

Research Report

Hemispheric lateralization of number comparison

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Abstract

In order to clarify the respective contribution of the right and left posterior parietal cortex (PPC) to number comparison, transcranial magnetic stimulation (TMS) was used to disrupt PPC processing in subjects instructed to determine whether a digit was smaller or larger than 5. Single pulse TMS was applied over the PPC, either unilaterally or bilaterally, 150, 200, or 250 ms after digit presentation. Sham TMS was used as a control condition to take into account the unspecific effects of TMS on reaction time (RT). The main finding of the present study is a significant increase in RTs when comparing digits close to 5 following a disruption either of the left PPC alone or of both PPC simultaneously. The comparison of digits far from 5 was unaltered by disrupting only one PPC but RTs were found increased after bilateral PPC stimulation. These disruptive effects were observed irrespective of the TMS delay. We concluded that coding precise numerical values requires the integrity of the left PPC, as suggested by the deficit in discriminating close digits consequent to its disruption. In contrast, approximate comparisons can be processed either by the left or right PPC, since simultaneous bilateral TMS was needed to alter the comparison of digits far from 5.

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1. Introduction

The current view about number processing in the brain is that information relative to number magnitude is accessible to both hemispheres [12]. However, a closer look to the literature reveals a large number of discrepancies. In particular, assuming that both hemispheres do indeed participate in the coding of number magnitude, it is unclear whether their respective contribution is unique or redundant. In this introduction, we will review previous results about the lateralization of number processing, with a particular attention to number comparison which is directly related to the representation of number magnitude.

The first studies on hemispheric lateralization of number processing have shown that patients with callosal lesions remained able to identify [18] and to compare Arabic digits presented either in the left or the right visual field [5,48]. In one patient, the ability to access number magnitude from either visual field was confirmed by the presence of a distance effect in a comparison task, i.e., discrimination between two digits improves as the numerical distance between them increases [4]. In such patients, simple mathematical operations were possible only when digits were presented in the right visual field, presumably because arithmetic requires processes only accessible by the left hemisphere [19].

Neuropsychological studies on number processing and calculation have also led to the conclusion that numerical deficits are more frequently observed following left than

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right lesions. Indeed, the Gerstmann syndrome, which consists of left–right confusion, finger agnosia, agraphia, and acalculia, is known to arise from left parietal lesions [20]. However, the impairment in processing number magnitude varies so widely among such patients that the respective contribution of both hemispheres remains unclear. Indeed, the study of a few patients with a Gerstmann syndrome has suggested that the integrity of the left parietal cortex is a necessary condition for number magnitude processing since the intact right hemisphere appeared unable to compensate for the dramatic effects of the left parietal lesion on calculation and number comparison [3,26,27]. In contrast, other studies have failed to show a deficit in the access of number magnitude in patients with left parietal lesions [9,13,52], suggesting that the right hemisphere may perform some magnitude processing. In some cases, left lesions led to impaired retrieval of arithmetical facts whereas magnitude processing was found unaffected [9,10]. Such a dissociation supports the existence of an independent left-lateralized system for simple arithmetic. Direct evidence in favor of a right hemisphere contribution to number magnitude processing can be found in group studies but, again, the numerical deficits were less frequent and less severe after right than left lesions [25,28,42].

In healthy subjects, Ratnckx and colleagues performed a series of lateralized visual field experiments based on the numerical distance effect to investigate the distinct contribution of each hemisphere to number processing [38,39]. In brief, a target number was displayed in one visual field, simultaneously with a distractor number in the other field. Subjects were asked to compare the target number with a fixed reference and to ignore the distractor. These studies showed that responses were faster when both the target and distractor were numerically close to each other, suggesting that their magnitude was processed in parallel by each hemisphere. Similar conclusions have been reached from a priming experiment where both the prime and target numbers were presented in the same visual field [40]. It was found that the numerical distance between the prime and target modified the priming effect to the same extent in each visual field suggesting comparable abilities for number magnitude processing in both hemispheres.

Brain imaging techniques have contributed to corroborate the key role played by the PPC in number processing [12]. Regarding the possible lateralization of the PPC activity, results are also confusing. Whereas some studies have shown that the comparison of Arabic digits mainly activated the left hemisphere [32,53], others have concluded to an equal contribution of both hemispheres [37] or to a right hemisphere dominance [2,7]. Arithmetical tasks usually lead to a strong left dominance [14,56], although increased activity in the right PPC was found during approximation of addition results [50]. Finally, both hemispheres are involved in the quantification of non-verbal material, like dot enumeration [33,34], sometimes with a right dominance [46].

Though brain imaging studies give a picture of the regions involved in processing number magnitude, inferences on the causal relationship between the activity of these regions and the cognitive processes under investigation are better made from lesion data. However, this approach is limited by the compensatory mechanisms occurring after a cerebral injury. Transcranial magnetic stimulation (TMS) has been shown to overcome this difficulty by inducing a transient virtual lesion in healthy subjects while performing a given task [54]. Göbel and colleagues [21] evidenced an increased RT when TMS was applied over the angular gyrus during the comparison of two-digit numbers to 65. Interestingly, the RT increase following left angular stimulation was specific to numbers close to and larger than 65, whereas a trend for a more general effect was observed after right angular stimulation. Sandrini and colleagues [45] found that TMS applied over the left supramarginal gyrus slowed down RTs when subjects were asked to select the largest digit among a pair whereas the right supramarginal gyrus stimulation had no effect. Finally, in six patients tested before a left tumor removal, electrical stimulation of inferior parietal areas generated deficits reminiscent of the symptoms of the Gerstmann syndrome [43].

The present study aimed at determining the relative contribution of the left and right PPC during the comparison of single digits to a fixed reference. The experiment included two conditions with unilateral TMS (left or right) and one with bilateral simultaneous TMS (left and right). Based on functional imaging data, bilateral TMS over the PPC should slow down RTs during number comparison. Predictions about the hemispheric lateralization of number comparison can be made in reference to the disruptive effects of unilateral TMS. Under the assumption that number comparison is performed by the left PPC, unilateral left TMS should induce an RT increase comparable to bilateral TMS, whereas no deficit should be elicited by unilateral right TMS. The opposite results are predicted if number comparison is right-lateralized. In contrast, an absence of impairment after unilateral TMS would indicate that each hemisphere can process number magnitude without the other's contribution, so that only bilateral TMS is likely to alter the subject's performance. Finally, an RT increase in both unilateral conditions would suggest that the left and right PPC play a specific role in number comparison, meaning that each hemisphere processes number distinctively.

2. Materials and methods

2.1. Subjects

Fifteen right-handed subjects (9 females; range of age: 21–28 years) gave their informed consent to participate in this experiment. None had any history of central nervous

system disease or of mathematical disabilities. In particular, all of them were negative for the risk factors associated with TMS [23]. The TMS protocol was approved by the ethical committee of the Université catholique de Louvain.

2.2. TMS protocol

TMS was delivered through two figure-of-eight coils, with 7 cm diameter windings, connected to separate stimulators (Magstim model 200; Magstim, UK). TMS intensity was set at 130% of the motor threshold, defined as the minimum intensity required to generate 5 out of 10 visible finger movements when TMS was applied over the contralateral hand area. There was no significant difference between the motor threshold of both hemispheres (average motor threshold and SD in the left and right hemispheres: $46.2 \pm 7.7\%$ and $45.4 \pm 9.4\%$ of the maximum stimulator output, respectively). Each coil was held by a mechanical arm, over the targeted area, with the handle pointing downwards and forming an angle of 90° with the sagittal midline. In the unilateral conditions, single pulse TMS was applied over one hemisphere. For bilateral PPC stimulation, the two coils were made to discharge simultaneously. Sham TMS was chosen as a control condition because it allowed us to discard unspecific TMS effects by reproducing the coil noise. To achieve sham TMS in the present experiment, a coil was placed on the sagittal midline, resting on the edge of the wings so that the magnetic field was not directed towards the brain tissue.

TMS was delivered 150, 200, or 250 ms after stimulus onset. The selection of three different interstimulus intervals (ISIs) aimed at increasing the probability to interfere with number magnitude processing in the parietal cortex. Indeed, event-related potential (ERP) experiments have shown that the semantic processing of Arabic digits in the parietal cortex occurred between about 170 and 240 ms after stimulus onset, with a peak activity at 200 ms [7,37,53].

Stimulation sites were selected in reference to the 10–5 EEG system [31]. The reference points P3–P4 were marked on the participant's scalp. Previous studies have shown that these sites are located in the PPC, along the IPS [22,44]. This location was confirmed in 3 participants whose anatomical MRI was available. The co-registration between TMS site and anatomical MRI proceeded in three steps [30]. First, the coordinates of about 200 points distributed randomly on the participant's scalp, in the physical space, were obtained using a digitized pen receiver connected to a forehead reference allowing for head movements (Polhemus Isotrak II system, Kaiser Aerospace Inc.). Second, the registration process created a transformation matrix that minimized the mean square distance between these points and a segmented scalp surface extracted from the MRI. Third, the figure-of-eight coil was placed over the target sites P3 and P4; three points were digitized at the intersection of the windings and converted within the transformation matrix; the position of the coil relative to

the scalp was then indicated through the visualization interface. A normal to the plane of the coil was drawn from its center to the brain, revealing the cortical impact point of TMS both on a segmented brain surface and on the MRI slices. This flexible method allows the visualization of the target sites on individual brain images with a spatial accuracy close to the millimeter. In the present study, the results of the TMS–MRI co-registration in 3 participants indicated that TMS on P3–P4 targeted the posterior part of the IPS (see Fig. 1). Increased activity in this region has been frequently reported during number comparison [32,36,37].

2.3. Stimuli and procedure

Arabic digits (Arial 48; vertical and horizontal visual angle: 1.2° and 0.5 to 0.8°) ranging from 1 to 9 (except 5) were displayed, on a 17-in. computer screen, in white on a black background. Participants were asked to press a button with the left index finger when digits were smaller than 5 and another button with the right index when it was larger. The stimulus remained on the screen till the participant responded. Interval between trials was 3000 ms. A personal computer Pentium III (Windows 98) was used to control the display of the stimuli. The presentation was designed by Superlab and a response box allowed the recording of the RT to the near millisecond. Stimulus onset and TMS occurrence were synchronized by the means of a CIO–DIO 24-card interface (Cedrus, USA).

Before the TMS session, participants performed 4 series of 32 trials and received a feedback after each of the first 3 blocks. They were asked to answer faster if the mean RT was higher than 500 ms and slower if the error rate was higher than 10%. All the participants reached the criteria after the fourth block. These data were not further analyzed given that they were biased by the experimenter's feedback. Such a practice was used in a previous study to align the subjects on the same level of performance [7].

The TMS session was divided into four blocks of 96 trials corresponding to the four TMS conditions (unilateral left TMS, unilateral right TMS, bilateral TMS, and sham TMS). Within a given block, all digits were presented 12 times in a pseudorandom order and TMS was delivered 150, 200, or 250 ms after stimulus onset with an equal proportion of occurrence for the 3 ISIs. Digit presentation and ISI were thus randomized in each block, with the double constraint that the same digit could not be presented twice in a row and the same response could not be produced on more than 3 consecutive trials. The order of TMS conditions was counterbalanced across participants, following a Latin square design.

2.4. Data analysis

Error trials were discarded from the analyses, as well as trials with an RT falling outside the range of the individual

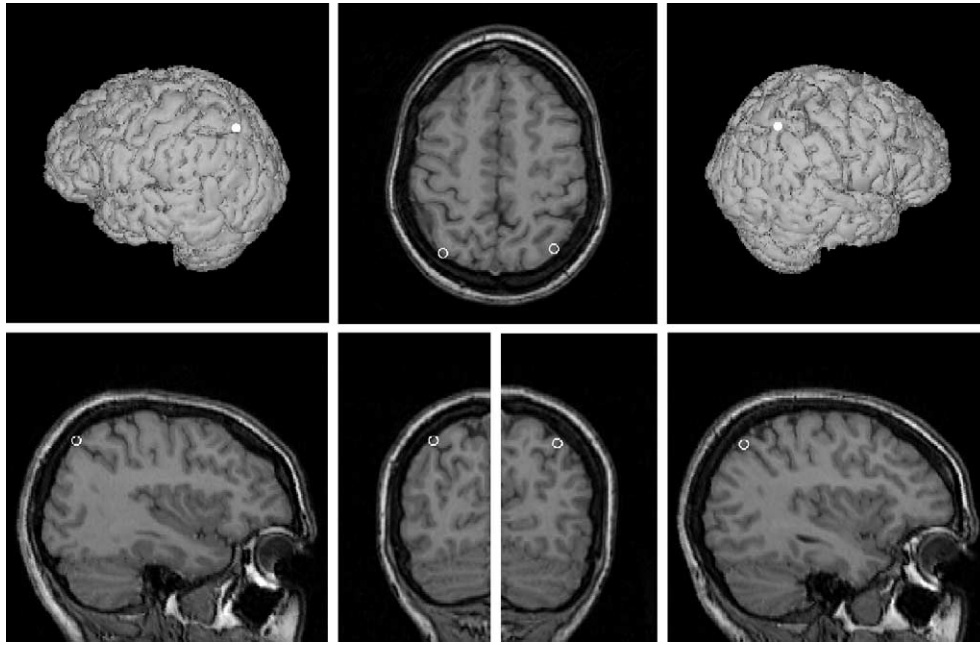


Fig. 1. Location of the target sites on reconstructed brain surfaces and IRM slices in a representative subject. The left panels refer to the left hemisphere and the right panels to the right hemisphere. On the central panels, the axial and coronal views are oriented in the same way, following the neurological conventions. Circles show the putative stimulation point of TMS in the posterior part of the IPS.

mean RT $\pm$ 2 SD. On the remaining trials (92% of the data), RTs were averaged for each combination of TMS condition (bilateral, unilateral left, unilateral right, sham), ISI (150, 200, or 250 ms), response type (smaller or larger), and numerical distance to the standard 5 (close or far). The data for far digits (1, 2, 8, 9) were pooled together, as well as for close digits (3, 4, 6, 7), in order to increase the power of the statistical analyses. The mean RTs were entered in an analysis of variance (ANOVA) for repeated measures. Post hoc comparisons were made using Tukey *t* tests ($\alpha < .05$) and linear contrasts reflecting our predictions.

3. Results

The practice session proved successful in reducing the inter-subject variability; indeed, over the whole TMS session, individual mean RT ranged from 344 to 490 ms (mean and SD: 414 ± 102 ms) and error rate from 0.26 to 5.99% (mean and SD: $3.58 \pm 1.6\%$).

The ANOVA on correct RTs revealed a main effect of numerical distance with respect to 5 [$F(1,14) = 45.56$, $P < .001$, $.90 < Pw < 1$], indicating longer RTs for close digits than for far ones (411 ± 55 vs. 395 ± 47 ms). A marginal effect of response type was also found [$F(1,14) = 3.85$, $P < .07$, $.40 < Pw < .50$], suggesting that RTs for digits smaller than 5 were longer than those for larger digits (407 ± 55 vs. 399 ± 49 ms). These two effects were integrated in a two-way interaction as illustrated in Fig. 2 [$F(1,14) = 15.10$, $P < .002$, $.90 < Pw < 1$]: when close to 5, smaller digits yielded longer RTs than larger ones (418 ± 57 vs. 404 ± 53 ms) whereas no difference in RT appeared between smaller and

larger digits far from 5 (396 ± 50 vs. 393 ± 44 ms). However, the distance effect remained significant when both responses were considered separately.

The timing of the TMS interference was also found to influence RTs [$F(3,42) = 3.60$, $P < .021$, $.70 < Pw < .80$]. Actually, responses got slower as the ISI increased (ISI 150: 399 ± 49 ; ISI 200: 403 ± 52 ; ISI 250: 407 ± 53 ms). Importantly, the ISI effect did not interact with TMS condition or with any other variable ($F_s \leq 1$): the slowing was similar across all stimulus categories, whether the stimulation was real or sham.

Moreover, a main effect of TMS condition [$F(3,42) = 3.60$, $P < .021$, $.70 < Pw < .80$] indicated that RTs increased significantly after bilateral and unilateral left TMS (412 ± 58 and 407 ± 51 ms, respectively) compared to right and sham TMS (394 ± 47 and 399 ± 49 ms, respectively). However, this effect interacted with the numerical distance [$F(3,42) = 4.42$, $P < .009$, $.80 < Pw < .90$]. As illustrated in Fig. 3,

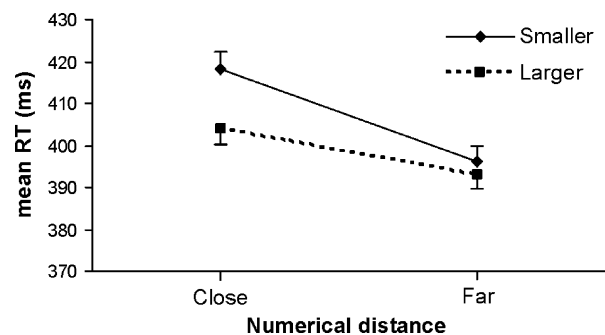


Fig. 2. Mean RT (± 1 SE) as a function of numerical distance and response type.

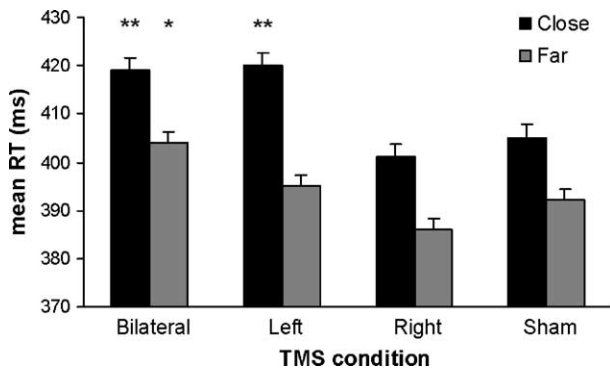


Fig. 3. Mean RT (± 1 SE) in each TMS condition, separately for the digits close to and far from the standard. Asterisks signal the TMS conditions where the RT was significantly increased compared with the control condition (* $P < .01$, ** $P < .001$).

responses to far digits were significantly slower after bilateral TMS when compared with all other conditions (bilateral: 404 ± 51 ; left: 395 ± 45 ; right: 386 ± 44 ; sham: 392 ± 48 ms), whereas both bilateral and unilateral left TMS slowed down the responses to close digits relative to right and sham TMS (bilateral: 419 ± 64 ; left: 420 ± 54 ; right: 401 ± 50 ; sham: 405 ± 50 ms). The disruptive effect of bilateral and left TMS on the processing of close digits was confirmed by the linear contrast opposing these conditions to right and sham TMS [$F(1,14) = 6.89$, $P < .02$, $.60 < Pw < .70$]. Other planned contrasts on the effects of unilateral and bilateral TMS in close digit comparison were not significant ($F_s \leq 1$). For far digits, the results were better explained by the contrast of bilateral TMS against the three other conditions [$F(1,14) = 5.32$, $P < .037$, $.50 < Pw < .60$] than by the contrast opposing bilateral and left TMS to right and sham stimulation [$F(1,14) = 3.14$, $P < .1$, $.30 < Pw < .40$]. All other interactions related to TMS condition were not significant ($F_s \leq 1$).

4. Discussion

The main conclusion of the present experiment is that the left and right PPC play a distinct role in number comparison depending on the numerical distance with respect to the standard. Indeed, we found a significant RT increase when comparing close digits after disrupting either the left PPC alone or both PPC simultaneously, whereas the comparison of digits far from 5 was slowed down only when disrupting the activity of both PPC simultaneously.

The interaction between TMS condition and numerical distance suggested that TMS impaired selectively the processing of number magnitude. Direct interference of the motor response was ruled out since the TMS-induced deficit in number comparison was identical when the right or left hand was used to provide the response. Disruption of perceptual processes involved in digit identification is also unlikely to have hampered the interpretation of the left–right asymmetry we found because split brain studies [4,18]

and lateralized visual field experiments [38,39] indicated that the ability to identify Arabic digits was identical in both hemispheres.

The timing of TMS did not affect the performance, except for a shortening of RTs as the delay between digit presentation and TMS decreased, probably because of an unspecific effect of TMS. Such an intersensory facilitation has been consistently reported in TMS studies [41,47] and refers to the finding that RTs decrease because of the close occurrence of a visual stimulus and the noise generated by the coil, irrespective of its position on the scalp [51]. Although the absence of trials without TMS makes it difficult to interpret the unspecific shortening of RTs in the present study, this shortening is congruent with the time course of intersensory facilitation reported in the literature. Indeed, facilitation was found inversely proportional to the delay between the visual stimulus and coil noise [51].

Finally, our results replicated the classical numerical distance effect: overall RTs were larger when the comparison involved digits close to rather than far from the standard [7,29]. The distance effect is generally interpreted as reflecting the access to an internal magnitude representation where the activation associated to one quantity partially overlaps with the activation associated to neighboring quantities, which explains that close digit comparison is more difficult. Moreover, our internal representation of magnitude is assumed to be compressed on the side of large values. As a result, during the comparison to a fixed standard, the classification of the digits in the middle of the continuum is biased towards the larger response because they appear subjectively closer to the larger extremity than to the smaller one [6,11]. This internal compression accounts for the observed asymmetry between smaller and larger digits close to the standard.

The present study indicates that the left hemisphere is necessary for fine digit discrimination, whereas the need to disrupt the activity of both PPC simultaneously to affect the comparison of far digits suggests that each hemisphere is able to perform the task by itself. These observations are consistent with the results of previous TMS studies showing that left angular TMS induced an RT increase in the range of numbers close to and larger than the standard whereas the effects of right angular TMS were found less disruptive and less specific [21]. In addition, the comparison of digit pairs has been shown to be altered by left supramarginal TMS and the RT increase was almost twice larger for close than for far digits, although statistical analyses failed to reveal a significant interaction between TMS and numerical distance [45].

A differential involvement of the left and right PPC in number comparison was also suggested by Pinel and colleagues who showed that the left PPC was more active during the comparison of digits close to than far from 5 whereas numerical distance had an opposite effect on the right PPC activity [36]. Moreover, magnitude judgement on a triplet of digits recruited preferentially the left PPC with

little contribution of the right hemisphere [32]. Finally, the number size effect in exact additions was found to rely on a left-lateralized network that includes the IPS areas [50].

The assumption that the left hemisphere plays a special role in coding precise numerical values could account for the dramatic effects of left parietal lesions on calculation and number processing [3,26,28]. Actually, even in left brain-lesioned patients in whom residual abilities were reported in number comparison, performance in other magnitude-related tasks was rarely accurate [9,13]. The absence of deficit after unilateral right TMS disagrees with the hypothesis that the right parietal cortex is necessary for number comparison, as suggested by some functional imaging studies [2,7]. We rather suggest that the numerical competence of the right hemisphere is limited to approximate numerical judgements.

The present results are not incompatible with the view that both hemispheres are endowed with a basic system for number discrimination, which would be available early in the development, ratio-limited, cross-modal, and present in other species [8,16,17]. However, our results highlight the dominance of the left PPC in adults while making precise numerical judgements. Further researches are necessary to explain how the numerical representations of the left and right hemispheres differentiate during the development. In particular, it is not clear whether the greater precision of the left PPC is due to qualitative or quantitative differences between both PPC. In a recent fMRI study, brain activation was estimated in response to numerosity changes after habituation [35]. When a deviant numerosity was presented to adult subjects, the BOLD signal in the PPC increased as a function of the ratio between the deviant and the habituated numerosity. Interestingly, the response curve was steeper in the left than in the right PPC, meaning that the left PPC was more sensitive to the variations of the ratio than the right PPC.

Along these lines, the low probability to observe deficits after right parietal cortex lesion or TMS disruption can be explained by the fact that the basic knowledge of the right hemisphere is contained in the numerical representations of the left hemisphere. Because approximate relations between numbers can be processed either by the left or right hemisphere, bilateral TMS is necessary to disrupt the comparison of far digits. However, it could be argued that longer RTs were observed after bilateral TMS because a double pulse was used as opposed to a single pulse in other conditions. Although we cannot exclude that the behavioral effect of bilateral TMS resulted from a stronger, but unspecific, neuronal interference, this appears very unlikely given the large body of evidence supporting a bilateral PPC contribution to number comparison [4,40,48]. In any case, this possible limitation does not dispute the main finding of a left PPC dominance for the comparison of close digits.

What could explain the left hemisphere advantage in finer discrimination of number magnitude? It has been suggested that our basic numerical knowledge evolves to a

systematic numerical thinking via counting strategies [15,49]. In particular, the combined use of fingers and counting words facilitates the assignment of a number to empirical objects [1]. Moreover, the merging of counting and language makes it possible to associate relations between numbers with relations between objects and to transfer these properties to various symbolic representations (e.g., Arabic numerals) [55]. Language abilities as well as the coordination of finger movements develop under the control of the left hemisphere in most right-handed people [24]. Therefore, we suggest that the numerical representations of the left hemisphere may become more accurate because of a specialization in the processing of discrete entities by the means of finger and verbal counting.

In conclusion, the present experiment highlights the role of the left PPC in close digit comparison. We propose that the numerical competence of the left hemisphere gained in precision through the local development of cerebral circuits devoted to finger and verbal counting. The absence of deficit following TMS over the right PPC indicates that this region is not crucial for number comparison. Its contribution seems to be limited to approximate comparisons and is not unique given that the processing of far digits is also accessible to the left PPC. Future research should thus consider the accuracy required in numerical judgements as a possible factor of hemispheric lateralization.

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