

No inherent left and right side in human 'mental number line': evidence from right brain damage

Marilena Aiello,^{1,2} Sophie Jacquin-Courtois,^{3,4} Sheila Merola,^{1,2} Teresa Ottaviani,¹ Francesco Tomaiuolo,⁵ Domenica Bueti,^{2,6} Yves Rossetti^{3,4} and Fabrizio Doricchi^{1,2}

1 Dipartimento di Psicologia 39, Università degli Studi di Roma 'La Sapienza', 00185 Roma, Italy

2 Fondazione Santa Lucia IRCCS, 00179 Roma, Italy

3 ImpAct (Integrative multisensory perception Action cognition team) Centre de Recherche en Neurosciences de Lyon, INSERM U1028, CNRS UMR5292 and Université de Lyon, 6976 Bron Cedex, France

4 Mouvement et Handicap, Hôpital Henry Gabrielle, Hospices Civils de Lyon et Université de Lyon, 69230 Saint Genis Laval, France

5 Auxilium Vitae, 56048 Volterra, Pisa, Italy

6 Département des Neurosciences Cliniques, Centre Hospitalier Universitaire Vaudois CHUV, 1011 Lausanne, Switzerland

Correspondence to: Prof. Fabrizio Doricchi,
Centro Ricerche di Neuropsicologia –
Fondazione Santa Lucia – IRCCS,
Via Ardeatina 306 – 00179 Roma,
Italy
E-mail: fabrizio.doricchi@uniroma1.it

Correspondence may also be addressed to: Prof. Yves Rossetti. ImpAct, Centre de Recherche en Neurosciences de Lyon, 16 Avenue Lépine, 69676 Bron, France. E-mail: yves.rossetti@inserm.fr

Spatial reasoning has a relevant role in mathematics and helps daily computational activities. It is widely assumed that in cultures with left-to-right reading, numbers are organized along the mental equivalent of a ruler, the mental number line, with small magnitudes located to the left of larger ones. Patients with right brain damage can disregard smaller numbers while mentally setting the midpoint of number intervals. This has been interpreted as a sign of spatial neglect for numbers on the left side of the mental number line and taken as a strong argument for the intrinsic left-to-right organization of the mental number line. Here, we put forward the understanding of this cognitive disability by discovering that patients with right brain damage disregard smaller numbers both when these are mapped on the left side of the mental number line and on the right side of an imagined clock face. This shows that the right hemisphere supports the representation of small numerical magnitudes independently from their mapping on the left or the right side of a spatial-mental layout. In addition, the study of the anatomical correlates through voxel-based lesion–symptom mapping and the mapping of lesion peaks on the diffusion tensor imaging-based reconstruction of white matter pathways showed that the rightward bias in the imagined clock-face was correlated with lesions of high-level middle temporal visual areas that code stimuli in object-centred spatial coordinates, i.e. stimuli that, like a clock face, have an inherent left and right side. In contrast, bias towards higher numbers on the mental number line was linked to white matter damage in the frontal component of the parietal–frontal number network. These anatomical findings show that the human brain does not represent the mental number line as an object with an inherent left and right side. We conclude that the bias towards higher numbers in the mental bisection of number intervals does not depend on left side spatial, imagery or object-centred neglect and that it rather depends on disruption of an abstract non-spatial representation of small numerical magnitudes.

Keywords: spatial neglect; mental number line; right brain damage; imagery; human

Abbreviations: SNARC = Spatial Numerical Association of Response Code; VLSM = voxel-based lesion–symptom mapping

Introduction

Spatial reasoning has helped high achievements in mathematics (Boyer, 1968) and frames simple daily mental computational activities such as comparing, ordering, adding or subtracting numerical quantities. At the turn of the 19th century, in two *Nature* issues (Galton, 1880a, b) Francis Galton first described the introspective reports of humans possessing the strong tendency to see numbers in 'definite and constant arrangements' readily and vividly 'raising before the mind's eye', upon spoken number presentation. Ensuing studies systematically explored the variety of the introspective mental-spatial arrangements assigned by healthy adults to the series of ascending numerals (Seron *et al.*, 1992; Sagiv *et al.*, 2006). These studies demonstrated that in cultures with left-to-right reading, numbers are prevalently organized along the mental equivalent of a ruler, the mental number line, with small magnitudes located to the left of larger ones. The idea that the introspective left-to-right arrangement of ascending numerals faithfully reflects an inherent spatial coding of number magnitudes in the human brain was endorsed by the observation that humans respond faster to small numbers when motor responses are released in the left side of space and to higher numbers when responses are in the right side of space [i.e. Spatial Numerical Association of Response Code (SNARC); Dehaene *et al.*, 1993].

An apparently crucial finding adding to this set of data is the pathological bias towards higher numbers displayed by patients with right brain damage during the mental bisection of number intervals (Zorzi *et al.*, 2002), i.e. reporting without calculation what number is halfway between two other numbers. This has been ascribed to enhanced attentional bias towards high numbers on the right side of the mental number line and attentional neglect for small numbers on the left side of the mental number line. However, in contrast with this conclusion, several investigations have found that in patients with right brain damage the 'rightward' bias in mental-number space is not correlated with the severity or the presence of an analogous attentional bias in visual space (Rossetti *et al.*, 2004; Doricchi *et al.*, 2005, 2009; Loetscher and Brugger, 2009; Loetscher *et al.*, 2010; van Dijck *et al.*, 2011; Pia *et al.*, in press). A similar dissociation was also recently documented in schizophrenic patients that suffer from a pathological leftward spatial-attentional bias (Tian *et al.*, 2011).

Here we sought to obtain a clearer picture of the mechanisms allowing the use of the mental number line in humans by investigating whether orienting in a mental number space is supported by the same mechanisms allowing the inspection of mental visual images. This can be done by assessing whether neglect for smaller numbers on the left side of the mental number line is functionally and anatomically correlated with neglect for the left side of mental visual images (Guariglia *et al.*, 1993). One reliable instrument for the evaluation of imagery neglect is the O'Clock task (Grossi *et al.*, 1989). In this task, patients are required to mentally recollect the position of hours and minutes on a clock-face or to

mentally compare the amplitude between clock-hands' angles indicating different times within the right half (e.g. 2:20 versus 4:25) and the left half (e.g. 6:45 versus 7:40) of the clock-face. Patients with right brain damage are likely to be worse at recollecting hour positions and comparing clock-hands' angles in the left side of the clock-face (Grossi *et al.*, 1989). Interestingly, comparing the performance of patients with right brain damage in the bisection of number intervals and in the O'Clock task can directly reveal whether the origin of the bias towards higher numbers on the mental number line is spatial-attentional or whether it derives from a non-spatial-attentional impairment in the representation of small magnitudes (Vuilleumier *et al.*, 2004). If the bias is a spatial-attentional one, then patients with right brain damage should display a bias towards high numbers on the right side of the mental number line and better performance with small hour-numbers on the right side of the imagined clock face. In contrast, if right brain damage disrupts an abstract, non-spatial-attentional representation of small magnitudes, then patients with right brain damage should display directionally opposed biases in the two tasks, i.e. a bias towards high numbers on the right side of the mental number line and better performance with high hour-numbers on the left side of the imagined clock face.

Here, we report the results from two independent studies providing converging evidence in favour of the latter hypothesis.

Study 1

Participants

Nine patients with right brain damage admitted to the rehabilitation unit of the Hôpital Henry Gabrielle (Lyon) and 10 age-matched healthy controls were included in this study. Clinical and demographic data of patients and controls are reported in Table 1. Patients had no history of previous neurological illness, and at the time of clinical and experimental examination they were free from confusion and from temporal or spatial disorientation. On clinical examination, all patients showed a rightward attentional bias either in the line bisection task (five trials, line length 200 mm; neglect cut-off score = 6.5 mm), in the star cancellation task (Wilson *et al.*, 1987; neglect cut-off score <44 cancelled items) or in both tasks. In two cases (Cases 4 and 6), the bias was below the cut-off score in both tasks. In each patient, the localization and extent of brain damage was defined through CT or MRI scan. Informed consent was obtained from all patients prior to testing.

Experimental procedure

Patients and controls performed first a mental number interval bisection task (e.g. 'What is the midway between 1 and 5?'; Session

Table 1 Study 1: clinical and demographic data of patients with right brain damage with spatial neglect and healthy controls

Patients Case	Sex	Age (years)	Stroke onset (months)	Lesion	Line bisection (200 mm) rightward deviation (mm)	Star cancellation cancelled items (54)
1	F	60	5	Fronto-parietal	3	24
2	M	72	5.8	Capsulo-thalamic	34	43
3	M	46	7	Capsulo-lenticular	22	47
4	M	78	5.6	Fronto-parietal	3.4	49
5	F	75	3	Capsulo-lenticular	55	39
6	F	63	2.3	Capsulo-lenticular	4	47
7	F	41	2	Fronto-parietal	23	53
8	M	56	14.5	Parietal	30.4	14
9	M	75	1.2	Fronto-parietal	62	37
Controls (n = 10)	M = 5 F = 5	61.9 SD 7.8				

Age (years), stroke onset (months), line bisection (rightward deviation in mm from the objective line midpoint; line length = 200 mm), star cancellation (cancelled targets over the total number of targets = 54; in all patients, missed items were in the left side of the test sheet).

F = female; M = male.

1) and then an 'hour bisection' task (e.g. 'What is the midway hour between 1 o'clock and 5 o'clock?'; Session 2). This order was used to ensure that subjects would not be primed towards time numbers before they performed the classical version of the test. In both of these tasks, the same 3-, 5-, 7-, 9- and 11-unit number pairs delimiting number/time intervals were verbally presented. All pairs were presented in ascending/clockwise order with the smaller number in the pair positioned at the beginning of the interval (the complete list of intervals is reported in Supplementary Table 1). Fifteen intervals were presented in each task and each of these intervals was presented twice for a total of 30 trials in each task. Trials were presented in pseudo-random order. The 'hour bisection task' was performed facing a round clock-face (diameter = 145 mm) with hour-numbers. It is crucial to note that in France the 24-h clock is used. That is, times are not referred to using a.m. or p.m., but rather children learn to tell the time as '2 heure' (2 a.m.) or '14 heure' (2 p.m.). It is important to note that on the clock face, half of the pairs were oriented from left to right, i.e. with the smaller number indicating the beginning of the interval on the left side of the clock face and the higher number indicating the end of the interval on the right side of the clock face (e.g. 9 o'clock to 15 o'clock) and the other half of the pairs were oriented from right to left, i.e. with the smaller number indicating the beginning of the interval on the right side of the clock face and the higher number indicating the end of the interval on the left side of the clock face (e.g. 3 o'clock to 9 o'clock). Left-to-right (L-R) pairs are referred to as 'congruent' ones, because both spatial neglect for the left side of the interval on the clock-face and a non-spatial deficit in the representation of smaller numbers positioned at the beginning of the interval predict a bisection bias towards larger hour/numbers on the right side of the clock face. In contrast, right-to-left pairs (R-L) are referred to as 'incongruent' since, crucially, left spatial neglect should result in a bisection bias towards smaller hour-numbers at the beginning of the interval on the right side of the clock face whereas a non-spatial deficit in the representation of smaller numbers should cause a bias towards larger numbers towards the end of the interval on the left side of the clock face.

A strong emphasis was put on avoiding performing arithmetic calculations during task performance.

Results

Individual error frequencies and bisection deviations (in units) from the objective midpoint of number and hour intervals were used for statistical analysis. Deviations towards numbers higher than the interval midpoint were scored as positive ones, whereas deviations towards numbers lower than the midpoint as negative ones. Inspection of data showed that, in neglect patients, the number of errors (range: 44.4–51.5%) and the bisection bias (range 0.25–0.90 units) were both significantly larger and positioned outside the error range (3.33–21.6%) and the bisection bias range (–0.13 to 0.12 units) showed by healthy controls (Supplementary Table 2). Individual bisection biases of neglect patients were entered in a Task (number interval bisection, hour interval bisection) × Type of trial (L-R congruent and R-L incongruent) within-subjects ANOVA. Average bisection biases (with standard error) showed by neglect patients in the two tasks and in the two types of trials are reported in Fig. 1, together with confidence intervals gathered from the virtually perfect performance of healthy controls. Two main results were found. First, the bisection bias was not different both between the two tasks [$F(1,8) = 3.6$, $P = 0.15$ not significant] and between congruent L-R and incongruent R-L pairs [$F(1,8) = 1.6$, $P = 0.24$ not significant]. Secondly, and crucially, the bisection bias in congruent L-R and incongruent R-L did not change as a function of the task [Task × Type of trial interaction: $F(1,8) = 0.10$, $P = 0.76$ not significant]. Neglect severity in the line bisection and star cancellation tasks was unrelated to the bias towards higher numbers in the Number Interval Bisection task (Pearson's r : line bisection all $P > 0.45$; star cancellation all $P > 0.2$). Rightward bias in the line bisection task was correlated with a decrease in the leftward bias towards higher numbers in the bisection of incongruent R-L hour-intervals on the clock-face ($r = -0.6$, $P = 0.01$). No other correlation was present between neglect severity and biases in the bisection of hour-intervals on the clock-face (all $P > 0.5$).

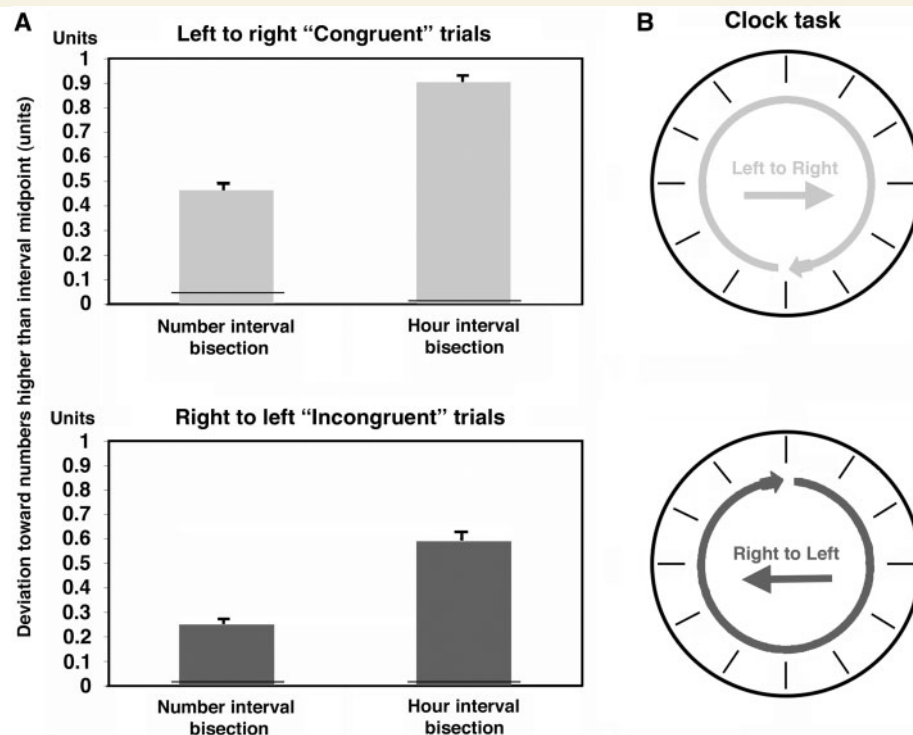


Figure 1 Study 1. (A) Averaged bisection biases (in number units, with standard error) reported by patients with right brain damaged (right brain damage) with left spatial neglect in the number interval and hour interval bisection tasks. Intervals are delimited by congruent number pairs directed from left-to-right on the clock-face (light grey) or by incongruent pairs directed from right-to-left on the clock-face (dark grey). The endpoints of number/time intervals were presented verbally in ascending/clockwise order. Thin black lines superimposed on graph bars represent the upper limits of the 99% confidence intervals gathered from the performance of healthy controls. Positive values correspond to bisection bias towards numbers higher than the interval midpoint. It is important to note that in the hour bisection task, an attentional explanation of the bisection bias predicts a positive bias towards numbers higher than the interval midpoint (i.e. towards the right side of the clock face) with congruent left-to-right pairs and a negative bias towards numbers lower than the interval midpoint (i.e. towards the right side of the clock face) with incongruent right-to-left pairs. This expectation is not confirmed by the observation of a positive bias in the bisection of incongruent right-to-left pairs (i.e. of a bias towards numbers on the left-side of the clock-face). (B) Spatial arrangement of hour-number intervals in the clock-face in congruent (left-to-right) and incongruent (right-to-left) trials.

Discussion

The findings from this study show that when neglect patients bisect the same number intervals in the reversed right-to-left clock version rather than in the putative default left-to-right mental format, neither an inversion of the bias towards smaller hour-numbers on the right side of the clock nor a significant reduction of the pathological bias towards higher hour-numbers is observed. Most importantly, despite the rightward attentional bias in the line bisection task correlated with a reduction of the leftward bias in the bisection of R–L incongruent hour-intervals, no inversion of this latter bias was found. This shows that when a spatial conflict between the rightward attentional bias of neglect patient and the position of higher numbers in a number interval is created by placing higher numbers on the left side of a clock-face, the 'winning' format determining the number bisection bias is the numerical one and not the spatial-attentional one. In line with previous findings (Rossetti *et al.*, 2004; Doricchi *et al.*, 2005, 2009; Loetscher and Brugger, 2009; Loetscher *et al.*, 2010; Tian *et al.*, 2011; van Dijck *et al.*, 2011; Pia *et al.*, in press), these

results suggest that the number bisection bias in patients with right brain damage cannot be merely accounted for by defective attentional processing of the left side of space, or of the left side of a mental representation of number intervals; rather, they suggest a non-spatial deficit in the representation of smaller number magnitudes.

Study 2

Study 2 provided an independent test of the consistency of the results from Study 1. In Study 2, two additional control conditions were introduced: the inclusion of a sample of patients with right brain damage without spatial neglect and the use of a purely imagery version of the O'Clock task.

Participants

In this second parallel study we directly assessed the functional and anatomical relationships between neglect in mental number space and neglect in mental imagery. The study was carried out

Table 2 Study 2: clinical data of patients with right brain damage with (N+) and without (N–) left spatial neglect

	n	Age (years)	Stroke onset (days)	Line bisection (length 200 mm)	Letter cancellation	
					Left	Right
Neglect (N+)	16					
Mean		60.8	83.06	10.9	7.8	29
SD		7.6	160.9	9.4	14.7	17.3
No neglect (N–)	21					
Mean		58.3	117.1	2.8	51	49.6
SD		12.8	210.4	7	3.4	1.9

Age (years), stroke onset (days), line bisection (rightward deviation in millimetre from the objective line midpoint), letter cancellation (cancelled targets in the left and in the right side of the display; maximum score is 53 on the left and 51 on the right).

on a sample of 37 patients with chronic right brain damage admitted for physical and neuropsychological rehabilitation at the Fondazione Santa Lucia Istituto Di Ricovero e Cura a Carattere Scientifico (Rome). Patients were consecutively screened for inclusion in the study on admission to rehabilitation training. Patients with bilateral strokes, signs of dementia or history of previous neurological illness were excluded. At the time of clinical and experimental examination, all patients were free from confusion and from temporal or spatial disorientation. All patients gave their informed consent for participating in the study.

Left visual spatial neglect was assessed with the line bisection (five trials, line length 200 mm) and letter cancellation (Diller *et al.*, 1974) tasks. These tasks were chosen because they tap on different visual spatial abilities (parallel distribution of attention for the line bisection task and serial distribution of attention for the letter cancellation task; Binder *et al.*, 1992) and on partially non-overlapping sectors of the right hemispheric parietal–frontal attentional network (predominant role of parietal areas in line bisection versus predominant role of frontal areas in multiple item cancellation; Binder *et al.*, 1992; Fink *et al.*, 2000; Verdon *et al.*, 2010). The cut-off score for neglect on line bisection was taken from normative data collected in a sample of 206 patients with right brain damage by Azouvi *et al.* (2002; cut-off = 6.5 mm). The cut-off score for the letter cancellation task was taken from normative data collected in a sample of 140 patients with right brain damage by Pizzamiglio *et al.* (1992; cut-off: left minus right omissions > 4).

Sixteen patients had left spatial neglect (N+) in both tasks whereas 21 had normal performance in the same tasks (N–). These two groups differed both in the in-line bisection [$F(1,35) = 8.9$, $P < 0.01$] and letter cancellation task [$F(1,35) = 57$, $P < 0.001$]. Patients with and without left spatial neglect did not differ in age [$F(1,35) = 0.46$, $P = 0.49$; mean age = 59.4 years] or time elapsed from stroke onset [$F(1,35) = 0.28$, $P = 0.59$; mean = 102.3 days]. Clinical and demographic data are reported in Table 2.

Experimental procedure: behavioural study

In separate sessions, patients performed two different tasks aimed at the assessment of left side neglect-like symptoms in mental number space and left side neglect in imagery space, respectively.

The first task was the number interval bisection task (Zorzi *et al.*, 2002). In this task, 3- (e.g. 4–6), 5- (e.g. 3–7), 7- (e.g. 2–8) and 9-unit number intervals (e.g. 1–9) taken from the first three decades are verbally presented (the complete list of intervals is reported in Supplementary Table 3). The two numbers defining each interval are presented through headphones, both in ascending (48 trials) and descending order (48 trials). Patients are required to speak out the number that is in the centre of the interval without making arithmetic calculations. Deviations (in units) towards a number smaller than the true interval midpoint are coded as negative ones, whereas deviations towards a number higher than the true interval midpoint are coded as positive ones. For statistical analysis, individual deviations were entered in a Group (left spatial neglect, normal performing) \times Interval length (3-, 5-, 7-, 9-unit) ANOVA. In this study, in an ensuing control session, we asked patients to calculate the midpoint of number intervals by applying the exact formula: i.e. summing the value of interval endpoints and dividing the sum by two.

Neglect in mental imagery was assessed through the O’Clock task (Grossi *et al.*, 1989). In this task, in each trial, the examiner verbally indicates two different times. Patients are asked to imagine the two different times on a mental clock face and report in which of the two times clock hands have the greater angle. The task includes 16 trials with times to be compared in the left side of the imagined clock face (e.g. 7:30 and 8:30) and 16 trials with times in the right side of the clock face (e.g. 3:30 and 4:30; the complete list of intervals is reported in Supplementary Table 4). In each participant, the left/right lateral bias is calculated with the following formula: (number of correct responses on the left side – numbers of correct responses on the right side)/(number of correct responses on the left side + numbers of correct responses on the right side) \times 100. Positive values indicate leftward imagery bias whereas negative values indicate rightward imagery bias. For statistical analysis, individual laterality scores were entered in a one-way Group (left spatial neglect, normal performing) ANOVA.

Correlation among visual neglect, neglect in mental number space, imagery neglect and measures of working memory

We systematically explored in the entire sample of 37 patients the correlations (Pearson’s r) among the severity of visual neglect, the

lateral bias in the bisection of number intervals and the severity of imagery neglect in the O'Clock task. For the severity of visual neglect, we used two indexes: (i) the lateral deviation (in millimetres) from the objective centre in the bisection of 200 mm horizontal lines (with positive scores indicating rightward bias and negative scores indicating leftward bias); and (ii) the mean horizontal location of the cancelled items in the letter cancellation task (i.e. the Centre of Cancellation; Binder *et al.*, 1992). This index was calculated by averaging the individual positions of cancelled letters. The position of cancelled items was measured in mm with respect to the centre of the test sheet. Positive values were assigned to items positioned to the right of the page centre and negative values to items positioned to the left of the page centre. This index provides a more accurate measure of the lateral spatial bias as compared to indices based on the number of cancelled items (Rorden and Karnath, 2010). For the number interval bisection tasks, the mean bisection bias (in units) of 3-, 5-, 7- and 9-unit intervals and the line regression slope describing the bisection bias as a function of interval length were taken as performance indices. For the imagery neglect, the laterality score from the O'Clock task was used.

Based on previous findings (Doricchi *et al.*, 2005, 2009; Bachmann *et al.*, 2010; Fias *et al.*, 2011; van Dijck *et al.*, 2011), we also reinvestigated the correlations between measures of spatial (Corsi span) and verbal (Digit span) working memory and the indexes describing biases in the bisection of number intervals.

Results

In line with previously observed dissociations between left visual-spatial neglect and neglect-like behaviour in the mental bisection of number intervals (Rossetti *et al.*, 2004; Doricchi *et al.*, 2005, 2009; Loetscher and Brugger, 2009; Loetscher *et al.*, 2010; van Dijck *et al.*, 2011; Tian *et al.*, 2011), the performance of patients with and without left spatial neglect did not differ in the number interval bisection task [Group: $F(1,35) = 1.8$, $P = 0.2$; Group \times Interval Length: $F(3,105) = 1.01$, $P = 0.38$; Table 3 and

Fig. 2]. Notably, in the same task, a typical effect of interval length was found, so that the longer the interval was the higher the bisection bias towards higher numbers in the interval [Interval Length: $F(3,105) = 18$, $P < 0.001$]. In the control version of the number interval bisection task (i.e. calculating the midpoint of number intervals by applying the exact formula: i.e. summing the value of interval endpoints and dividing the sum by 2), the performance of patients was virtually perfect ($< 2\%$ error rate).

Also in line with previous findings (Guariglia *et al.*, 1993), left visual spatial neglect was unrelated to imagery neglect in the O'Clock task, where patients with and without left spatial neglect showed comparable lateral asymmetries [Group: $F(1,35) = 0.44$, $P = 0.51$; Table 3; Supplementary Fig. 1].

Correlation analyses

No significant correlations between neglect severity in the line bisection or letter cancellation task and equivalent rightward biases in the number interval bisection and O'Clock task were found (Table 4). In contrast, we found significant correlations between the bisection bias towards high numbers on the putative 'right' side of long mental number intervals (7- and 9-unit intervals and regression slope over all interval lengths) and a directionally opposite bias in the O'Clock task, i.e. better performance with high numbers on the left side of the imagined clock face (Table 4). Importantly, this finding shows that defective processing of smaller magnitudes in a number interval was present both when these magnitudes were mapped on the left and the right side of a mental visual image.

The significant correlation between the bias towards higher numbers in the bisection of number intervals and the bias towards higher hour-numbers in the O'Clock task, was explored in more detail by considering separately intervals belonging to each of the three different decades included in the number interval bisection task (i.e. 1–9, 11–19, 21–29). We discovered that the results of previous analyses were entirely accounted for by the highly significant correlations between the deviation towards higher time-numbers in the O'Clock tasks and the deviation towards

Table 3 Study 2: mean scores (with SD) of patients with right brain damage with and without left spatial neglect in the O'Clock and number interval bisection tasks

	n	O'clock	Numbers interval bisection				Slope
			Interval length				
			3 units	5 units	7 units	9 units	
Neglect (N+)	16						
Mean		−4.73	−0.22	0.02	0.29	0.65	0.14
SD		15.57	0.52	0.26	0.39	0.84	0.18
No neglect (N−)	21						
Mean		−2.05	−0.15	−0.07	0.13	0.34	0.08
SD		8.79	0.24	0.18	0.34	0.54	0.11

In the O'Clock task, negative scores correspond to better performance with hour-numbers in the right half of the imagined clock face. In the number interval bisection tasks, for each interval length (3-, 5-, 7- and 9-units), positive scores correspond to bisection deviation (in units) towards numbers higher than the interval midpoint and negative scores correspond to deviation towards numbers smaller than the midpoint. The slope is the value of the slope of the regression line describing bisection deviations as a function of number interval length. Positive slope values correspond to increasing deviation towards numbers higher than the interval midpoint for increasing interval lengths.

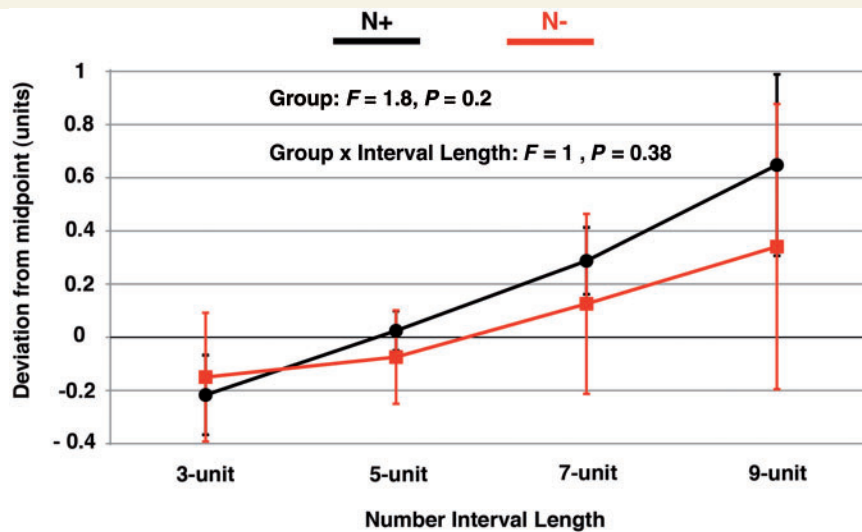


Figure 2 Study 2. Performance of patients with right brain damage with (N+) and without (N-) left spatial neglect in the number interval bisections tasks (mean deviations of the two groups from the interval midpoint with standard deviation; see also legend in Table 3).

Table 4 Study 2: correlations (Pearsons' *r* with corresponding *P*-values) between deviations in the bisection of number intervals (3-, 5-, 7- and 9-units intervals and slope of the regression line describing bisection deviations as a function of interval length) and lateral biases in the O'Clock, line bisection and letter cancellation tasks

	Number interval bisection				
	Interval length				
	3 units	5 units	7 units	9 units	Slope
O'Clock	-0.11	0.04	0.40	0.34	0.33
<i>P</i> -value	0.52	0.83	0.01	0.04	0.04
Line bisection	-0.37	-0.22	-0.22	0.06	0.18
<i>P</i> -value	0.02	0.18	0.19	0.71	0.28
Letter cancellation	-0.01	0.15	0.21	0.14	0.12
<i>P</i> -value	0.96	0.37	0.22	0.42	0.49

For the O'Clock task, positive *r*-values indicate correlations between leftward bias in the O'Clock task (i.e. better performance with higher hour-numbers) and 'rightward' bias towards higher numbers in the bisection of number intervals. For the line bisection and letter cancellation tasks, positive *r*-values indicate correlations between rightward bias in these tasks and 'rightward' bias towards higher numbers in the bisection of number intervals. Correlations were calculated in the entire sample of patients with right brain damage.

higher numbers in the bisection of long number intervals belonging to the first decade (7-unit intervals: 1–7, 2–8, 3–9; 9-unit interval: 1–9; regression slope over all interval lengths; Table 5). This result was confirmed by a series of multiple regression analyses (Table 6) and shows that right brain damage specifically interferes with the mental representation and manipulation of the smallest magnitudes in the series of ascending positive integers. In an additional control analysis (Supplementary material), we verified that the selective correlation between the bias in the bisection of number intervals from the first decade and the bias

Table 5 Correlations (Pearsons' *r* with corresponding *P*-values) between deviations in the bisection of number intervals belonging to the first (1–10), second (11–20) and third decade (21–30) (3-, 5-, 7- and 9-units intervals and slope of the regression line describing bisection deviations as a function of interval length) and lateral biases in the O'Clock task

	Number interval bisection				
	Interval length				
	3 units	5 units	7 units	9 units	Slope
O'Clock					
First decade	-0.03	0.09	0.49	0.45	0.39
<i>P</i> -value	0.84	0.59	0.00	0.01	0.02
Second decade	0.05	-0.14	0.15	-0.17	-0.14
<i>P</i> -value	0.78	0.42	0.37	0.31	0.42
Third decade	-0.13	0.07	0.30	0.08	0.15
<i>P</i> -value	0.43	0.66	0.07	0.63	0.36

Correlations were calculated in the entire sample of patients with right brain damage.

towards higher hour-numbers in the O'Clock task was not due to the use of different strategies in the bisection of number intervals from the first compared to intervals from the second and third decades.

Finally, in light of this set of results, we reanalysed data from the number interval bisection task administered in the first study. We found that, for all interval lengths (i.e. 11-, 9-, 7-, 5-, 3-unit), the smaller the starting point of the interval (starting ranges: 1–5, 7–11, 13–17) the higher the deviation towards numbers higher than the interval midpoint [$F(2,16) = 5.3, P = 0.01$; Supplementary Tables 1, 5 and 6].

Table 6 Study 2: results of the multiple regression analyses (standard method) assessing the relationship between the rightward bias in the performance of the O’Clock task (dependent variable) and the following independent variables: (i) the bias towards higher numbers in the bisection of 7-unit intervals belonging to the first, second and third decade; (ii) the bias towards higher numbers in the bisection of 9-unit intervals belonging to the first, second and third decade; and (iii) the slope of the regression line describing the bisection deviation as a function of interval length (3-, 5-, 7- and 9-unit intervals) in the first, second and third decade

	B	β	T	P	Decade
7-unit interval	11.7	0.52	2.8	0.007	First
($R = 0.52$, $R^2 = 0.27$, $F = 4.2$, $P = 0.01$)	–5.2	–0.23	–1.1	0.25	Second
	3.9	0.18	0.8	0.38	Third
9-unit interval	4.8	0.47	2.9	0.006	First
($R = 0.48$, $R^2 = 0.23$, $F = 3.4$, $P = 0.03$)	–1.6	–0.14	–0.95	0.35	Second
	–1	–0.06	–0.38	0.7	Third
Slope bisection error (9-, 7-, 5- and 3-unit intervals)	31.8	0.53	2.9	0.006	First
($R = 0.50$, $R^2 = 0.25$, $F = 3.7$, $P = 0.01$)	–11.3	–0.17	–1.04	0.3	Second
	–5.9	–0.08	–0.42	0.67	Third

Spatial working memory scores were negatively correlated both with the slope describing number bisection biases as a function of number interval length (Pearson’s $r = -0.32$, $P = 0.05$ both for raw scores and for scores corrected for age and educational level) and with the bias in the bisection of 7-unit intervals (raw scores: $r = -0.39$, $P = 0.01$; corrected scores: $r = -0.35$, $P = 0.04$). The same negative correlation approached significance for the bisection of 9-unit intervals ($r = -0.27$, $P = 0.10$ both for raw and corrected Corsi scores). These findings confirm the relationship between spatial working memory impairments and number interval bisection bias (Doricchi *et al.*, 2005, 2009; Fias *et al.*, 2011; van Dijck *et al.*, 2011).

Anatomical study

To shed light on the origin of the associations and dissociations found in the behavioural data, we investigated the anatomical correlates of rightward bias in the line bisection, letter cancellation, number interval bisection and O’Clock tasks. This was done by using the voxel-based lesion–symptom mapping (VLSM) technique (Bates *et al.*, 2003), which allows analysing continuous behavioural data on a voxel-by-voxel basis and evaluating statistical similarity between the anatomical correlates of different behavioural tasks. We also defined the localization of VLSM lesion peaks on the DTI based reconstruction of subcortical white matter fibre pathways (Thiebaut de Schotten *et al.*, 2011a; Thiebaut de Schotten *et al.*, 2011b).

Voxel-based lesion–symptom mapping

Following mapping of individual lesions based on 1.5 T MRI scans (Supplementary material), we performed a VLSM analysis (Bates, 2003) to produce anatomical maps representing the Z statistics of the voxel-wise comparison between the average performance scores of the groups of patients with, versus without, lesion of a given voxel. This allows for isolation of lesioned voxels that

predict rightward bias in the number interval bisection, O’Clock, line bisection and letter cancellation tasks. We used the non-parametric Brunner–Munzel test (Brunner and Munzel, 2000) to perform statistical comparisons on a voxel-wise basis, as implemented in the NPM and MRICron software (Rorden *et al.*, 2007). Brunner–Munzel tests were performed at each voxel using the performance measure as dependent variable. In order to avoid producing inflated Z-scores, tests were run using permutation derived correction (permFWE; Kimberg *et al.*, 2007; Medina *et al.*, 2010). This procedure is assumption-free and more powerful compared to other procedures, such as the Bonferroni correction (Kimberg *et al.*, 2007). P significance level was set at 0.05. Only voxels affected in at least three cases were included in the analysis.

Using the VLSM Matlab toolbox, we also investigated the correlations among the anatomical maps of the bisection bias towards higher numbers in the number interval bisection task (regression slope over all interval lengths) and rightward bias in the O’Clock, line bisection and letter cancellation task.

Mapping of VLSM lesion peaks on white matter pathways

The localization of VLSM lesion peaks on white matter pathways was determined in MNI space using the diffusion tensor imaging-based atlases by Thiebaut de Schotten *et al.* (2011a, b) and by Oishi *et al.* (2008). White matter pathways were visualized using MRICron software (Rorden *et al.*, 2007b).

Results

The anatomical results gathered from the study of the whole sample of 37 patients with right brain damage are reported in Fig. 3. The VLSM analysis showed that the rightward bias in the line bisection task was correlated with a subcortical lesion located in the white matter below the rostral sector of the supramarginal gyrus [Brodmann area (BA) 40] in the inferior parietal lobule. In

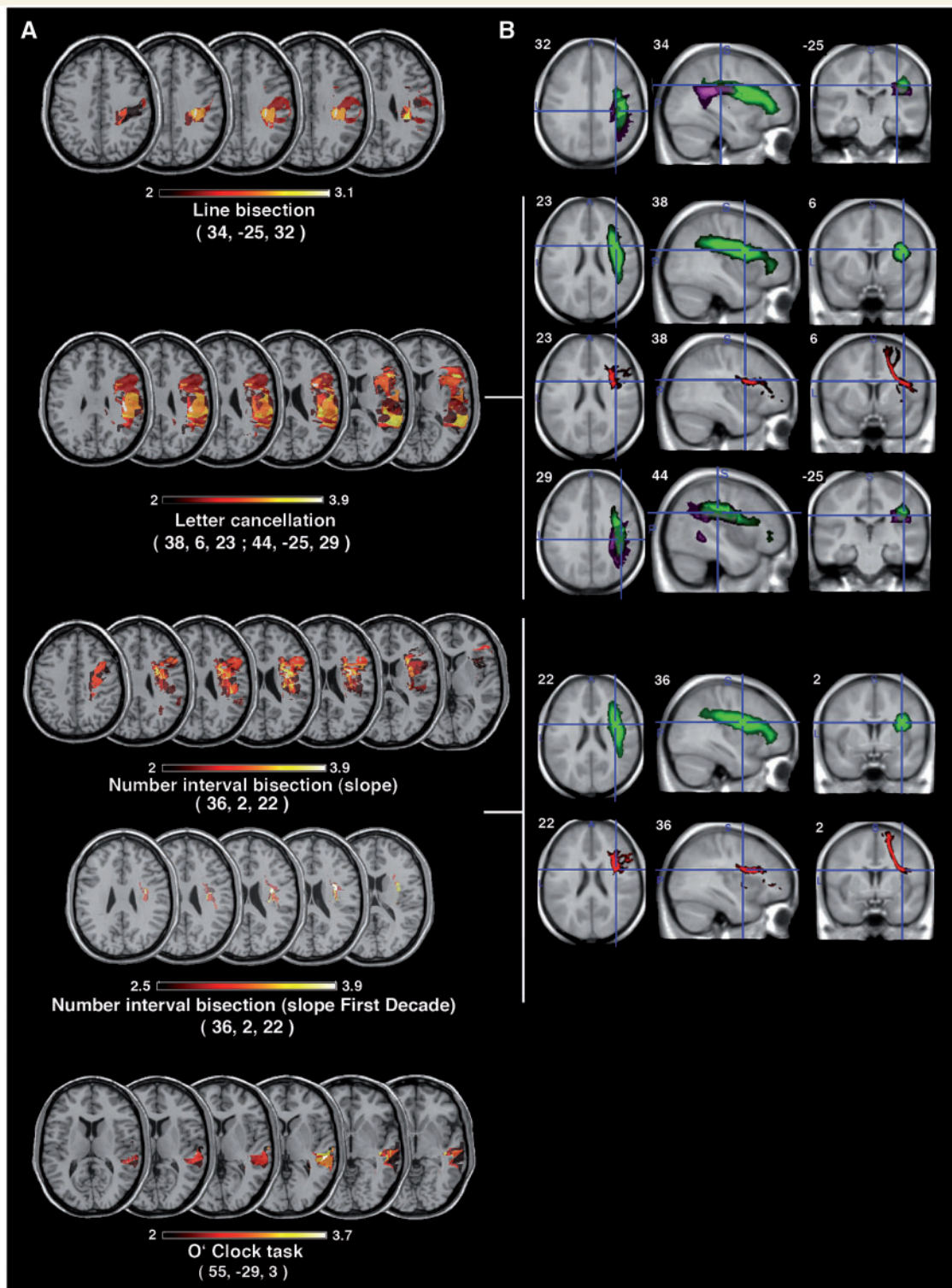


Figure 3 Study 2. (A) Representative slices from maps showing the anatomical correlates of the rightward attentional bias in the line bisection, letter cancellation, number interval bisection and O'Clock tasks in the entire sample of patients with right brain damage. The localization of lesion peaks is defined in MNI coordinates. Maps show the Z-statistics calculated with Brunner and Munzel rank order statistics with permutation derived correction (Brunner and Munzel, 2000; Medina *et al.*, 2010) All peaks are significant at $P < 0.05$ level. (B) Representative slices showing the localization of the VLSM anatomical peaks of each task in the white matter pathways: superior longitudinal fasciculus third branch (green); arcuate fasciculus (purple); pathway linking the superior frontal gyrus and the supplementary motor area with the middle and inferior frontal gyrus (red).

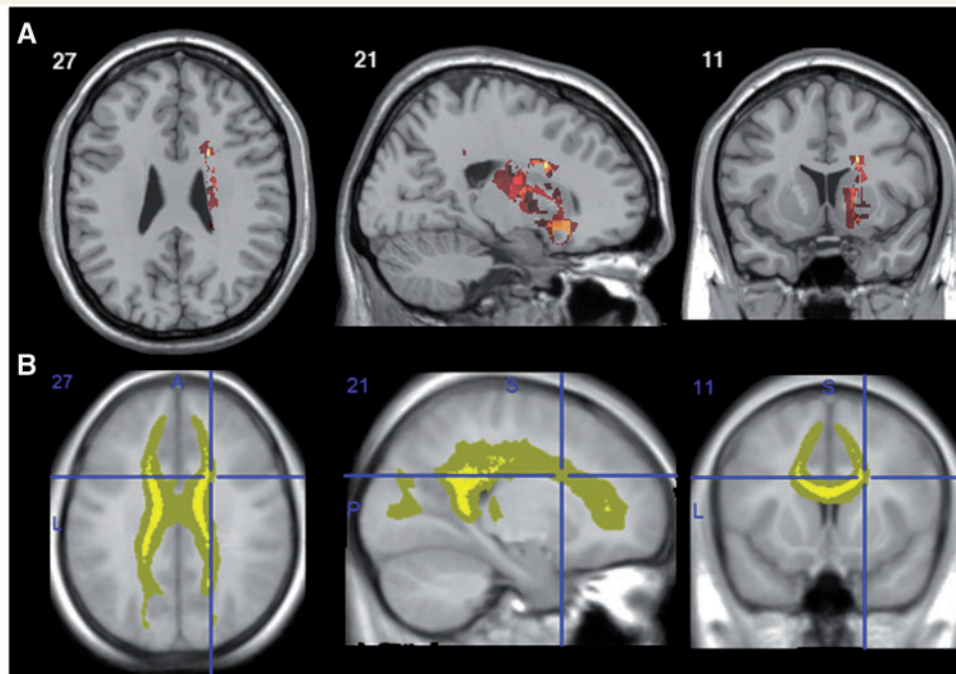


Figure 4 Study 2. VLSM correlates of the leftward bias towards higher hour-numbers in the O' Clock task. (A) Localization of the VLSM peak in MNI coordinates (21, 11 and 27). (B) Localization of the VLSM peak on diffusion tensor imaging based reconstruction of white matter fibre pathways (Thiebaut de Schotten *et al.*, 2011b). The peak is located on callosal fibres projecting to lateral prefrontal and frontal areas, according to cyto-architectural parcellation and high angular resolution diffusion imaging tractography (see Fig. 5 in Chao *et al.*, 2009; Target cortical areas: BA 6, 8, 9, 44, 45 and 46).

agreement with the role of parietal–frontal disconnection in spatial neglect (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten *et al.*, 2005; Bartolomeo *et al.*, 2007; He *et al.*, 2007; Doricchi *et al.*, 2009; Shinoura *et al.*, 2009; Verdon *et al.*, 2010), this lesion causes a disconnection of the second and third most ventral branches of the superior longitudinal fasciculus and of the arcuate fasciculus. These pathways link inferior parietal with inferior-middle frontal areas (Thiebaut de Schotten *et al.*, 2011b). The bias in the letter cancellation task was correlated with two concomitant lesions: a subcortical parietal lesion corresponding to that found for the line bisection task and another subcortical lesion located in the white matter below the frontal cortex. This anterior lesion produces a double disconnection encroaching both on the rostral projections of the third branch of the superior longitudinal fasciculus (Thiebaut de Schotten *et al.*, 2011a, b) and on a pathway linking the supplementary motor area and the superior frontal gyrus with the inferior frontal gyrus (Lawes *et al.*, 2008; Oishi *et al.* 2008; Thiebaut de Schotten *et al.*, 2012). Importantly, the bias towards higher numbers in the bisection of number intervals (as indexed by the line regression slope describing the bisection bias as a function of interval length) was correlated to a sub-cortical frontal lesion that was virtually coincident to that found in the letter cancellation task. This correlation was present both when the bias was measured over all decades and when the bias was measured within the first decade. In contrast, the number bisection bias was not correlated with the subcortical parietal lesion that disrupted performance in the line bisection and letter

cancellation tasks. The bias towards small numbers on the right side of the imagined clock face was produced by cortical–sub-cortical lesion in the middle temporal gyrus. Converging evidence from lesion, functional MRI and diffusion–perfusion MRI investigations (Committeri *et al.*, 2004; Medina *et al.*, 2009; Verdon *et al.*, 2010; Khurshid *et al.*, 2012) show that this ventral high-level visual processing area codes the inherent left and right side of visual objects, which, like clock faces, maintain their left-to-right orientation independently of changes in their absolute position with respect to the observer (i.e. ‘object centred’ coordinates). The evaluation of the statistical similarity between the anatomical correlates of the different behavioural tasks confirmed the anatomical dissociations documented by the main VLSM analyses (Supplementary Figs 2–4). The results from this series of analyses were confirmed in a series of supplementary VLSM analyses that were run to control for the influence of lesion size (Supplementary material and Supplementary Figs 6–11).

Interestingly (Fig. 4), the main VLSM analysis showed that the bias towards higher numbers on the left side of the clock face was correlated with subcortical frontal damage located underneath the supplementary motor area and the superior frontal gyrus and impinging on callosal connections directed to these areas and to the lateral prefrontal cortex (BA 6, 8, 9, 44, 45 and 46; Chao *et al.*, 2009). This type of lesion is therefore in a good anatomical location to cause a functional disruption, and disconnection from the left hemisphere, of the right frontal network whose lesion correlates with the bias towards higher numbers in the number

interval bisection task (i.e. supplementary motor area–superior frontal gyrus–inferior frontal gyrus). When the same analysis was repeated taking into account lesion size, two additional lesion peaks emerged (Supplementary material and Supplementary Fig. 11). The first peak was located in the frontal section of the superior longitudinal fasciculus. The second peak was located at the level of the Jensen sulcus, separating the angular from the supra-marginal gyrus in the inferior parietal lobule. This lesion is located just below the horizontal segment of the intraparietal sulcus, an area that is classically related to number processing (Dehaene *et al.*, 2003). The finding that damage to the parietal number module in the right hemisphere produces a deficit in the processing of small numbers located on the ipsilesional right-side of the mental clock-face rather than an attentional deficit for the contralesional left side of the mental clock-face, further supports the abstract-representational rather than spatial-attentional nature of the number processing deficit observed in patients with right brain damage.

Discussion

Several studies have documented systematic dissociations between left spatial neglect-like behaviour in the mental bisection of number intervals, i.e. bias towards higher numbers on the putative right side of a number interval, and the presence or severity of left visual spatial neglect (Rossetti *et al.*, 2004; Doricchi *et al.*, 2005, 2009; Loetscher and Brugger, 2009; Loetscher *et al.*, 2010; Rossetti *et al.*, 2011; Tian *et al.*, 2011; van Dijck *et al.*, 2011; Pia *et al.*, in press). This study allowed us to test the consistency of two alternative hypotheses that might have still pointed to a link between the number bisection bias observed in right brain damage and pathological lateral biases of spatial attention.

First, neglect in imagery space can be dissociated from neglect in visual space (Guariglia *et al.*, 1993). Thus, it could be argued that dissociations between neglect-like behaviours along the mental number line and neglect in visual space do not necessarily imply that neglect for the mental number line has no spatial origin and that, on the contrary, neglect in number space is nothing but a special instance of imagery neglect. Results from our study show that orienting in mental number intervals has a peculiar status that does not correspond, both from neural and functional standpoints, to orienting in imagery space. The correlation between the seemingly 'rightward' bias towards higher numbers in the bisection of number intervals and a leftward, rather than rightward, bias in an imagined clock-face, shows that the number interval bisection bias in patients with right brain damage does not rely on a spatial read-out, i.e. it cannot be taken as an index of left spatial-imagery neglect.

Secondly, lesion studies and functional MRI evidence have demonstrated that the inherent left and right sides of visual objects (i.e. object-centred spatial coordinates) are coded in a right middle temporal area (Committeri *et al.*, 2004; Medina *et al.*, 2009; Verdon *et al.*, 2010; Khurshid *et al.*, 2012). It would be reasonable to hypothesize that this area is in charge of coding spatially oriented mental lines used to represent series of ascending numbers, days in a week, months in a year and so on

(Eagleman, 2009). Therefore, neglect-like behaviour in the bisection of number intervals could be considered a special instance of object-centred neglect. This would entail that dissociations between ego-centred neglect and biases in the bisection of number intervals do not necessarily mean that number intervals are not coded spatially and that, on the contrary, they are coded in object- rather than ego-centred spatial coordinates. The anatomical findings from the second study demonstrate that number intervals are not coded in brain areas that help the recollection of number positions within objects that, like a clock-face, have an inherent left-to-right orientation. This finding is in agreement with psychophysical evidence suggesting no intrinsic spatial organization of number magnitudes (Iuculano and Butterworth, 2011; Karolis *et al.*, 2011).

These two negative findings from our study are counterbalanced by the positive finding that biases towards higher numbers in the bisection of number intervals are due to disruption of a non-spatial abstract representation of small numbers or, in other words, that the right hemisphere supports the representation of small numerical magnitudes independently from their spatial mapping on the left or the right side of a mental layout. Taken together, these results have a number of interesting implications and can provide a unitary explanation of contrasting findings that were reported in the literature.

It has been reported that when patients with right brain damage have to choose between a left side and a right side button-press to decide whether a number is smaller or larger than the centre (i.e. 5) of a number interval (i.e. 1–9) or whether an hour-number comes earlier or later than a central reference on an imagined clock face (i.e. 6 o'clock), their reaction times are slower both for small numbers on the left side of the mental number line and for high hour-numbers on the left side of the clock-face (Vuilleumier *et al.*, 2004). Unlike these manual reaction time tasks, the tasks used in our study required no left versus right coding of the response. We show that, in this case, the deficit of right brain damage is no longer related to the left side of the mental number line and the left side of the clock face but rather, to the processing of small number magnitudes, independently of their spatial localization on the putative left side of a number interval or on the right side of a clock-face. This finding importantly suggests that the left-to-right arrangement of ascending positive integers is not inherent to number magnitudes and that it is rather elicited by the explicit left versus right coding of the motor responses that are used to provide an estimate of number magnitude (Ansorge and Wuhr, 2004; Keus and Schwarz, 2005; Gevers *et al.*, 2010). This interpretation provides a coherent explanation for the absence of a systematic relationship between the presence and severity of left spatial neglect and the bias towards high numbers in the bisection of number intervals. The verbal bisection of number intervals does not require the left versus right spatial coding of responses and, consequently, does not induce a mental left-to-right arrangement of numbers that would be vulnerable to left spatial neglect. In contrast, the same interpretation predicts that the severity of left spatial or imagery neglect is correlated with an equivalent bias in reaction time to numbers when, like in the magnitude or hour comparison task, the left versus right coding of the manual response induces a

left-to-right arrangement of adjacent number magnitudes along a mental-spatial continuum where spatial distances correspond to numerical distances between numbers to be compared (e.g. 4 is closer to 5 than 2 is to 5). We note that the same correlation between bias in reaction times and neglect severity could not be found in odd–even judgements where left versus right motor responses are related to categorical rather than quantitative judgements (Kosslyn *et al.*, 1989; e.g. 4 is not more or less ‘even’ than 2 when compared with 5).

The anatomical dissociations documented in our study also provide a coherent account for the finding that patients with right brain damage and with slowed reaction time both to numbers on the left side of the mental number line and to hour-numbers on the left side of an imagined clock face, can exhibit a SNARC effect only for hours on the clock-face (Vuilleumier *et al.*, 2004). Our anatomical findings (Doricchi *et al.*, 2003, 2009) show that in right brain damage the deficit in the processing of small number magnitudes depends on lesion involvement of frontal areas. Interestingly, frontal areas regulate the association of left versus right motor responses to spatially congruent or incongruent stimuli (Matsumoto *et al.*, 2004). Consequently, right frontal damage can disrupt both the representations of small number magnitudes and the association of left versus right responses to number magnitudes, thus precluding the appearance of the SNARC effect. Abolition of the SNARC by transcranial magnetic inactivation of the right superior and inferior frontal areas supports this interpretation (Rusconi *et al.*, 2011). In contrast, the SNARC can be preserved in the O’Clock task because, in this case, the reaction times bias for hour-numbers on the right side of the clock-face can be due to left side object-centred neglect, which depends on lesion of high-order visual areas that do not contribute to the SNARC effect.

Our data offer the challenging conclusion that the right hemisphere has a specific competence in representing and managing small numerical arabic magnitudes in the course of approximate numerical intuitions, such as estimating the midpoint of a number interval without applying exact calculations. More precisely, the specialization of the right hemisphere seems to concern the smallest arabic magnitudes belonging to the first decade. This functional advantage might be rooted in the dominance of the right hemisphere in the visual-spatial analysis of the numerosness of small sets of one to four visual items (i.e. subitizing; Ansari *et al.*, 2007; Vetter *et al.*, 2011) and is compatible both with the sensitivity of the right hemisphere to arabic notation (Cohen Kadosh *et al.*, 2007; Piazza *et al.*, 2007) and with its role in approximate numerical judgements (see Piazza *et al.* 2007 for a concise review of evidence). In line with our study, recent event-related potential investigations point out that right hemispheric dominance could extend to the processing of small arabic digits and not be limited to visual-spatial subitizing. This is suggested by findings showing that in patients with right brain damage the P300 response is delayed for small (i.e. ‘1’) as compared with large spoken numerical targets (i.e. ‘8’; Priftis *et al.*, 2008) and that in healthy participants visual arabic cues evoke parietal and frontal event-related potential components that are relatively larger over the left hemisphere for large numbers (i.e. ‘8’ and ‘9’) and over the right

hemisphere for small numbers (i.e. ‘1’ and ‘2’; Ranzini *et al.*, 2009).

Neurophysiological studies in the monkey and functional MRI investigations in humans show that estimating and manipulating number magnitudes depends on a bilateral parietal–frontal network (Dehaene, 2009). Both the posterior module of the network in the intraparietal sulcus and the anterior module in the prefrontal cortex are endowed with populations of neurons showing Gaussian tuning to specific numerosities (Nieder and Miller, 2004). The parietal module provides fast initial decoding of numerosity whereas the prefrontal module helps numerosity processing in working memory (Nieder and Miller, 2004) and high-level functions such as the application of simple rules (i.e. ‘greater/less than’; Bongard and Nieder, 2010), the appreciation of proportions between different magnitudes (Vallentin and Nieder, 2010) and the association of visual numerosities with Arabic symbols (Diester and Nieder, 2007). Interestingly, a short-term shift from prevalent prefrontal to parietal activity is observed in adults acquiring familiarity with new arithmetic problems and an equivalent long-term shift is observed across developmental acquisition of mathematical competence in children (Ansari *et al.*, 2005; Rivera *et al.*, 2005; Ansari and Dhital, 2006). Both of these observations are congruent with the negative effect of right frontal damage on the performance of human adults facing the unusual task of bisecting a number interval. The impact of right frontal damage on the representation of small magnitudes and the number bisection bias can be mediated by a number of different mechanisms. First, the bisection bias might be caused by defective voluntary access to intact representations of small magnitudes in the parietal module. Dissociation between preserved automatic and defective voluntary access has been proposed to explain normal SNARC in categorical odd-parity judgements performed by right brain damage showing number bisection bias (Priftis *et al.*, 2006). However, other authors have argued that preserved SNARC might depend on the maintained ability of managing associations between small/large numbers and left/right motor responses (Gevers *et al.*, 2010) rather than on spared automatic access to number representations. Alternatively, it can be proposed that due to dense white matter interconnections, a frontal lesion causes a general functional breakdown of the entire hemispheric number network, producing functional hypoactivation in the representations of small number magnitudes in structurally undamaged parietal areas. Our study confirmed that defective spatial working memory was correlated with biased bisection of number intervals (Doricchi *et al.*, 2005, 2009; Bachmann *et al.*, 2010; Fias *et al.*, 2011; Rossetti *et al.*, 2011; van Dijck *et al.*, 2011): this suggests that defective activation of small number representations could have been particularly detrimental for the bisection of large 7- and 9-unit number intervals, because bisection of these intervals implies processing large sets of numerical items and stronger competition for cognitive resources in working memory, which can penalize items that are more weakly represented.

To summarize, our investigation demonstrates that a pathological bias towards higher numbers in the mental sequence of ascending integers (i.e. the usually assumed left-to-right mental number line) can stem from the disruption of the abstract non-spatial representations of small number magnitudes. It is

worth noting that in terms of cultural evolution, neural representations of number magnitudes that are free from spatial-directional coding can be considered multipotent-plastic structures that can easily be recycled (Dehaene and Cohen, 2007) and tailored to learn and organize the mental sequence of natural numbers according to different culture-dependent reading styles. In conclusion, the results of our study provide clues that help to clarify the interaction between spatial and mathematical reasoning and suggest that the term ‘mental number line’ can be used properly only if devoid of fixed spatial connotations, just to indicate overlapping in the representation of numerically adjacent magnitudes.

Acknowledgements

The authors wish to thank Dr Michel Thiebaut de Schotten for useful suggestions and advice on the anatomical study, Prof. Clelia Rossi-Arnaud and Dr Jacinta O’ Shea for help in revising the manuscript and three anonymous referees for sharp and useful criticisms on the original version of the manuscript. The authors wish to thank Dr Luigi Amadio and the staff of the Fondazione Santa Lucia for their support to clinical and experimental neuroscience research.

Funding

F.D. was supported by a grant from the Fondazione Santa Lucia. Y.R. and S.J.C. were supported by the Inserm and the Hospices Civils de Lyon.

Supplementary material

Supplementary material is available at *Brain* online.

References

- Ansari D, Dhital B. Age-related changes in the activation of the intraparietal sulcus during nonsymbolic magnitude processing: an event-related functional magnetic resonance imaging study. *J Cogn Neurosci* 2006; 18: 1820–8.
- Ansari D, Garcia N, Lucas E, Hamon K, Dhital B. Neural correlates of symbolic number processing in children and adults. *Neuroreport* 2005; 16: 1769–73.
- Ansari D, Lyons IM, van Eimeren L, Xu F. Linking visual attention and number processing in the brain: the role of the temporo-parietal junction in small and large symbolic and nonsymbolic number comparison. *J Cogn Neurosci* 2007; 19: 1845–53.
- Ansorge U, Wuhr P. A response-discrimination account of the Simon effect. *J Exp Psychol Hum Percept Perform* 2004; 30: 365–77.
- Bachmann V, Fischer MH, Landolt HP, Brugger P. Asymmetric prefrontal cortex functions predict asymmetries in number space. *Brain Cogn* 2010; 74: 306–11.
- Bartolomeo P, Thiebaut de Schotten M, Doricchi F. Left unilateral neglect as a disconnection syndrome. *Cereb Cortex* 2007; 17: 2479–90.
- Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, et al. Voxel-based lesion-symptom mapping. *Nat Neurosci* 2003; 6: 448–50.
- Binder J, Marshall R, Lazar R, Benjamin J, Mohr JP. Distinct syndromes of hemineglect. *Arch Neurol* 1992; 49: 1187–94.
- Bongard S, Nieder A. Basic mathematical rules are encoded by primate prefrontal cortex neurons. *Proc Natl Acad Sci USA* 2010; 107: 2277–82.
- Boyer CB. A history of mathematics. New York: Wiley; 1968.
- Brunner E, Munzel U. The nonparametric Behrens-Fisher problem: asymptotic theory and a small-sample approximation. *Biometrical J* 2000; 42: 17–25.
- Chao YP, Cho KH, Yeh CH, Chou KH, Chen JH, Lin CP. Probabilistic topography of human corpus callosum using cytoarchitectural parcellation and high angular resolution diffusion imaging tractography. *Hum Brain Mapp* 2009; 30: 3172–87.
- Cohen Kadosh R, Kadosh KC, Kaas A, Henik A, Goebel R. Notation-dependent and -independent representations of numbers in the parietal lobes. *Neuron* 2007; 53: 307–14.
- Committeri G, Galati G, Paradis AL, Pizzamiglio L, Berthoz A, LeBihan D. Reference frames for spatial cognition: different brain areas are involved in viewer-, object-, and landmark-centred judgments about object location. *J Cogn Neurosci* 2004; 16: 1517–35.
- Dehaene S. Origins of mathematical intuitions the case of arithmetic. *Ann NY Acad Sci* 2009; 1156: 232–59.
- Dehaene S, Cohen L. Cultural recycling of cortical maps. *Neuron* 2007; 56: 384–98.
- Dehaene S, Bossini S, Giraux P. The mental representation of parity and number magnitude. *J Exp Psychol Gen* 1993; 122: 371–96.
- Dehaene S, Piazza M, Pinel P, Cohen L. Three parietal circuits for number processing. *Cogn Neuropsychol* 2003; 20: 487–506.
- Dierker I, Nieder A. Semantic associations between signs and numerical categories in the prefrontal cortex. *PLoS Biol* 2007; 5: e294.
- Diller L, Ben-Yishay Y, Gerstman L, Goodkin R, Gordon W, Weinberg J. Studies in cognition and rehabilitation in hemiplegia (Rehabilitation Mono graph No, 50). New York University Medical Center, Institute of Rehabilitation Medicine, 1974.
- Doricchi F, Tomaiuolo F. The anatomy of neglect without hemianopia: a key role for parietal-frontal disconnection? *NeuroReport* 2003; 14: 2239–43.
- Doricchi F, Guariglia P, Gasparini M, Tomaiuolo F. Dissociation between physical and mental number line bisection in right hemisphere brain damage. *Nat Neurosci* 2005; 8: 1663–5.
- Doricchi F, Merola S, Aiello M, Guariglia P, Bruschini M, Gevers W, et al. Spatial orienting biases in the decimal numeral system. *Curr Biol* 2009; 19: 682–7.
- Doricchi F, Thiebaut de Schotten M, Tomaiuolo F, Bartolomeo P. White matter (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness. *Cortex* 2008; 44: 983–95.
- Eagleman DM. The objectification of overlearned sequences: a new view of spatial sequence synesthesia. *Cortex* 2009; 45: 1266–77.
- Fias W, van Dijck JP, Gevers W. How is space associated with number? The role of working memory. In: Dehaene S, Brannon E, editors. *Space, time and number in the brain – searching for evolutionary foundations of mathematical thought: attention and performance XXIV*. Amsterdam: Elsevier Science, 2011. p. 133–48.
- Fink GR, Marshall JC, Shah NJ, Weiss PH, Halligan PW, Gosses-Ruyken M, et al. Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI. *Neurology* 2000; 54: 1324–31.
- Galton F. Visualized numerals. *Nature* 1880a; 21: 252–6.
- Galton F. Visualized numerals. *Nature* 1880b; 21: 494–5.
- Gevers W, Santens S, Dhooge E, Chen Q, Van den Bossche L, Fias W, et al. Verbal-spatial and visuospatial coding of number-space interactions. *J Exp Psychol Gen* 2010; 139: 180–90.
- Grossi D, Modafferi A, Pelosi L, Trojano L. On the different roles of the cerebral hemispheres in mental-imagery: the o'clock test in 2 clinical cases. *Brain Cogn* 1989; 10: 18–27.
- Guariglia C, Padovani A, Pantano P, Pizzamiglio L. Unilateral neglect restricted to visual-imagery. *Nature* 1993; 364: 235–7.
- He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M. Breakdown of functional connectivity in frontoparietal networks

- underlies behavioral deficits in spatial neglect. *Neuron* 2007; 53: 905–18.
- Iuculano T, Butterworth B. Understanding the real value of fractions and decimals. *Q J Exp Psychol* 2011; 64: 2088–98.
- Karolis V, Iuculano T, Butterworth B. Mapping numerical magnitudes along the right lines: differentiating between scale and bias. *J Exp Psychol Gen* 2011; 140: 693–706.
- Keus IM, Schwarz W. Searching for the functional locus of the SNARC effect: evidence for a response related origin. *Mem Cogn* 2005; 33: 681–95.
- Khurshid S, Trupe LA, Newhart M, Davis C, Molitoris JJ, Medina J, et al. Reperfusion of specific cortical areas is associated with improvement in distinct forms of hemispatial neglect. *Cortex* 2012; 48: 530–9.
- Kimberg DY, Coslett HB, Schwartz MF. Power in Voxel-based lesion-symptom mapping. *J Cogn Neurosci* 2007; 19: 1067–80.
- Kosslyn SM, Koenig O, Barrett A, Cave CB, Tang J, Gabrieli JD. Evidence for two types of spatial representations: hemispheric specialization for categorical and coordinate relations. *J Exp Psychol Hum Percept Perform* 1989; 15: 723–35.
- Lawes INC, Barrick TR, Murugam V, Spierings N, Evans DR, Song M, et al. Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. *NeuroImage* 2008; 39: 62–79.
- Loetscher T, Brugger P. Random number generation in neglect patients reveals enhanced response stereotypy, but no neglect in number space. *Neuropsychologia* 2009; 47: 276–9.
- Loetscher T, Nicholls MER, Towse JN, Bradshaw JL, Brugger P. Lucky numbers: spatial neglect affects physical, but not representational, choices in a Lotto task. *Cortex* 2010; 46: 685–90.
- Matsumoto E, Misaki M, Miyachi S. Neural mechanisms of spatial stimulus-response compatibility: the effect of crossed-hand position. *Exp Brain Res* 2004; 158: 9–17.
- Medina J, Kimberg DY, Chatterjee A, Coslett HB. Inappropriate usage of Brunner–Munzel test in recent voxel-based lesion symptom mapping studies. *Neuropsychologia* 2010; 48: 341–3.
- Medina J, Kannan V, Pawlak MA, Kleinman JT, Newhart M, Davis C, et al. Neural substrates of visuospatial processing in distinct reference frames: evidence from unilateral spatial neglect. *J Cogn Neurosci* 2009; 21: 2073–84.
- Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* 2002; 15: 1–25.
- Nieder A, Miller EK. A parieto-frontal network for visual numerical information in the monkey. *Proc Natl Acad Sci USA* 2004; 101: 7457–62.
- Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, et al. Human brain white matter atlas: identification and assignment of common anatomical structures in superficial white matter. *NeuroImage* 2008; 43: 447–57.
- Pia L, Neppi-Modona M, Crevasco L, Gindri P, Dal Monte O, Folegatti A. Functional independence between numerical and visual space: evidence from right-brain damaged patients. *Cortex* (in press).
- Piazza M, Pinel P, Le Bihan D, Dehaene S. A magnitude code common to numerosities and number symbols in human intraparietal cortex. *Neuron* 2007; 53: 293–305.
- Pizzamiglio L, Antonucci G, Judica A, Montenero P, Razzano C, Zoccolotti P. Cognitive rehabilitation of the hemineglect disorder in chronic patients with unilateral brain damage. *J Clin Exp Neuropsychol* 1992; 14: 901–23.
- Priftis K, Piccione F, Giorgi F, Meneghello F, Umiltà C, Zorzi M. Lost in number space after right brain damage: a neural signature of representational neglect. *Cortex* 2008; 44: 449–53.
- Priftis K, Zorzi M, Meneghello F, Marenzi R, Umiltà C. Explicit versus implicit processing of representational space in neglect: dissociations in accessing the mental number line. *J Cogn Neurosci* 2006; 18: 680–8.
- Ranzini M, Dehaene S, Piazza M, Hubbard EM. Neural mechanisms of attentional shifts due to irrelevant spatial and numerical cues. *Neuropsychologia* 2009; 47: 2615–24.
- Rivera SM, Reiss AL, Eckert MA, Menon V. Developmental changes in mental arithmetic: evidence for increased functional specialization in the left inferior parietal cortex. *Cereb Cortex* 2005; 15: 1779–90.
- Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci* 2007; 19: 1081–8.
- Rorden C, Karnath HO. A simple measure of neglect severity. *Neuropsychologia* 2010; 48: 2758–63.
- Rossetti Y, Jacquin-Courtois S, Aiello M, Ishihara M, Brozzoli C, Doricchi F. Neglect 'around the Clock': dissociating number and spatial neglect in right brain damage. In: Dehaene S, Brannon E, editors. *Space, time and number in the brain – searching for evolutionary foundations of mathematical thought: attention and performance XXIV*. Amsterdam: Elsevier Science, 2011. p. 149–72.
- Rossetti Y, Jacquin-Courtois S, Rode G, Ota H, Michel C, Boisson D. Does action make the link between number and space representation? Visuo-manual adaptation improves number bisection in unilateral neglect. *Psychol Sci* 2004; 15: 426–30.
- Rusconi E, Bueti D, Walsh V, Butterworth B. Contribution of frontal cortex to the spatial representation of number. *Cortex* 2011; 47: 2–13.
- Sagiv N, Simner J, Collins J, Butterworth B, Ward J. What is the relationship between synaesthesia and visuo-spatial number forms? *Cognition* 2006; 101: 114–28.
- Seron X, Pesenti M, Noel MP, Deloche G, Cornet JA. Images of numbers, or “When 98 is upper left and 6 sky blue”. *Cognition* 1992; 44: 159–96.
- Shinoura N, Suzuki Y, Yamada R, Tabei Y, Saito K, Yagi K. Damage to the right superior longitudinal fasciculus in the inferior parietal lobe plays a role in spatial neglect. *Neuropsychologia* 2009; 47: 2600–3.
- Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Levy R, Dubois B, et al. Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. *Science* 2005; 309: 2226–8.
- Thiebaut de Schotten M, Dell'Acqua F, Forkel S, Simmons A, Vergani F, et al. Lateralized brain network for visuo-spatial attention. *Nat Neurosci* 2011a; 14: 1245–6.
- Thiebaut de Schotten M, Ffytche DH, Bizzi A, Dell'Acqua F, Allin M, et al. Atlas location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *NeuroImage* 2011b; 54: 49–59.
- Thiebaut de Schotten M, Dell'Acqua F, Valabregue R, Catani M. Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex* 2012; 48: 82–96.
- Tian Y, Wei L, Wang C, Chen H, Jin S, Wang Y, et al. Dissociation between visual line bisection and mental number line bisection in schizophrenia. *Neurosci Lett* 2011; 491: 192–5.
- Vallentin D, Nieder A. Representations of visual proportions in the primate posterior parietal and prefrontal cortices. *Eur J Neurosci* 2010; 32: 1380–7.
- van Dijk JP, Gevers W, Lafosse C, Doricchi F, Fias W. Non-spatial neglect for the mental number line. *Neuropsychologia* 2011; 49: 2570–83.
- Verdon V, Schwartz S, Lovblad KO, Hauert CA, Vuilleumier P. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion symptom mapping. *Brain* 2010; 133: 880–94.
- Vetter P, Butterworth B, Bahrami B. A candidate for the attentional bottleneck: set-size specific modulation of the right TPJ during attentive enumeration. *J Cogn Neurosci* 2011; 23: 728–36.
- Vuilleumier P, Ortigue S, Brugger P. The number space and neglect. *Cortex* 2004; 40: 399–410.
- Wilson BA, Cockburn J, Halligan P. Behavioral inattention test. Titchfield, Hampshire: Thames Valley Test Company; 1987.
- Zorzi M, Priftis K, Umiltà C. Brain damage - neglect disrupts the mental number line. *Nature* 2002; 417: 138–9.