CHAPTER

11

Neglect "Around the Clock": Dissociating Number and Spatial Neglect in Right Brain Damage

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Summary

Since the seminal observation of the SNARC effect by Dehaene, Bossini, and Giraux [(1993) *Journal of Experimental Psychology: General*, 122(3), 371–396] several studies have indicated the existence of an intrinsic-automatic spatial coding of number magnitudes. In the first part of this chapter we summarize recent work with healthy participants and expand on this original claim. Some of our evidence can be used to support a theory of spatial mapping of mental numbers onto mental space where smaller numbers are associated with the left and larger numbers with the right side of space. In the second part of the chapter we review investigations of spatial neglect and relate them to "small number neglect", which initially seemed to provide crucial support for a tight link between mechanisms of spatial attentional orienting and

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the mental manipulation of number magnitudes [Zorzi *et al.* (2002). *Nature* 417, 138–139]. We will see that although left unilateral neglect after right-brain damage can occur in both visual and number space, recent behavioral dissociations, controlled studies and neuroanatomical correlations have consistently confirmed the functional dissociation of these two deficits and the absence of a causal effect of lateralized spatial–attentional impairments on numerical cognition. Finally, based on recent data gathered from experiments specifically designed to generate a mismatch in the "default" association of small numbers with the left side of space and large numbers with the right side of space, we argue that the pathological deviation toward larger numbers shown by right-brain-damaged patients in the bisection of number intervals may not arise from a basic spatial–attentional impairment. Taken together, these findings suggest that to assume a close phenomenological, functional and anatomical equivalence between orienting in visual space and orienting in representational number space could be partially misleading. It is concluded that careful reassessment of empirical evidence and consideration of the combined contributions of sensorimotor, conceptual, and working memory factors to mathematical cognition may provide a more coherent understanding of the adaptive interaction between spatial and mathematical thought.

In their seminal study, Dehaene, Bossini, and Giraux [1] described behavioral evidence for spatially oriented number lines in normal subjects. When asked to classify a single digit as being odd or even by pressing on one of two buttons, subjects reacted faster to smaller numbers with the left hand and more quickly to larger numbers with the right hand. Interestingly this effect could be reversed by crossing hands, showing that it is spatially based. Dehaene *et al.* [1] termed this effect the SNARC effect, standing for spatial numerical association of response codes. This effect reflects an automatic activation of number magnitude even when it is task-irrelevant (for reviews, see [2,3]). After briefly reviewing some of the work that enlarges on this phenomenon in the healthy brain, this chapter will examine the link between number and the spatial biases observed in spatial neglect. We will see that a number of studies agree about the co-occurrence of these two intriguing deficits in neglect, further evoking the existence of a default association between left–right and small–large. In addition, we will describe more recent studies that all confirm the absence of a causal link between the two deficits.

NUMBER–SPACE ASSOCIATION IN THE HEALTHY BRAIN

Three main questions have been addressed since Dehaene's pioneering study. First, the SNARC effect may depend on relative number magnitude and can be found with other ordinal dimensions (see beautiful data on this issue in Chapter 10 of this volume). Experiments examining this issue with a similar paradigm found that the ordinal information for both months and letters is spatially organized [4,5] (see also Chapter 10 of this volume). In addition, further investigations showed that this number–space link could be expanded to other dimensions such as time (e.g., see the introduction to this book by Stan Dehaene, Chapter 20 of this volume, and [6–9]).

The second main issue addressed in this field concerns the neuroanatomical correlates of the number–space association. Specifically, is this effect the result of shared resources or simply the result of anatomical vicinity? Brain imaging [2], lesion studies [10], and brain stimulation (e.g., [11]) experiments have addressed this intriguing question. Some of the results provided at the end of this chapter will address this issue.

Third, the origin of this left–right association to small–large numbers was investigated. In Western subjects, the left–right oriented number line seems to be like a default representation in that it can be altered if a different reference frame is introduced. Bächtold *et al.* [12] designed a very interesting number comparison experiment (involving deciding whether a target number is larger or smaller than the number 6) that could be performed in two ways. They elegantly showed that responses to digits 1–5 were faster with the left hand when the format reference, although only mental, was a ruler, while responses to the same digits were faster with the right hand when the mental reference was a clock face. A contrasting pattern of results was found for numbers larger than the reference number 6. This result suggested that the default left-to-right format of the mental number line is subject to contextual modifications.

In an elegantly simple experiment using a task derived from neglect examination, Fischer [13] reported data further supporting the fact that the left–right oriented number line seems to be the dominant default representation in European subjects. First, when subjects were asked to bisect long digit strings (e.g., 111…11 vs 999…99) with a pencil, they demonstrated a systematic pattern of results, i.e. small digits induced a left-bias in the bisection task whereas larger digits induced a right-bias. This effect was obtained [14] with lines made up of digit names expressed in letters (DEUX…DEUX *vs* NEUF…NEUF, which stand for TWO…TWO *vs* NINE…NINE in French) (Fig. 11.1A) and also applied even when the letter string was presented in mirror orientation (Fig. 11.1B). These experiments further support the hypothesis of an automatic association between numerical magnitude information and spatial response codes in the healthy brain. Interestingly, interactions between number and space are sensitive to cultural factors (see also Chapter 20 of this volume), as was indirectly suggested by Dehaene *et al*. [1]. Building on the effect of numbers on line bisection, we investigated manual bisection performed by French and Moroccan medical students with lines made up of Roman or Arabic letters representing small and large digits (Fig. 11.1C). The results obtained with French students on Roman letters replicated the findings of Calabria and Rossetti [14]. The French students did not show a significant effect on the Arabic version of the task. Even though the Moroccan students had been learning French since elementary school, had used it extensively at school, and their courses were conducted 100% in French (i.e. they can be considered as bilingual), their pattern of results was clearly different. When bisecting Arabic letter strings, they showed a bias towards the *right* for the *smaller* number, which suggests that their spatial–numerical association was different from that of the French students. In addition, they surprisingly showed no significant bias for the Roman letter stimuli.

Beyond its cultural and contextual aspects, the association between number and space appears to be quite robust. When it was compared to another obvious reference frame in which numbers are encoded using fingers [15,16], the spatial association was stronger than the finger association [17] (Fig. 11.2). In order to test this issue we used a corporeal modality, by investigating the attentional effects induced by numbers on the perception of touches delivered to fingers. When the right hand was in the palm-down position,

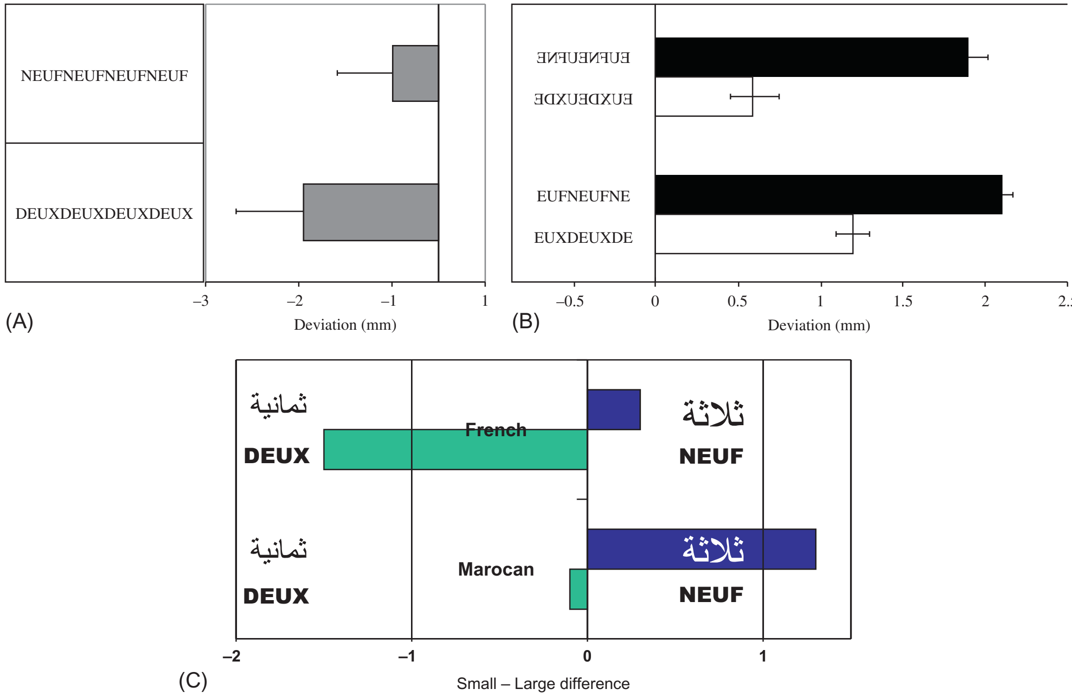


FIGURE 11.1 Number-line bisection. Building on Fischer *et al*. [13], bisection of lines consisting of letter strings was investigated. The string lines could be composed of letters making up the word "DEUX" or "NEUF" (Two and Nine in French, chosen for their resemblance). Bisections obtained for the higher number were biased to the right of the ones made for the smaller number and this held true whether the letter strings were oriented canonically (A) or in mirror image presentation (B), suggesting that direction of writing did not affect the numerical bias. In contrast, when bilingual Moroccan students were compared to non-bilingual French students on letter strings made up of Arabic characters [ثلاثة (thalatha) and ثمانية (thamania)], i.e. 3 and 8, again chosen to maximize resemblance) their bisections were biased towards the left for the larger number (C). This was not observed when Roman letter strings were used. This comparison emphasizes the importance of the role of reading direction for the native language as compared to current reading direction during the test. A and B adapted from [14].

subjects' detection of brief tactile stimuli applied to the little finger improved as a function of the preceding number magnitude. The opposite pattern of results was found when the same little finger was stimulated with the hand in the palm-up posture. In this condition, subjects' tactile performances actually decreased as the preceding number increased (see Fig. 11.2A, yellow panels). Results for the thumb mirrored those for the little finger (see Fig. 11.2A, blue panels). The spatial cueing effect arising in the external space coordinates was present irrespective of the emphasis in the instructions either concerning fingers (Fig. 11.2B: "you will feel a touch on either the thumb or the little finger") or side of space (Fig. 11.2C: "you will feel a touch on either the left or right side of your hand"). A similar modulation was indeed present in both manipulations. We thus found that the numerical cueing of touch does not follow a number–finger association, but a number–space association, akin to the mental number line. By using an embodied approach based on tactile perception, this study not only showed that number-based attentional cueing crosses sensory modalities but also demonstrated that number-based tactile priming is mapped early in life

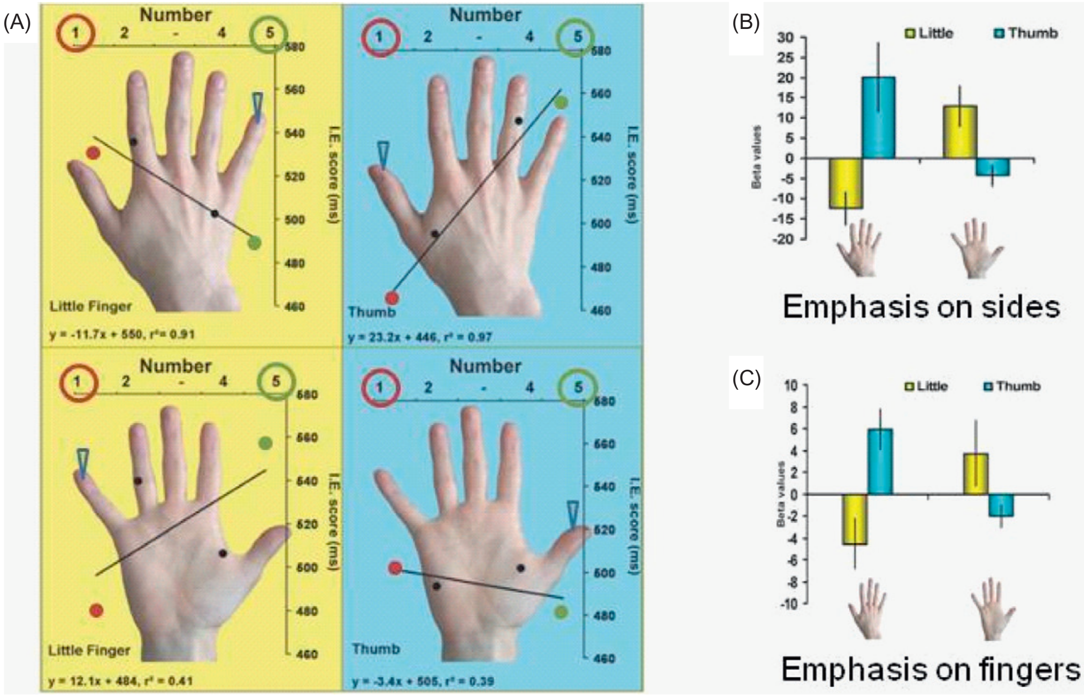


FIGURE 11.2 A conflict between space-based and finger-based representations of numbers. In this study, we investigated which spatial representation is dominant in the human brain: an embodied representation of numbers, arising from the finger-digit association common in Western European countries (thumb for digit 1 and little finger for digit 5) or a disembodied representation of numbers along the mental number line, in ascending order from left to right. (A) The tactile modality allowed us, through a simple postural manipulation of the hand (palm-up *vs* palm-down) to contrast the embodied and disembodied representations of numbers. A further manipulation was introduced to avoid any left–right arrangement in the response space, possible confounding of previous studies in the event they encouraged a space-based representation of numbers, and any motor bias in the response effector, that might favor a finger-based representation: subjects were asked to respond to tactile stimulation by pressing a centrally located pedal with one foot. Participants were thus requested to perform a simple tactile detection task by making speeded foot-pedal responses to a tactile stimulus delivered to either the thumb or the little finger of their right (preferred and counting) hands. When the right hand was in the palm-down position, subjects' detection of brief tactile stimuli applied to the little finger improved as a function of the preceding number magnitude. The larger the number, the better the performance in terms of an inverse efficiency (IE) score, jointly indexing accuracy, and response latency. The opposite pattern of results was found when the same little finger was stimulated with the hand in the palm-up posture. (B, C) Yellow bars: for stimuli applied to the little finger, a difference was apparent between the slopes of IE regression lines in the palm-down and palm-up positions (-4.55 *vs* $+3.70$, respectively; $P < 0.05$); blue bars: the opposite pattern for the stimuli applied on the thumb ($+5.94$ *vs* -2.04 for the palm-down and palm-up postures, respectively). Adapted from [17].

according to an extra-personal spatial representation, thus providing compelling support for the dominant role played by the spatial representation of numbers known as the "mental number line".

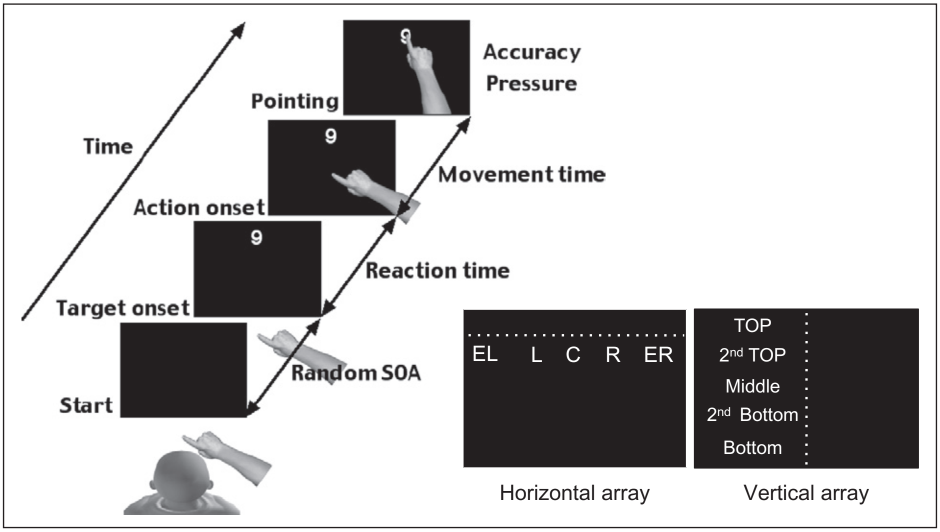
Now a crucial question surrounding the SNARC and its related effects is whether the left–right space association to small–large numbers supports the concept of a mental number line (Box 11.1; see also [18]). In most of the empirical data available, associations

BOX 11.1

EVIDENCE FOR CONTINUOUS MAPPING BETWEEN NUMBER AND SPACE

This experiment aimed at testing whether healthy individuals would automatically match number magnitude with spatial location in a continuous manner [19]. It had been previously shown that numbers can affect implicit parameters of motor control [64], but as for the SNARC paradigm, it remained difficult to ascribe the observed effects to a continuous mapping or to a simple categorization (see also [18]).

Participants were instructed to make a parity judgment to digits appearing on a touch screen. In each trial, they were asked to point at the odd numbers whilst ignoring the even numbers. Their motor task thus consisted of pointing to a given numeric

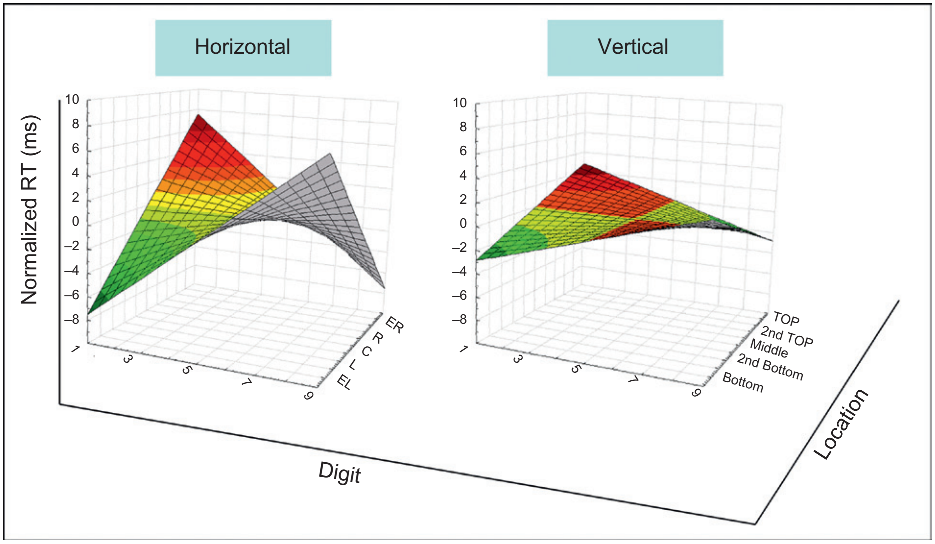


BOX 11.1 FIGURE 1 Method. A schematic representation of the experimental procedure. A numeric stimulus (either an odd number: 1, 3, 5, 7 or 9, or an even number: 2, 4, 6, or 8) was presented as the target at one of five horizontal locations [extreme left (EL), left (L), center (C), right (R), extreme right (ER)] on a touch screen. Participants (n = 12) were asked to point to the target by quickly moving their right index finger from the starting position to the target as soon as it appeared, but only when the target was an odd number (GO). They were asked to hold their finger on the starting position when the target was an even number (NO-GO). This instruction was used in order to ensure that the participants accessed semantic and not only topographic information from the number target. Reaction times were measured from the onset of the visual target until the release of the index finger from the starting position. The diagram shows an example of the target (No. 9) which appears at the "C" location. In a vertical pointing experiment (n = 10), procedures and stimuli in the experiment were identical to those used in horizontal number pointing except that the target was presented at one of five vertical locations (bottom, 2nd from the bottom, middle, 2nd from the top, top) on the screen.

BOX 11.1 *(cont'd)*

target (1, 3, 5, 7, or 9) as quickly and accurately as possible by moving their right index finger from the starting position. In the horizontal condition [19] the five target locations were organized along a horizontal array at the top of the touch panel. In the vertical condition [7] in each trial the target was presented at one of five vertical locations on the screen.

In the horizontal condition, analyses on pointing reaction times revealed a pure number magnitude effect with faster processing for smaller numbers (compared to larger numbers) at each of five individual target locations. The magnitude effect suggests that digits are represented on a unidimensional scale. A classical position effect was also obtained (see [65]). More interestingly, analyses revealed an interaction between number magnitude and position. In the horizontal condition, participants automatically and implicitly associated smaller numbers



BOX 11.1 FIGURE 2 **Results.** The normalized reaction times representing "continuous" space–number mapping for the horizontal alignment of visual stimuli (left panel, derived from [19]) and for the vertical alignment of visual stimuli (right panel) [7]. Since the pointing action was executed in response to digits at different target locations, pointing reaction times include a variable motor preparation component needed for executing the pointing movement to each target (i.e. location effect). Additionally, pointing reaction times were modulated by number magnitudes (i.e. magnitude effect). To eliminate such influences from the reaction times and to look at a pure number-space congruent/incongruent effect without location and number magnitude influences, normalized reaction times were calculated. The curved surface was fitted to the resulted normalized reaction times by the least-squares method (see [19] for details). The space–number association for the vertical array of stimuli appeared to be weaker compared to the horizontal array. These findings demonstrate that in the vertical axis a facilitatory effect resulting from the number–space congruity is not as strong as for the horizontal array of stimuli.

BOX 11.1 *(cont'd)*

(i.e. numbers 1 and 3) with leftward locations and larger numbers (i.e. numbers 7 and 9) with rightward locations. In addition, the digit No. 5 induced the shortest processing time when it was presented in the central location (see [19]). These results suggest that horizontal space–number mapping is performed parametrically across the relative locations of the target in a given visual work space, which provides direct evidence for a continuous mapping between numbers and locations rather than for a simple left–right categorization.

In the vertical condition, a very similar simple magnitude effect was obtained. A marginally significant interaction between space and number was obtained with the vertical array. Normalized reaction time values obtained for digits 1 and 9 tended to be minimal when they were presented in the congruent location (i.e. Bottom and Top, respectively) and slightly increased when they were presented in the incongruent location (i.e. Top and Bottom, respectively). The comparison of normalized reaction times variation between horizontal and vertical arrays reveals that the space–number association is obviously much weaker for the vertical arrayed stimuli than for horizontal stimuli. This suggests that, at least in European subjects, the default and dominant spatial mapping used for number is a horizontal line on which numbers increase from left to right.

have been investigated in a categorical manner, i.e. by testing the association in a discrete way (left *vs* right, space, left *vs* right hand, small *vs* large numbers, …). In an attempt to investigate the existence of a *continuous* mapping of numbers and space, Ishihara *et al.* [7,19] tested for an implicit, default association of 5 digits (1, 3, 5, 7, 9) with five spatial locations. Number-targets were displayed on a touch-panel and subjects were asked to point at them when odd numbers were presented but to ignore even numbers. When the five spatial locations were arranged along a horizontal axis, subjects showed a strong interaction between digits and space, revealing a continuous mapping between number and space: RTs were relatively shorter for their implicitly mapped location, i.e. 1 on the left, 5 in the center, and 9 on the right. Interestingly, this interaction did not appear when the spatial locations were arranged vertically, unlike what has been suggested for Japanese subjects who are frequently exposed to vertical reading and writing [20]. This result provides a strong argument for an automatic, default mapping of digits onto a horizontal spatial array (see Box 11.1).

This section has concentrated on gathering arguments in support of an association between spatial and analogical numerical representations. The evidence reviewed suggests that there may be a default association between number and space that is compatible with the mental number line hypothesis. Several authors, however, challenged this view and provided alternative explanations for this phenomenological association (e.g., [18,21], and Chapter 10 in this volume). The following sections will address in more detail the supporting and challenging arguments to the space–number association hypothesis in the case of unilateral neglect.

NEGLECT IN VISUAL AND NUMBER SPACE

Right-brain-damaged patients affected by left unilateral neglect are characterized by a pathological attentional bias to the right side of space. This left-sided deficit encompasses eye and head deviations, visual, somatosensory and auditory sensory processing, action initiation and realization, and mental representations. It may affect the left side of space and/or the left side of individual objects [22]. When setting the midpoint in horizontal visual lines, patients typically shift the subjective line midpoint to the right of the objective one [23]. The combination of neglect and hemianopia makes this rightward bias more severe and can engender a significant and paradoxical leftward shift in the bisection of very short lines (the "cross-over" effect) [24,25].

In a seminal study published in 2002, Zorzi *et al.* [26] asked four right-brain-damaged (RBD) patients with left spatial neglect to mentally bisect, without calculating, 3-, 5-, 7- and 9-unit number intervals (i.e. saying what number is halfway between two orally presented numbers ; e.g., what is the midpoint between 21 and 29?). Compared with both a sample of four RBD patients without neglect and a sample of four healthy control participants, neglect patients showed a "rightward" shift towards greater numbers during the bisection of 5-, 7- and 9-unit number intervals (i.e. responses tended to be larger than the actual interval center). This shift increased as a function of interval length, as has been previously reported for physical line bisection. Three out of the four neglect patients also showed leftward "cross-over" in the bisection of short 3-unit number intervals (i.e. in this case, responses tended to be smaller than the actual interval center). These original findings seemingly provided crucial support for the idea that small numbers are automatically mapped on the left side of (representational) space and that this mapping is linked to brain mechanisms regulating the deployment of attention in space. This pioneering observation also suggested a superimposition of the networks underlying number representation and the orientation of spatial attention in the brain. This surprising aspect of neglect in the number space generated a whole new spate of research (for reviews, see [2,3,27,28]) on number representation in neglect patients [10,29–31] and neglect-like effects induced in healthy individuals (see Fig. 4 in [32]; [33]). Although this finding opened up a whole new line of enquiry into the study of the interaction between spatial and mathematical thought, the original investigation by Zorzi *et al*. [26] left a number of very relevant questions unanswered: (1) is the bisection bias in the mental number line correlated with a similar bias in the bisection of equivalent stimuli in visual space (i.e. horizontal lines)? (2) Is the bisection bias in number space positively correlated with neglect severity? (3) Is the bisection bias in number space caused by damage of the same cortical areas and subcortical white matter pathways whose damage provokes spatial neglect [34–36]? Since spatial neglect is a heterogenous syndrome, and since different visual, exploratory and representational/working memory features of the syndrome can impinge on different sectors of the right hemispheric parietal–frontal network regulating spatial attention [34–36], is the disruption of one of these anatomical–functional components responsible for the "rightward" shift in the bisection of number intervals ?

These points were specifically addressed in a study by Doricchi *et al*. [10]. Based on evidence showing important variations in performance on the line bisection test by neglect patients which suggests that left homonymous hemianopia accompanied by spatial neglect, increases both the rightward bias for the bisection of long horizontal lines and the leftward bias (i.e. "cross-over") for the bisection of very short lines, Doricchi and co-workers investigated bisection biases for visual and number space in a group of 11 RBD patients with neglect and in 5 RBD patients without neglect. Neglect patients population manifested a clear cut double dissociation. Some of the patients displayed very severe neglect on the bisection of visual lines and normal performance for the bisection of number intervals (i.e. comparable to that of controls). In contrast, other neglect patients showed the opposite trend, i.e. a strong rightward bias for the bisection of number intervals and performance on line bisection that fell within the range of the entire sample of patients included in the study. Correlational analyses confirmed the absence of any significant relationship between the rightward bias for the bisection of number intervals and measures of neglect severity. This was also true for the paradoxical leftward "cross-over" in the bisection of very short horizontal lines (i.e. 2cm): in fact, this had no significant correlation with any equivalent effect in the bisection of the shortest number intervals (i.e. 3 units). The analysis of the anatomical correlates of the number interval bisection task revealed that the subcortical–cortical lesion of the prefrontal, rather than parietal, module of the network that underlies number processing in monkeys and humans was involved [37,38]. This finding led to the examination of patients' working memory. In the experimental sample, neglect patients who showed a "rightward shift" in the bisection of number intervals had the most severe spatial working memory impairments (i.e. Corsi span). Although the number of patients involved was relatively small, this latter finding suggested that the main pathological reason for the rightward bias in the bisection of number intervals lay in the patients' inability to construct or retain an active representation of the initial part of the number intervals on the mental number line.

Recently, a single-case study by van Dijck *et al*. [39] (for a full theoretical discussion and development of the role of working memory in number cognition see Chapter 10 of this volume) shed new light on this hypothesis. This work documents a striking behavioral dissociation by a left-brain-damaged patient suffering from right-sided neglect for extra-personal and representational space and left-sided neglect on the mental number line. A complete neuropsychological examination revealed that the apparent left-sided neglect in the bisection of number intervals was purely non-spatial in origin and was based on a poor memory for the initial items of verbal sequences presented visually at a fixed position in space. These findings clarify the possible role of working memory in the bisection of the mental number line, showing that effective position-based verbal working memory may be crucial for numerical tasks that are usually thought to involve purely spatial representations of numerical magnitudes.

Consistent double-dissociations between visual neglect and neglect in number space have been reported by other authors. For example, the two patients studied by Rossetti *et al*. [30] whose performance improved on the number interval bisection task after prism-adaptation showed no sign of neglect on the line bisection test. Loetscher and Brugger [40] and Loetscher *et al*. [41] demonstrated that patients with clearcut left spatial neglect on conventional line bisection or cancellation tasks display no lateral bias for the bisection of number intervals, on random number generation tasks or when asked to pick six lottery ticket numbers within the range 1–45.

The issue concerning the dissociation between lateral spatial biases in the bisection of visual lines and number intervals was recently re-assessed by Doricchi *et al*. [42] in an extended sample of 43 RBD patients (22 with and 21 without neglect) and 31 age-matched controls. This study explored whether the position of a number interval of a given length within a decade on the mental number line had any influence on the size and direction

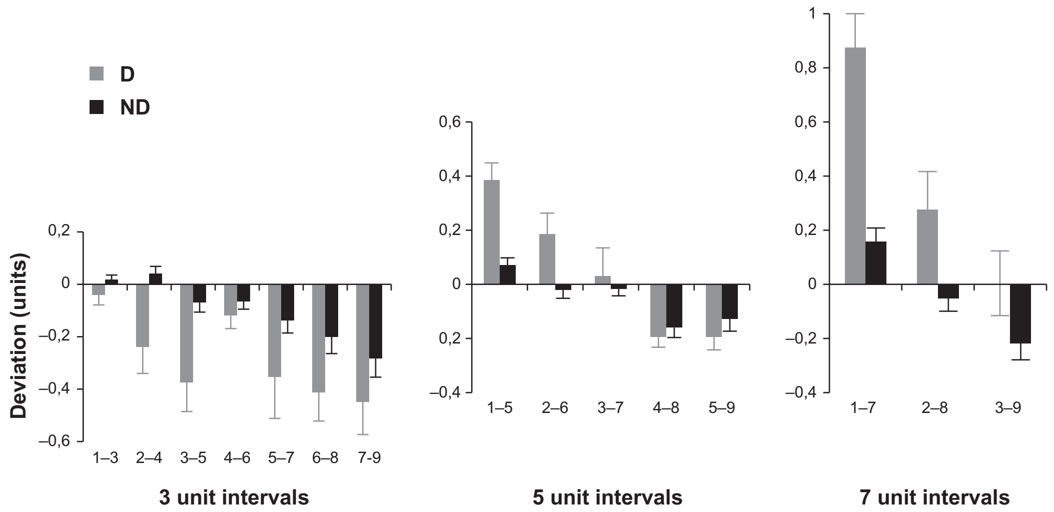


FIGURE 11.3 Bisection of number intervals as a function of their position within a decade. Bisection of 3-, 5- and 7-unit number intervals as a function of their position within a decade, in RBD and healthy elderly controls demonstrating significant rightward deviation (Deviating participants: D) and in RBD patients and healthy elderly controls showing no deviation (Non-Deviating participants: ND; modified from [42]). Positive values indicate rightward deviation and negative values leftward deviation from the objective midpoint (0 value on y-axis). For each interval, deviation is averaged from the bisection of intervals occupying the same position within the first three decades (e.g. deviation for the interval "1–7" corresponds to the average deviation across intervals "1–7", "11–17" and "21–27").

of the bisection error. As an example, the 7-unit interval "1–7" is positioned on the initial "left" part of the decade whereas the equivalent 7-unit interval "3–9" is positioned on the end "right" part of the decade: does this difference in interval position have an influence on bisection behavior? For large, 7-unit intervals a centripetal deviation toward the center of the decades was found in the bisection error: intervals were erroneously bisected further to the right the closer they were to the left starting point of a decade and further to the left the closer they were to the right endpoint of a decade (see Fig. 11.3). It is worth noticing that this effect was also present for intervals bridging different decades. A similar error trend was present with 5-unit intervals though here the centripetal error had shifted slightly towards the initial part of the decade. This tendency was even more pronounced with 3-unit intervals, where there was a null-error for intervals positioned on the left-side at the beginning of a decade, whereas the greater the proximity of the interval to the right-end of a decade the more the bisection error was shifted toward the left side of the interval. Interestingly, in a control study (second study in [42]) 31 healthy participants were asked to perform both the number intervals bisection task and a line bisection task, with 2-cm, 10-cm and 20-cm horizontal lines positioned in the left, central or right side of egocentric space. Whereas centripetal errors toward the center of decades were again found on the number task a centrifugal, rather than centripetal, error was observed for all line lengths on the line bisection task.

In addition to uncovering the effects of the recursive grouping of symbolic numerals within the tens on the non-symbolic spatial representation of magnitudes, this study provided confirmation of previous findings and new insights into the dissociation between neglect in visual and number space. In fact, no significant correlation was again found between neglect severity on line bisection or multiple item cancellation tasks and left side neglect in the bisection of number intervals. In contrast, neglect for number intervals correlated with poor immediate recall of sequences of spatial positions (Corsi span) and digits (Digit span). Most interestingly, the use of confidence intervals calculated over the entire sample of participants allowed us to classify participants as Deviating (D: 10 neglect, 5 non-neglect, 10 elderly healthy controls) or Non-Deviating (ND: 12 neglect, 16 non-neglect, 21 elderly healthy controls) on the bisection of number intervals. This showed that a number of healthy elderly participants (10) actually suffered from "neglect" in the bisection of the mental number line and, most of all, that the distribution of bisection errors as a function of interval position within a decade was different for D participants compared to ND participants (see Fig. 11.3**).** With 7- and 5-unit intervals, D showed enhanced rightward deviation in the bisection of number intervals located toward the "left" starting point of decades and made few or no errors with intervals located toward the right endpoint of decades. With 3-unit intervals the progressively increasing "leftward" bisection error for intervals located closer to the "right" end of the decade was greater for D than for ND participants. The study of anatomical correlates confirmed the role of prefrontal–frontal damage in number interval bisection and the well-known role of the inferior parietal lobe and the underlying parietal–frontal connections in neglect and line bisection [34–36,43,44].

The increasing rightward error displayed by D participants in the bisection of large 7-unit interval located to "left" side of decades offers another example of the apparent similarity between bisection behavior in visual and number space: in fact, it is well known that the pathological rightward shift in the bisection of long horizontal lines increases in patients with left spatial neglect as the egocentric position of lines moves leftward (i.e. toward the contralesional neglected space) [23]. However, repeated observation of no significant relationship between the extent of neglect and rightward shift in the bisection of number intervals clearly emphasizes the fact that phenomenological similarities in behavior can be misleading and do not necessarily imply functional or neuroanatomical equivalence. To further clarify this point, we reanalyzed line bisection and number interval bisection performance and, crucially, their correlation on a larger sample of RBD patients. This sample was obtained by merging the sample of 74 patients studied over several years by one of the authors of the present chapter (F. Doricchi) with a sample of 12 patients examined by Wim Fias and co-workers (unpublished data). No correlations between line and number interval bisection were found either in the entire sample (see Fig. 11.4C: Pearson's r = 0.09, $P = 0.36$) or in the subsamples of patients with (see Fig. 11.5C: Pearson's r = 0.1, $P = 0.52$) and without spatial neglect (see Fig. 11.6C: Pearson's r = 0.03, $P = 0.8$). To summarize, these findings clearly point towards the absence of a causal link between the pathological deviation of attention in visual space and the deviation toward higher numbers in the bisection of number intervals observed in RBD patients

Finally, it should be noted that Knops *et al*. [46] in a recent fMRI study using a multivariate approach for the analysis of the BOLD signal, showed that in the superior parietal lobes of the two hemispheres there are populations of neurons that are specifically activated by non-symbolic/symbolic subtraction and by the planning of leftward saccades and populations that are activated by non-symbolic/symbolic addition and by the planning of rightward saccades. Although the study suggests a link between saccadic programing and

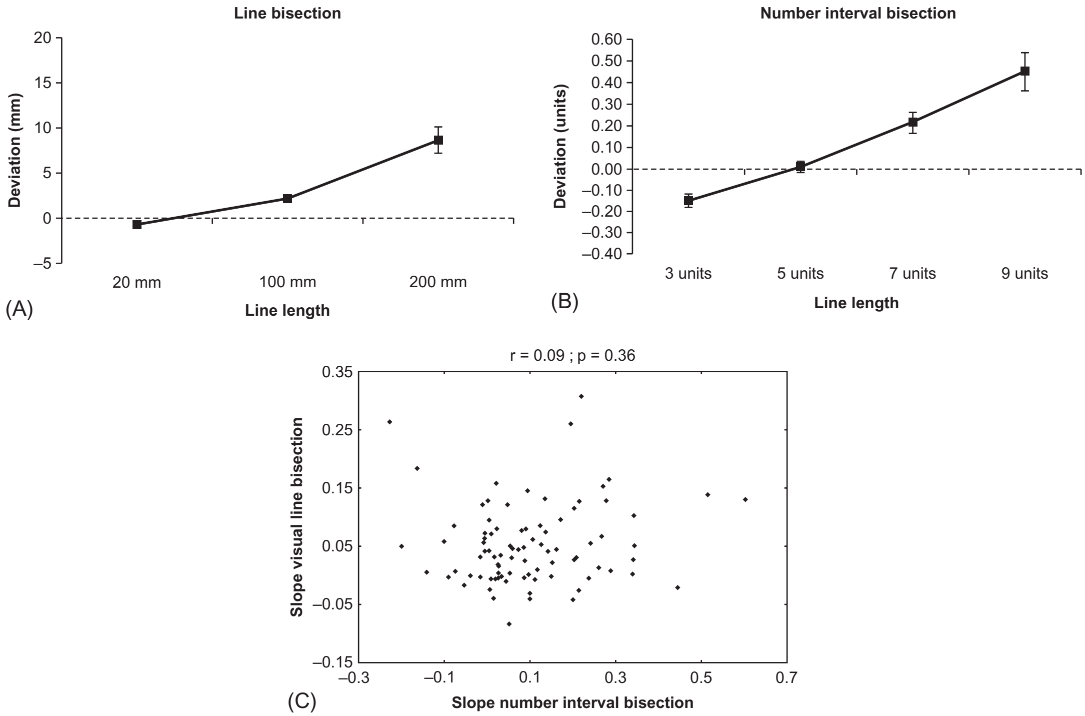


FIGURE 11.4 Line bisection and number interval bisection in right brain damage: patients with and without left spatial neglect (unpublished data by Doricchi and Fias). Bisection of visual horizontal lines and number intervals in a sample of 86 RBD patients (42 with left spatial neglect and 44 without neglect on the bisection of 200-mm lines. The cut off score, i.e. +6.5 mm, is based on a sample of 206 RBD patients studied by Azouvi *et al.* [45]. (A) Bisection of horizontal visual lines (length: 20, 100 and 200 mm). (B) Bisection of number intervals (size: 3-, 5-, 7- and 9-unit). In both (A) and (B) positive values indicate rightward deviation and negative values leftward deviation from the objective midpoint (0 value on y-axis); vertical bars indicate S.E. (C) Correlation between individual slopes describing the bisection deviation as a function of the length visual lines and the length of number intervals.

orienting in number-operational space, it leaves the issue of the hemispheric lateralization of the subtraction/addition neuron populations unresolved. Similarly, it would be very interesting to study whether left *vs* right brain damage can engender specific disruptions in addition *vs* subtraction abilities and associated, or dissociated, impairments in leftward *vs* rightward orienting.

A FURTHER TWIST TO NUMBER SPACE NEGLECT: BISECTING “AROUND THE CLOCK”

The clinical observation of number biases in patients with unilateral neglect is extremely easy and is done frequently. Following the studies of Zorzi *et al.* [26], Bächtold *et al.* [12], and Vuilleumier *et al.* [31], we had the opportunity to study a sub-population of selected neglect

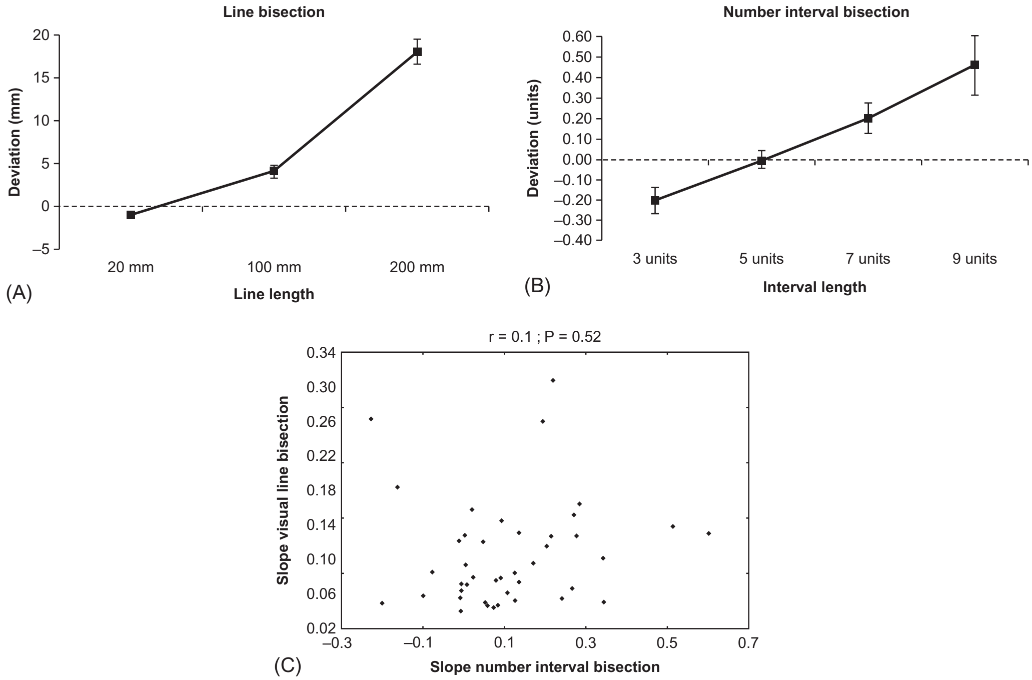


FIGURE 11.5 Line bisection and number interval bisection in right brain damage: patients with left spatial neglect (unpublished data by Doricchi and Fias). Bisection of horizontal visual lines and number intervals in the sample including 42 RBD patients with left spatial neglect. Panels (A), (B) and (C): same legend as Fig. 11.4.

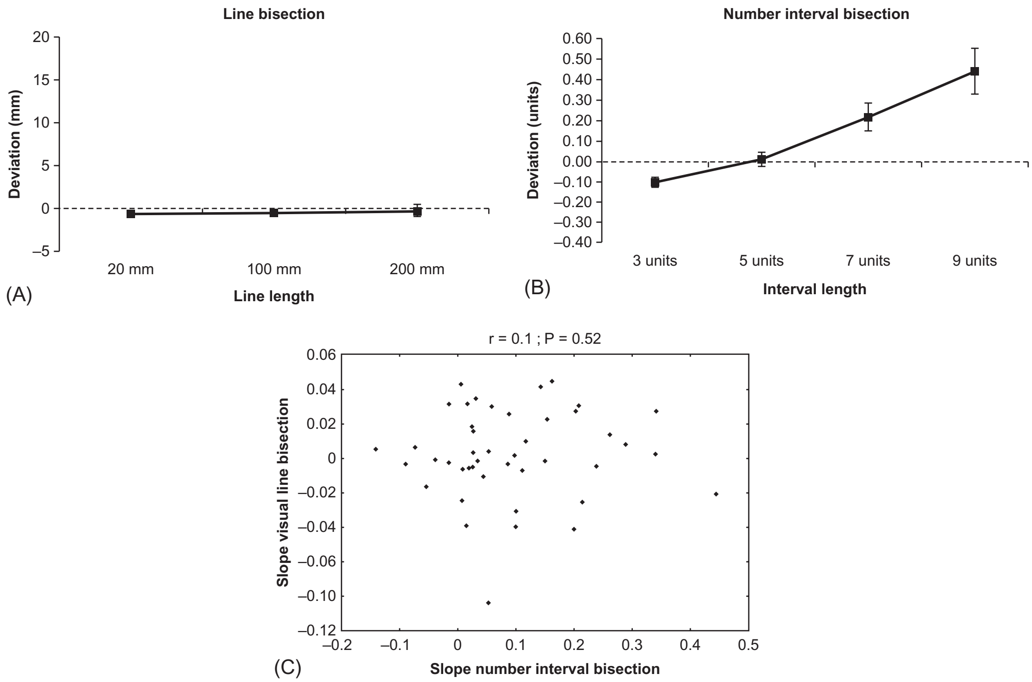


FIGURE 11.6 Line bisection and number interval bisection in right brain damage: patients without left spatial neglect (unpublished data by Doricchi and Fias). Bisection of horizontal visual lines and number intervals in the sample pertaining to 44 RBD patients without left spatial neglect. Panels (A), (B) and (C): same legend as Fig. 11.4.

patients who exhibited a peculiar behavior pattern when asked to perform the classical clock drawing task, where patients have to fill in the numbers on an empty clock face [47]. These patients all started with number 12, as most subjects do, but then used numbers ranging from 13 to 23 instead of the correct numbers ranging from 2 to 11 (see Fig. 11.7B–D). Even if it is common in France to refer to p.m. times as numbers greater than 12, numbers on all clock faces are always less than 13. We hypothesized that this pattern reflected a strong numerical bias towards larger numbers and systematically investigated five of these patients with a set of clock drawing tasks. Interestingly, only some of them exhibited spatial neglect on their clock drawings while the others placed them (the wrong numbers) at their appropriate virtual locations, suggesting a loose association between spatial and numerical deficits. Strikingly, when they were provided with an empty clock face containing a single numerical landmark (3, 6 or 9, at their canonical locations), their drawings included numbers higher than the landmark going up to 23 or 24 (Fig. 11.7E–G). Furthermore, some of them now revealed right spatial neglect: they frequently left an empty space between 12 and 3, or even more strikingly between 6 and 12. These tasks thus suggest that the patients were unable to activate numbers lower than the landmark. In the absence of a landmark, they thus used 12 as the default landmark and wrote larger numbers on the clock face. We conjectured that an impairment prevented patients from moving towards smaller numbers on their mental number line. As a matter of fact, the move from 12 to 1 during the normal drawing of a clock face requires a large jump towards smaller numbers on the mental number line; and when our patients ended their drawing with number 24, the jump to 1 was even greater. To investigate their ability to move towards smaller numbers, we asked them to draw clock faces counterclockwise (as in [48]). Surprisingly all patients were able to use correct numbers ranging from 12 to 1 when they performed counterclockwise. Starting with 12, all patients could count down to 1 and the spatial pattern of results described by Grossi was frequently observed, i.e. some patients placed numbers from 12 to 1 using only the left side of the clock face, while others used the entire clock space (Fig. 11.7H,I). This implies that their left-sided neglect was turned into a right-sided neglect on this particular test, showing a further dissociation between spatial and numerical performance. In addition, their ability to use the correct numbers proved that their previous pattern of results cannot be attributed to a general cognitive deficit. Improved competence on the counterclockwise versions would appear to indicate that these patients had preserved the capacity to move from the landmark to smaller numbers, but only if the size of the step was sufficiently small (i.e. 1 and not 11). Alternatively, it can be conjectured that moving spatially to the left from 12 was congruent with moving towards smaller numbers on the patients' mental number line, whereas in the first version of the task the requested jump from 12 to 1 was associated with a spatial movement to the right. In addition to these tasks, patients were also tested with empty clock faces including only the number 1 (Fig. 11.7J). Three of the patients made a very striking response: they started by adding 12 to the clock face, and then added a 3 next to the pre-existing 1 in order to transform it into 13 or 15, thus demonstrating the influence of the dominant landmark 12 even in its absence! This peculiar response can also be observed when more than one landmark is provided on the clock face, e.g., 12 and 1 (Fig. 11.7K), 12, 3, 6, and 9 (Fig. 11.7L) or even 12, 1, 2, and 3 (Fig. 7M).

The advantage of using the representation of a clock face to study number and space processing in brain damaged patients was originally demonstrated in an elegant study by

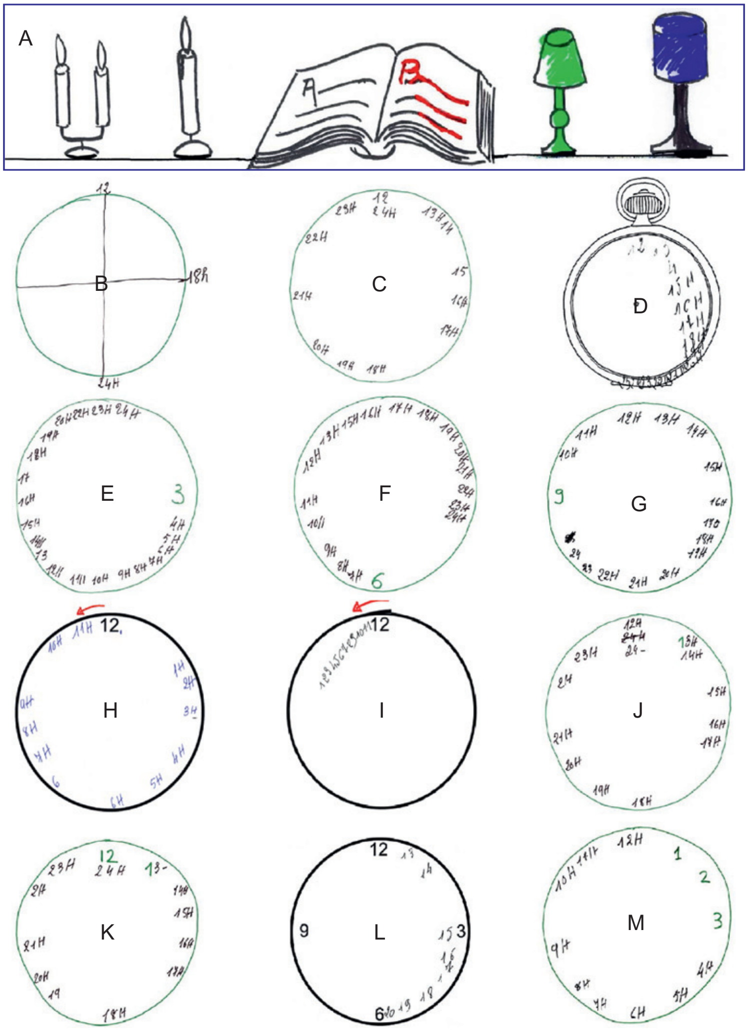


FIGURE 11.7 Clock drawings made by neglect patients. (A) Characteristic coloring made by a patient with left neglect. Not only is the left side of the original drawing omitted, but the left side of individual items is also missing. (B–D) A simple clock face test where numbers below 12 are omitted. (E–G) The clock face test performed with one pre-marked landmark number (3, 6, and 9). The patient systematically omits the numbers that are less than the landmark, giving rise to an apparent right neglect in the first two cases. (H,I) Counter-clockwise filling of the clock face showing that the number aspect of the task is improved whilst the spatial aspect may indicate right neglect. (J–M) Drawings with pre-marked landmarks that are either transformed or ignored by the patient. It is only when the three first numbers are indicated (M) that the patient can draw a correct clock face. From [47].

Vuilleumier *et al*. [31]. In the first experiment, RBD patients with and without contralesional neglect were required to press a key on the right when a target number was greater than a reference number (e.g., 5) and a left-hand one when the target was smaller. Results showed slower reaction times for the number “4” (the closest to the reference, on the neglected side) compared to other higher numbers. When the reference number was set at 7, the highest increase in reaction time was found for "6". These results showed that the time required to activate a number representation in neglect was systematically increased when the number was smaller than the reference value, whereas control subjects displayed a symmetrical increase on both sides of the reference. This result suggested that neglect patients are unable to activate smaller numbers on the left side of the mental number line. In an ensuing experiment, the authors also demonstrated that when asked to classify numbers as indicating hours earlier or later than six o'clock, neglect patients provided slower responses to numbers larger than "6", i.e. to numbers located on the left side of the clock face. Very interestingly, the study by Vuilleumier and co-workers suggests that comparing the performance of neglect patients in the bisection of number intervals with their performance in the "o'clock" task reveals whether the bias toward higher numbers in the bisection of number intervals is due to a pathological ipsilesional attention bias or whether it is due to a faulty representation of small magnitudes. In the first case, in fact, patients should display a congruent spatial bias in the two imagery tasks, i.e. bisection deviated toward higher numbers on the right side of number intervals and better performance with small time-hours located on the right side of the clock face. In contrast, a non-attentional deficit in the representation of small magnitudes should predict incongruent spatial biases on the two tasks, i.e. bisection deviated toward higher numbers on the right side of number intervals and better performance with high time-numbers on the left side of the clock face.

This line of reasoning constituted the rationale behind two complementary investigations that were independently run by Rossetti, Jacquin-Courtois and co-workers in Lyon and by Doricchi, Aiello and co-workers in Rome. These two studies are now merged into a single scientific communication [49,50]. It is worth noting that, unlike the investigation by Vuilleumier *et al.* [31], none of these studies adopted a SNARC-like paradigm requiring the explicit left *vs* right mapping of the (motor) response. As detailed below, these two studies provide convergent findings that are different from those that assess the coding of numbers on a clock face with a SNARC-like paradigm.

Just as it is possible to test number line bisection for letter strings vs mirror letter strings, it is possible to create a mismatch between the spatial and the mental number line reference frame in unilateral neglect. Jacquin-Courtois and Rossetti compared two mental number bisection tasks in a group of RBD patients with left spatial neglect (Fig. 11.8). In the clock version of the task, patients were seated in front of a large clock face made up of a circle and 12 numbers (diameter 145 mm, printed in the center of an A4 page). They were then asked to bisect pairs of numbers provided orally, in such a way that each pair corresponded to a horizontal or vertical line on the clock (e.g., 2 and 5, 7 and 23, 3 and 9, 4 and 8). As time numbers between 0 and 24 are currently used in France, we also included pairs with numbers higher than 12 (e.g., 15 to 21, 10 and 14). The crucial feature of the task was that bisections could be performed vertically on either the left or the right half of the clock face (e.g., 13 and 17 *vs* 19 and 23), and horizontally from left to right or right to left (e.g., 3 and 9 *vs* 9 to 15). In this task, the instructions given to the patient used an explicit reference to time around the clock, e.g., "what is midway between 1 o'clock and 5 o'clock?". The second bisection task, performed first, was similar to the classical number bisection task, and included all the same pairs of numbers to bisect, but it was performed without the clock face and in the classical way (e.g., what is midway between 3 and 9?). In both tasks,

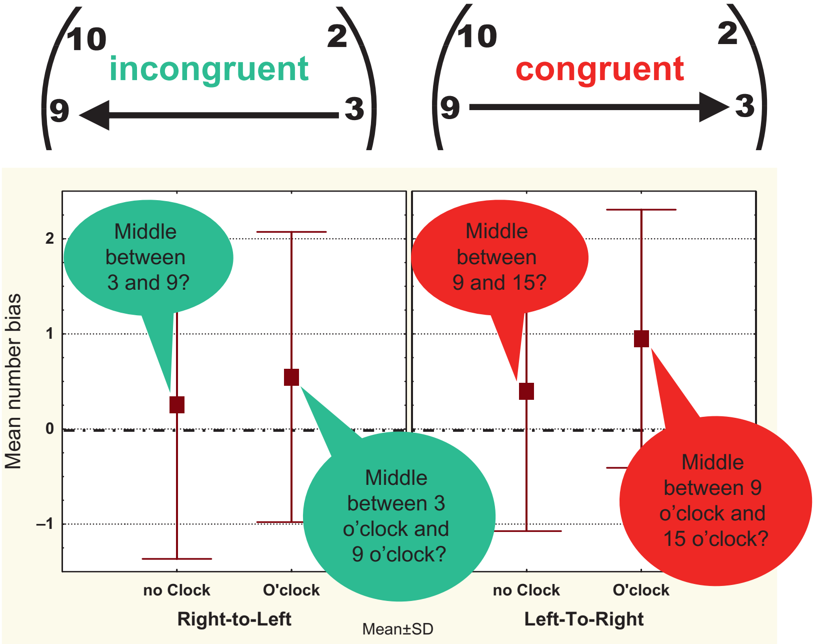


FIGURE 11.8 Number bisection around the clock. This experiment used two versions of the number bisection task. In addition to the classical version, an o'clock version was designed in which the task was performed in front of a large clock face and the question asked was, for example, "where is the middle between 3 o'clock and 9 o'clock". In each of these conditions two types of number pair that corresponded either to left-to-right or to right-to-left comparisons in the o'clock version were used. The left-to-right version is referred to as the congruent version, because both left-spatial neglect and small number neglect rightly predicted a bias towards larger numbers. In the right-to-left version, incongruent predictions resulted from the left spatial neglect and the small number neglect hypotheses: left neglect predicted that bisection responses should be biased to smaller numbers in the o'clock version whereas small number neglect should give rise to similar biases for the classical and the o'clock versions. The means (±SEM) for the neglect patient group displayed in this figure show that o'clock bisection responses were not biased towards smaller numbers. This clearly shows that spatial neglect cannot provide an explanation for the constant over-estimation of bisection responses.

emphasis was put on avoiding arithmetic calculations and preferably estimating the central number. Our main prediction was that if number bisections are processed on the basis of the spatial reference frame, patients' answers to right-to-left intervals should be biased toward smaller numbers in the clock version and biased towards larger numbers in the classical version. Two main results were obtained in this experiment. First, there was no significant difference between the horizontal bisections performed in the two versions of the task. In fact, the bias towards larger numbers was even slightly higher in the clock version, which was clearly incompatible with the spatial reference frame hypothesis (see Fig. 11.8). Second, the result obtained for vertical line bisection did not yield significant differences between the left side and the right side of the clock face. The main outcome of this study is that the spatial constraints imposed by the clock version of the number bisection task did not interfere in the expected way, i.e. there was no evidence of a spatial read-out of the numbers. This experiment, therefore, confirmed that the spatial bias and the numerical bias observed in spatial neglect cannot be assumed to depend on a single basic pathophysiological deficit.

In parallel, Doricchi, Aiello and co-workers considered that although neglect for the left side of number intervals is not systematically related to neglect for the left side of space, one can still assume that neglect in mental number space is only a special case of "imagery" neglect and that, as such, its occurrence can be independent of visual neglect (as in the case of clinical observations pioneered by Guariglia *et al*. [51]). This hypothesis suggested a systematic investigation of the relationship between neglect in mental number space and neglect for the left side of mental visual images. One consolidated instrument for the assessment of imagery neglect is the "o'clock" task devised by Grossi and co-workers [52]. In its original version, this task requires the mental comparison of the amplitude of two clock-hand angles indicating different times within the right or left half of the clock face. Typically, neglect patients have more difficulty comparing clock-hands' angles on the left side of the clock face. The correlation between neglect in the bisection of number intervals and imagery neglect in the "o'clock" task was assessed in 16 RBD patients with neglect and 21 RBD controls without neglect. Patients were administered a standardized battery for the assessment of spatial neglect, with the Number Interval Bisection task [26] and with the "o'clock task" [52]. The evaluation of correlations between the lateral bias in the bisection of number intervals, the severity of visual neglect and the severity of representational neglect in the "o'clock" task, revealed that the rightward shift towards higher numbers in the bisection of number intervals was significantly and exclusively correlated to better performance with higher times-numbers on the left side of the clock face (Pearson's r = 0.4, $P = 0.01$ for 7-unit number intervals, Pearson's r = 0.34, $P = 0.04$ for 9-unit intervals and Pearson's r = 0.33, $P = 0.04$ for the slope describing deviation as a function of number interval length). Put in other words, impaired spatial-imagery processing of small magnitudes was present when these were mapped on both the left and the right side of a mental visual image (i.e. as in the findings by Jacquin-Courtois and Rossetti reported in Fig. 11.8). The anatomical correlates of the two imagery tasks were defined using the Voxel Lesion Symptom Mapping approach [53]. This showed (Fig. 11.9) that the "rightward" error in the bisection of number intervals resulted from cortical–subcortical frontal–prefrontal damage (as previously documented with the classical lesion subtraction approach in [10,42]) whereas the rightward bias in the "o'clock" task was linked to lesion in the ventral temporal areas that code for the inherent left and right side of visual objects (i.e. "object-centered" coordinates) [36,54,55]. To summarize, this evidence allows for two important conclusions: (1) the right hemisphere supports the representation of small numerical magnitudes, regardless of their spatial mapping on the left or the right side of a mental layout; (2) unlike a clock face, number intervals on the mental number line, and possibly the mental number line itself, are not coded as objects with an inherent left and right side.

DISCUSSION AND CONCLUSIONS

The empirical evidence that we have reviewed in this chapter sketches a coherent outline of the available knowledge on the links between spatial and mathematical thought. On

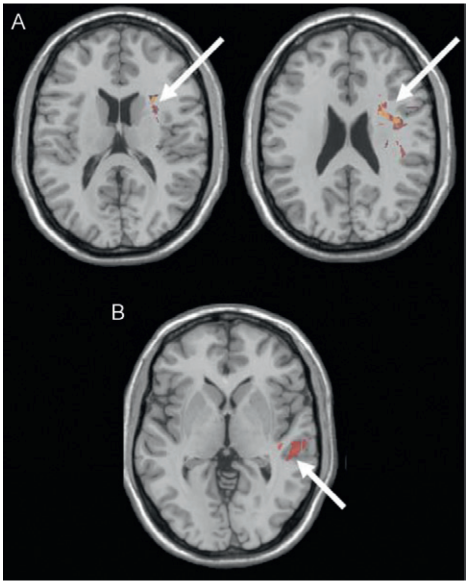


FIGURE 11.9 Anatomical correlates of the "Number Interval Bisection" and the "o'clock" tasks in right brain damage. Representative transverse slices show peaks of VLSM (Voxel Lesion Symptom Mapping) maps computed for (A) the slope describing rightward bisection deviation as a function of number interval length (Tailarach coordinates: top left: x = 28, y = 15, z = 16; top right: x = 30, y = 5, z = 24) ; (B) the rightward bias in the "o'clock" task (Talairach coordinates: x = 57, y = −24 , z = 0; modified from Aiello *et al.* [49]. Note that the cortical–subcortical ventral temporal lesion area correlated to rightward bias in the "o'clock" task corresponds to the area involved in the "object centered" coding of the left side of visual objects, described in the lesion study by Verdon *et al*. [36] and the perfusion imaging study by Medina *et al*. [54].

the one hand, a number of findings from healthy participants and the study of the effects of prism adaptation in brain damaged patients [30] seem to confirm that mathematical knowledge and sensorimotor mechanisms regulating action in space are lodged together and interact. On the other hand, evidence gathered from the study of RBD patients clearly provides no support for a causal link between deficits in the orienting of spatial attention (i.e. contralesional neglect) and phenomenologically similar deficits on tasks that assess the non-symbolic manipulation of numerical magnitudes (i.e. bisection of number intervals). Altogether these data offer a far more complex, and probably stimulating, scenario than what might be envisaged with a simple and point-to-point correspondence between brain mechanisms dedicated to the treatment of spatial attention and number magnitudes. This, on the one hand, does not mean that sensorimotor experience does not contribute to the acquisition and shaping of mathematical skills. Though, on the other hand, it clearly indicates that recycling [56] of sensorimotor networks for mathematical thought, is a complex process. This process can be enriched, in the maturing brain, by the parallel development of mechanisms that improve the voluntary planning and control of the allocation of attentional/motor resources and the development of working memory and language-based conceptual abilities. Based on this consideration, different interpretations of the dissociation between spatial–attentional and non-symbolic mathematical processing can be advanced. First, one can argue that dissociations arise because a specific task does not adequately tap the sensorimotor roots of mathematical processing: note, however, that in this case it is still assumed that, the sensorimotor component that the task fails to activate maintains its original functional properties and its full anatomical-functional integration within sensorimotor networks. Alternatively, it can be argued that dissociation between spatial and non-symbolic mathematical processing is observed because during the recycling process, the sensorimotor root of mathematical cognition ceases to be integrated into attentional–motor networks and is partially or totally blended into sensorimotor-independent networks subserving non-symbolic and/or symbolic mathematical operations.

Another point that needs careful consideration when we discuss the associations and dissociations between numerical and spatial coding that can be observed in the healthy brain is whether the influence of numerical cues on spatial processing is as strong as the reciprocal influence of spatial cues on number processing. As an example, in the paradigm devised by Fischer *et al*. [57] numerical cues presented at central fixation are spatially neutral: does this type of cue have the same effect as numerical cues presented at varying horizontal spatial positions as in the investigation by Ishihara *et al*. [19] or as in the case of line bisection [58] or number bisection tasks [59] in which number pairs are presented in a horizontal configuration with the smallest number on the spatially congruent left side or incongruent right side? This point is of relevance because spatial aspects of number representation can be sensitive to top-down control [60,61] and because the addition of an explicit spatial connotation to numerical cues may be more efficient at activating the default left-to-right organization of number magnitudes linked to reading habits and educational factors.

Although the evidence and hypotheses that we have sketched in this review do not allow for a coherent and complete understanding of number–space interaction, they offer insights into new exciting avenues of investigation. In the following paragraphs we will try to summarize a few questions that, in our opinion, should be assessed or re-assessed in future research

1. Is the spatial coding of number magnitudes linked to mechanisms regulating the automatic or the voluntary allocation of attentional resources? As an example, Fischer *et al.* [57] presented Arabic digits 1, 2 or 8, 9 at central fixation and reported observing an automatic facilitation in the detection of ensuing targets appearing to the left of fixation when these followed the presentation of small digits (1 and 2) and to the right of fixation when these followed the presentation of higher digits (8 and 9). This is usually considered as evidence for the automatic intrinsic link between number magnitude and reflexive shifts of attention. It is worth noting, however, that other authors using the same paradigm found weak facilitatory effects (i.e. around 2.5 ms, $P > 0.05$) [62] or no effect [63]. In contrast, other investigators have demonstrated that spatial–attentional facilitatory effects induced by numerical cues may crucially depend on the spatial–mental set that is voluntarily adopted by participants in the representation of numerical cues [60,61].
2. What role is played by the numerical–mental set maintained in working memory during the performance of tasks assessing the interaction between numbers and space? For example, in experiments that adopt the task devised by Fischer *et al.* [57], the use of magnitudes positioned at the extreme “left” or “right” side of a number decade (or a

fixed number range) may have favored the implicit dichotomic-conceptual recoding of cues as "left" ones (e.g., 1 and 2) or "right" ones (8 and 9), thus producing a SNARC-like effect. This "caveat" implies a number of very relevant empirical questions: Does the size of the sample of digits used as numerical cues have an influence on spatial–attentional facilitatory effects? Would facilitatory effects induced by digit-cues still be present when all the numbers in a decade are used cues? Would these effects show a continuous linear increment as a function of the progressively increasing positioning of numerical cues away from the center of a decade and towards the beginning or the end of the same decade?

To conclude, we would like to propose that current empirical evidence suggests that the assumption of a close phenomenological, functional and anatomical equivalence between orienting in number space and orienting in physical space may be untimely or, at least, partially misleading. A new look on the complex and combined contributions of sensorimotor, linguistic–conceptual, abstract–representational and working memory factors on the manipulation of number magnitudes (see also Chapter 10 in this volume) could perhaps provide a better and more coherent understanding of the adaptive and dynamic interaction between spatial and mathematical thought.

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References

[1] S. Dehaene, S. Bossini, P. Giraux, The mental representation of parity and number magnitude, J. Exp. Psychol. General 122 (3) (1993) 371–396.
[2] E.M. Hubbard, M. Piazza, P. Pinel, S. Dehaene, Interactions between number and space in parietal cortex, Nat. Rev. Neurosci. 6 (6) (2005) 435–448.
[3] G. Wood, K. Willmes, H.C. Nuerk, M.H. Fischer, On the cognitive link between space and number: a meta-analysis of the SNARC effect, Psychol. Sci. Q. 50 (2008) 489–525.
[4] W. Gevers, B. Reynvoet, W. Fias, The mental representation of ordinal sequences is spatially organized, Cognition 87 (2003) B87–B95.
[5] M. Zorzi, K. Priftis, F. Meneghello, R. Marenzi, C. Umiltà, The spatial representation of numerical and non-numerical sequences: evidence from neglect, Neuropsychologia 44 (7) (2006) 1061–1067.
[6] M. Ishihara, P.E. Keller, Y. Rossetti, W. Prinz, Horizontal spatial representations of time: evidence for the STEARC effect, Cortex 44 (2008) 454–461.
[7] M. Ishihara, Y. Rossetti, P.E. Keller, W. Prinz, Horizontal spatial representation of number and time: continuous number and categorical time lines, (2011 in press).
[8] V. Walsh, A theory of magnitude: common cortical metrics of time, space and quantity, Trends Cogn. Sci. 7 (11) (2003) 483–488.
[9] D. Bueti, V. Walsh, The parietal cortex and the representation of time, space, number and other magnitudes. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 364 (2009) 1831–1840.
[10] F. Doricchi, P. Guariglia, M. Gasparini, F. Tomaiuolo, Dissociation between physical and mental number line bisection in right hemisphere brain damage, Nat. Neurosci. 8 (12) (2005) 1663–1665.

[11] S.M. Göbel, M. Calabria, A. Farne, Y. Rossetti, Parietal rTMS distorts the mental number line: simulating 'spatial' neglect in healthy subjects, Neuropsychologia 44 (2006) 860–868.

[12] D. Bächtold, M. Baumuller, P. Bruegger, Stimulus–response compatibility in representational space, Neuropsychologia 36 (1998) 731–735.

[13] M.H. Fischer, Number processing induces spatial performance biases, Neurology 57 (5) (2001) 822–826.

[14] M. Calabria, Y. Rossetti, Interference between number processing and line bisection: a methodology, Neuropsychologia 43 (5) (2005) 779–783.

[15] G. Wood, M.H. Fischer, Numbers, space, and action—from finger counting to the mental number line and beyond, Cortex 44 (4) (2008) 353–358.

[16] F. Domahs, K. Moeller, S. Huber, K. Willmes, H.C. Nuerk, Embodied numerosity: implicit hand-based representations influence symbolic number processing across cultures, Cognition 116 (2) (2010) 251–266.

[17] C. Brozzoli, M. Ishihara, S.M. Gobel, R. Salemme, Y. Rossetti, A. Farne, Touch perception reveals the dominance of spatial over digital representation of numbers, Proc. Natl. Acad. Sci. USA. 105 (2008) 5644–5648.

[18] S. Santens, W. Gevers, The SNARC effect does not imply a mental number line, Cognition 108 (2008) 263–270.

[19] M. Ishihara, S. Jacquin-Courtois, V. Flory, R. Salemme, K. Imanaka, Y. Rossetti, Interaction between space and number representations during motor preparation in manual aiming, Neuropsychologia 44 (2006) 1009–1016.

[20] Y. Ito, T. Hatta, Spatial structure of quantitative representation of numbers: evidence from the SNARC effect, Mem. Cognit. 32 (4) (2004) 662–673.

[21] M.H. Fischer, The future of SNARC could be stark… Cortex 42(8) (2006) 1066–1068.

[22] H. Ota, T. Fujii, M. Tabuchi, K. Sato, J. Saito, A. Yamadori, Different spatial processing for stimulus-centered and body-centered representations, Neurology 60 (11) (2003) 1846–1848.

[23] T. Schenkenberg, D.C. Bradford, E.T. Ajax, Line bisection and unilateral neglect in patients with neurologic impairment, Neurology 30 (5) (1980) 509–517.

[24] F. Doricchi, P. Guariglia, F. Figliozzi, M. Silvetti, G. Bruno, M. Gasparini, Causes of cross-over in unilateral neglect: between-group comparisons, within-patient dissociations and eye movements, Brain 128 (2005) 1386–1406.

[25] S. Ishiai, Y. Koyama, K. Seky, K. Hayashi, Y. Izumi, Approaches to subjective midpoint of horizontal lines in unilateral spatial neglect, Cortex 42 (2006) 685–691.

[26] M. Zorzi, K. Priftis, C. Umilta, Brain damage: neglect disrupts the mental number line, Nature 417 (2002) 138–139.

[27] C. Umiltà, K. Priftis, M. Zorzi, The spatial representation of numbers: evidence from neglect and pseudoneglect, Exp. Brain Res. 192 (3) (2009) 561–569.

[28] S. Lacour, S. Jacquin, Y. Rossetti, Liens entre représentations spatiales et représentations numériques: apport de la négligence spatiale unilatérale et de la plasticité visuo-motrice. in: Y. Coello, S. Casalis, C. Moroni (Eds.), Vision, espace et cognition: fonctionnement normal et pathologique, Septentrion, 2004, pp. 61–72.

[29] K. Priftis, M. Zorzi, F. Meneghello, R. Marenzi, C. Umiltà, Explicit versus implicit processing of representational space in neglect: dissociations in accessing the mental number line, J. Cogn. Neurosci. 18 (4) (2006) 680–688.

[30] Y. Rossetti, S. Jacquin-Courtois, G. Rode, H. Ota, C. Michel, D. Boisson, Does action make the link between number and space representation? Visuo-manual adaptation improves number bisection in unilateral neglect, Psychol. Sci. 15 (6) (2004) 426–430.

[31] P. Vuilleumier, S. Ortigue, P. Brugger, The number space and neglect, Cortex 40 (2) (2004) 399–410.

[32] G. Rode, J. Luauté, T. Klos, S. Courtois-Jacquin, P. Revol, L. Pisella, et al., Bottom-up visuo-manual adaptation: consequences for spatial cognition, in: P. Haggard, Y. Rossetti, M. Kawato, (Eds.), Sensorimotor Foundations of Higher Cognition, Attention and Performance XXII, Oxford University Press.

[33] A.M. Loftus, M.E. Nicholls, J.B. Mattingley, J.L. Bradshaw, Left to right: representational biases for numbers and the effect of visuomotor adaptation, Cognition 107 (3) (2008) 1048–1058.

[34] P. Bartolomeo, M. Thiebaut de Schotten, F. Doricchi, Left unilateral neglect as a disconnection syndrome, Cereb. Cortex 45 (2007) 3127–3148.

[35] F. Doricchi, M.T. de Schotten, F. Tomaiuolo, P. Bartolomeo, White matter (dis) connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness, Cortex 44 (8) (2008) 983–995.

[36] V. Verdon, S. Schwartz, K.O. Lovblad, C.A. Hauer, P. Vuilleumier, Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion symptom mapping, Brain 133 (2010) 880–894.

[37] A. Nieder, E.K. Miller, A parieto-frontal network for visual numerical information in the monkey, Proc. Natl. Acad. Sci. USA. 101 (19) (2004) 7457–7462.
[38] S. Dehaene, N. Molko, L. Cohen, A.J. Wilson, Arithmetic and the brain, Curr. Opin. Neurobiol. 14 (2004) 218–224.
[39] J.P. van Dijck, W. Gevers, C. Lafosse, F. Doricchi, W. Fias, Non-spatial neglect for the mental number line, Neuropsychologia (under review).
[40] T. Loetscher, P. Brügger, Random number generation in neglect patients reveals enhanced response stereotypy, but no neglect in number space, Neuropsychologia 47 (1) (2009) 276–279.
[41] T. Loetscher, M.E. Nocholls, N.J. Towse, J.L. Bradshaw, P. Brügger, Lucky numbers: spatial neglect affects physical, but not representational, choices in a Lotto task, Cortex 46 (5) (2010) 685–690.
[42] F. Doricchi, S. Merola, M. Aiello, P. Guariglia, M. Bruschini, W. Gevers, et al., Spatial orienting biases in the decimal numeral system, Curr. Biol. 19 (8) (2009) 682–687.
[43] J. Binder, R. Marshall, R. Lazar, J. Benjamin, J.P. Mohr, Distinct syndromes of hemineglect, Arch. Neurol. 49 (1992) 1187–1194.
[44] G.R. Fink, J.C. Marshall, N.J. Shah, P.H. Weiss, P.W. Halligan, M. Grosse-Ruyken, et al., Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI, Neurology 54 (2000) 1324–1331.
[45] P. Azouvi, C. Samuel, A. Louis-Dreyfus, T. Bernati, P. Bartolomeo, J-M. Beis, et al., Sensitivity of clinical and behavioral tests of spatial neglect after right hemisphere stroke, J. Neurol. Neurosurg. Psychiatry 73 (2002) 160–166.
[46] A. Knops, B. Thirion, E.M. Hubbard, V. Michel, S. Dehaene, Recruitment of an area involved in eye movements during mental arithmetic, Science 324 (5934) (2009) 1583–1585.
[47] Y. Rossetti, S. Jacquin-Courtois, P. Revol, S. Lacour, G. Rode, Jamais avant midi: biais spatial et numérique dans le dessin d'horloge des héminégligents, in: Oral Communication at the Annual Meeting of the Société de Neuropsychologie de Langue Française, Paris, December 3d 2004.
[48] D. Grossi, G. Di Cesare, L. Trojano, Left on the right or viceversa: a case of "alternating" constructional allochiria, Cortex 40 (3) (2004) 511–518.
[49] M. Aiello, S. Courtois-Jacquin, S. Merola, T. Ottaviani, D. Bueti, F. Tomaiuolo, et al., No inherent left and right side in human mental number line, (2011, in prep.).
[50] M. Aiello, S. Courtois-Jacquin, S. Merola, T. Ottaviani, D. Bueti, F. Tomaiuolo, et al., Right brain damage: bias towards higher numbers in the bisection of number intervals is spatially and attentionally independent (poster presented at the second meeting of the European Societies of Neuropsychology—ESN—Amsterdam 22–24 September 2010).
[51] C. Guariglia, A. Padovani, P. Pantano, L. Pizzamiglio, Unilateral neglect restricted to visual imagery, Nature 364 (6434) (1993) 235–237.
[52] D. Grossi, A. Modafferi, L. Pelosi, L. Trojano, On the different roles of the cerebral hemispheres in mental imagery – the clock test in two clinical cases, Brain Cogn. 10 (1) (1989) 18–27.
[53] E. Bates, S.M. Wilson, A.P. Saygin, F. Dick, M.I. Sereno, R.T. Knight, et al., Voxel-based lesion-symptom mapping, Nat. Neurosci. 6 (2003) 448–450.
[54] J. Medina, V. Kannan, M.A. Pawlak, J.T. Kleinman, M. Newhart, C. Davis, et al., Neural substrates of visuospatial processing in distinct reference frames: evidence from unilateral spatial neglect, J. Cogn. Neurosci. 21 (2009) 2073–2084.
[55] G. Committeri, G. Galati, A.L. Paradis, L. Pizzamiglio, A. Berthoz, D. LeBihan, Reference frames for spatial cognition: different brain areas are involved in viewer-, object-, and landmark-centered judgments about object location, J. Cogn. Neurosci. 16 (9) (2004) 1517–1535.
[56] S. Dehaene, L. Cohen, Cultural recycling of cortical maps, Neuron 56 (2) (2007) 384–398.
[57] M. Fischer, A. D. Castel, M.D. Dodd J. Pratt, Perceiving number causes spatial shifts of attention. Nat Neurosci. 6(2003) 555–556).
[58] D. de Hevia, L. Girelli, G. Vallar, Numbers and space: a cognitive illusion? Exp. Brain Res. 168 (1–2) (2006) 254–264.
[59] M.R. Longo, S.F. Lourenco, Spatial attention and the mental number line: evidence for characteristic biases and compression, Neuropsychologia 45 (2007) 1400–1407.
[60] G. Galfano, E. Rusconi, C. Umilta, Number magnitude orients attention, but not against one's will, Psychon. Bull. Rev. 13 (5) (2006) 869–874.

[61] J. Ristic, A. Wright, A. Kingstone, The number line effect reflects top-down control, Psychon. Bull. Rev. 13 (5) (2006) 862–868.

[62] M. Ranzini, S. Dehaene, M. Piazza, E.M. Hubbard, Neural mechanisms of attentional shifts due to irrelevant spatial and numerical cues, Neuropsychologia 47 (12) (2009) 2615–2624.

[63] M. Jarick, M.J. Dixon, E.C. Maxwell, M.E.R. Nicholls, D. Smilek, The ups and downs (and lefts and rights) of synaesthetic number forms: validation from spatial cueing and SNARC-type tasks, Cortex 45 (10) (2009) 1190–1199.

[64] M. Andres, M. Davare, M. Pesenti, E. Olivier, X. Seron, Number magnitude and grip aperture interaction, Neuroreport 15 (2004) 2773–2777.

[65] M. Ishihara, K. Imanaka, Motor preparation of manual aiming at a visual target manipulated in size, luminance contrast, and location, Perception 36 (2007) 1375–1390.