children, and neuropsychological studies suggested that nonverbal numerical abilities served as the foundation for later, symbolic numerical representation, by mapping spoken and written numerals into the nonverbal core representation (Dehaene 1997; Butterworth 1999; Cantlon et al. 2006; Piazza et al. 2007). According to this idea, the effect of stimulation on symbolic notations, such as digits and verbal numbers in this study, should have yielded similar results independent of the adapted notation. In contrast, the results suggested that numerical information is accessible in a notation-dependent fashion.

Another theory that does not hold in the face of the current results is that digits are mapped into verbal numerals (Carey 2004). If that were the case, again adaptation for digits following TMS to the left IPS should have yielded a similar effect also for verbal numbers as digits in the adaptation stage was mapped into verbal numerals. From the same reason, in Experiment 2, adaptation for verbal numbers following TMS to the left IPS should have led to similar effects for digits. The double dissociation seen poses a challenge to this theory. Although this theory might hold for children, it seems that it does not receive support from our study with adults.

Although the current results demonstrate the specificity of neuronal substrates for numerical representation, this does not mean that the affected neuronal substrates in our experiments are active solely for digits or verbal numbers, and no other function, as they may be involved also in other parietal lobe functions (see Posner [2003] for a similar idea on the usage of the term “specific” in cognitive neuroscience). Indeed, previous single-cell neurophysiology showed that even if neurons are tuned to a specific quantity, they are still sensitive to other

features such as motion direction (Nieder et al. 2006) or other magnitudes such as space and time (Walsh 2003a, 2003b; Buetti and Walsh 2009).

In the current study, we initially found that different dependent variables are affected in different experiments. Namely, in Experiment 1, the effect was observed in RT, whereas in Experiment 2 the effect was observed in error rates. Although we stressed both accuracy and reaction time to our subjects, it is possible that different subjects might adopt different criterion for responding. Pachella (1974) suggested that if one adopt a conservative criterion for responding, then any effect will be observed mainly in RT, whereas if one adopts a more liberal criterion for response the effect will be present mainly in error rates. For this reason, in the current paper, we used diffusion modeling. The important point, however, is that diffusion modeling not only confirmed the findings in Experiments 1 and 2, but by taking both RT and error rates into account, we were able to show that the right IPS was also affected by the TMSA in Experiment 1.

In the current study, we used a combination of meta-analysis coordinates and anatomical MRI to localize the site of stimulation (see Materials and Methods). It is likely that a localization based on functional MRI would have been superior, most likely by reducing the variance between subjects, as was shown also in the case of parietal lobe stimulation and numerical cognition (Sack et al. 2009). However, in the current study, we found a differential effect both in Experiment 1 and Experiment 2, including a double dissociation, which indicates that our localization method was sufficient with the amount of subjects.

The current study extends the feasibility of TMSA paradigms in examining neuronal specialization from perceptual processes (Silvanto et al. 2008) to high-level cognitive processes. The results in Experiment 2, showing that the verbal numbers modulate the left IPS only, are in line with a previous fMRI results (Cohen Kadosh, Cohen Kadosh, Kaas, et al. 2007). However, the important findings are the double dissociation in the left IPS. Several previous fMRI studies have failed to find specific numerical representation in the IPS (Eger et al. 2003; Cohen Kadosh, Cohen Kadosh, Kaas, et al. 2007; Piazza et al. 2007; Jacob and Nieder 2009; Cantlon et al. 2009). It is noteworthy that recent evidence has demonstrated that fMRI can show regional blood oxygenation level-dependent change in the absence of activated neurons (Sirotnin and Das 2009), thus obscuring the detection of functional specialization in the brain. There are also other methodological reasons for some of these absences of difference (see Cohen Kadosh and Walsh 2009). In contrast, TMSA has clearly been shown to be capable of segregating functionally distinct but anatomically overlapping neuronal populations (Silvanto et al. 2007; Silvanto et al. 2008; Silvanto and Muggleton 2008b; Cattaneo et al. 2009) and, thus, reveal format-dependent numerical representations in both IPS. Thus, TMSA offers an attractive method to uncover neuronal specialization in the human brain in addition to providing causal inference about the neuronal populations that are involved in cognitive and perceptual domains (Price and Friston 2002; Walsh and Pascual-Leone 2003; Allen et al. 2007).

## Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

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## References

- Allen EA, Pasley BN, Duong T, Freeman RD. 2007. Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. *Science*. 317:1918–1921.
- Ansari D. 2008. Effects of development and enculturation on number representation in the brain. *Nat Rev Neurosci*. 9:278–291.
- Ashbridge E, Walsh V, Cowey A. 1997. Temporal aspects of visual search studied by transcranial magnetic stimulation. *Neuropsychologia*. 35:1121–1131.
- Bueti D, Walsh V. 2009. The parietal cortex and the representation of time, space, number and other magnitudes. *Philos Trans R Soc B Biol Sci*. 364:2369–2380.
- Butterworth B. 1999. *The mathematical brain*. London: Macmillan.
- Cantlon JF, Brannon EM, Carter EJ, Pelphrey KA. 2006. Functional imaging of numerical processing in adults and 4-y-old children. *PLoS Biol*. 4:e125.
- Cantlon JF, Libertus ME, Brannon EM, Pelphrey KA. 2009. The neural development of an abstract concept of number. *J Cogn Neurosci*. 21:2217–2229.
- Carey S. 2004. Bootstrapping and the origin of concepts. *Daedalus*. 133:59–68.
- Cattaneo Z, Rota F, Walsh V, Vecchi T, Silvanto J. 2009. TMS-adaptation reveals abstract letter selectivity in the left posterior parietal cortex. *Cereb Cortex*. 19:2321–2325.
- Cohen Kadosh R, Cohen Kadosh K, Kaas A, Henik A, Goebel R. 2007. Notation-dependent and -independent representations of numbers in the parietal lobes. *Neuron*. 53:307–314.
- Cohen Kadosh R, Cohen Kadosh K, Linden DEJ, Gevers W, Berger A, Henik A. 2007. The brain locus of interaction between number and size: a combined functional magnetic resonance imaging and event-related potential study. *J Cogn Neurosci*. 19:957–970.
- Cohen Kadosh R, Lammertyn J, Izard V. 2008. Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. *Prog Neurobiol*. 84:132–147.
- Cohen Kadosh R, Walsh V. 2009. Numerical representation in the parietal lobes: abstract or not abstract? *Behav Brain Sci*. 32:313–328.
- Dehaene S. 1996. The organization of brain activations in number comparison: event-related potentials and the additive-factors method. *J Cogn Neurosci*. 8:47–68.
- Dehaene S. 1997. *The number sense: how the mind creates mathematics*. Oxford: Oxford University Press.
- Dehaene S, Dehaene-Lambertz G, Cohen L. 1998. Abstract representations of numbers in the animal and human brain. *Trends Neurosci*. 21:355–361.
- Diester I, Nieder A. 2007. Semantic associations between signs and numerical categories in the prefrontal cortex. *PLoS Biol*. 5:e294.
- Eger E, Sterzer P, Russ MO, Giraud A-L, Kleinschmidt A. 2003. A supramodal number representation in human intraparietal cortex. *Neuron*. 37:719–725.
- Fischer MH, Rottmann J. 2005. Do negative numbers have a place on the mental number line? *Psychol Sci*. 47:22–32.
- Gordon P. 2004. Numerical cognition without words: evidence from Amazonia. *Science*. 306:496–499.
- Jacob SN, Nieder A. 2009. Notation-independent representation of fractions in the human parietal cortex. *J Neurosci*. 29:4652–4657.
- Kalla R, Muggleton NG, Juan C-H, Cowey A, Walsh V. 2008. Timing of involvement of frontal eye fields and posterior parietal cortex in visual search. *Neuroreport*. 19:1067–1071.
- Landauer TK, Dumais ST. 1997. A solution to plato's problem: the latent semantic analysis theory of acquisition, induction, and representation of knowledge. *Psychol Rev*. 104:211–240.
- Libertus ME, Woldorff MG, Brannon EM. 2007. Electrophysiological evidence for notation independence in numerical processing. *Behav Brain Funct*. 3:1.
- Lorch RF, Myers JL. 1990. Regression analyses of repeated measures data in cognitive research. *J Exp Psychol Learn Mem Cogn*. 16:149–157.
- Moyer RS, Landauer TK. 1967. Time required for judgment of numerical inequality. *Nature*. 215:1519–1520.
- Nieder A, Dehaene S. 2009. Representation of number in the brain. *Annu Rev Neurosci*. 32:185–208.
- Nieder A, Diester I, Tudusciuc O. 2006. Temporal and spatial enumeration processes in the primate parietal cortex. *Science*. 313:1431–1435.
- Nieder A, Freedman DJ, Miller EK. 2002. Representation of the quantity of visual items in the primate prefrontal cortex. *Science*. 297:1708–1711.
- Pachella R. 1974. The interpretation of reaction time in information processing research. In: Kantowitz BH, editor. *Human information processing: Tutorials in performance and cognition*. Hillsdale (NJ): Erlbaum. p. 41–82.
- Piazza M, Pinel P, Le Bihan D, Dehaene S. 2007. A magnitude code common to numerosities and number symbols in human intraparietal cortex. *Neuron*. 53:293–305.
- Posner MI. 2003. Imaging a science of mind. *Trends Cogn Sci*. 7:450–453.
- Price CJ, Friston KJ. 2002. Degeneracy and cognitive anatomy. *Trends Cogn Sci*. 6:416–421.
- Restle F. 1970. Speed of adding and comparing numbers. *J Exp Psychol*. 83:274–278.
- Sack AT, Cohen Kadosh R, Schuhmann T, Moerel M, Walsh V, Goebel R. 2009. Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. *J Cogn Neurosci*. 21:207–221.
- Shaki S, Fischer MH. 2008. Reading space into numbers—a cross-linguistic comparison of the SNARC effect. *Cognition*. 108:590–599.
- Silvanto J, Muggleton N, Walsh V. 2008. State dependency in brain stimulation studies of perception and cognition. *Trends Cogn Sci*. 12:447–454.
- Silvanto J, Muggleton NG. 2008a. New light through old windows: moving beyond the “virtual lesion” approach to transcranial magnetic stimulation. *Neuroimage*. 39:549–552.
- Silvanto J, Muggleton NG. 2008b. Testing the validity of the TMS state-dependency approach: targeting functionally distinct motion-selective neural populations in visual areas V1/V2 and V5/MT+. *Neuroimage*. 40:1841–1848.
- Silvanto J, Muggleton NG, Cowey A, Walsh V. 2007. Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. *Eur J Neurosci*. 25:1874–1881.
- Sirotnin YB, Das A. 2009. Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity. *Nature*. 457:475–480.
- Szucs D, Soltesz F, Jarmi E, Csepe V. 2007. The speed of magnitude processing and executive functions in controlled and automatic number comparison in children: an electro-encephalography study. *Behav Brain Funct*. 3:23.
- Turconi E, Jemel B, Rossion B, Seron X. 2004. Electrophysiological evidence for differential processing of numerical quantity and order in humans. *Cogn Brain Res*. 21:22–38.
- Tzelgov J, Ganor-Stern D. 2004. Automaticity in processing ordinal information. In: Campbell JID, editor. *Handbook of mathematical cognition*. New York: Psychology Press. p. 55–67.
- Van Opstal F, Gevers W, De Moor W, Verguts T. 2008. Dissecting the symbolic distance effect: comparison and priming effects in numerical and non-numerical orders. *Psychon Bull Rev*. 15:419–425.

- Verguts T, Fias W. 2004. Representation of number in animals and humans: a neural model. *J Cogn Neurosci*. 16:1493-1504.
- Verguts T, Van Opstal F. 2005. Dissociation of the distance effect and size effect in one-digit numbers. *Psychon Bull Rev*. 12:925-930.
- von Aster MG, Shalev RS. 2007. Number development and developmental dyscalculia. *Dev Med Child Neurol*. 49:868-873.
- Wagenmakers E-J, van der Maas HLJ, Grasman RPPP. 2007. An EZ-diffusion model for response time and accuracy. *Psychon Bull Rev*. 14:3-22.
- Walsh V. 2003a. A theory of magnitude: common cortical metrics of time, space and quantity. *Trends Cogn Sci*. 7:483-488.
- Walsh V. 2003b. Time: the back-door of perception. *Trends Cogn Sci*. 7:335-338.
- Walsh V, Cowey A. 2000. Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci*. 1:73-79.
- Walsh V, Pascual-Leone A. 2003. Transcranial magnetic stimulation: a neurochronometric of mind. Cambridge (MA): MIT Press.
- Wiese H. 2003. Iconic and non-iconic stages in number development: the role of language. *Trends Cogn Sci*. 7:385-390.
- Wilson AJ, Revkin SK, Cohen D, Cohen L, Dehaene S. 2006. An open trial assessment of "The Number Race," an adaptive computer game for remediation of dyscalculia. *Behav Brain Funct*. 2:20.
- Zilles K, Eickhoff S, Palmero-Gallagher N. 2003. The human parietal cortex: a novel approach to its architectonic mapping. In: Siegel AM, Andersen RA, Freund H-J, Spencer DD, editors. *The parietal lobes*. New York: Lippincott Williams & Wilkins.