Neuro-anatomical correlates of a number bisection bias: A neuropsychological voxel-based morphometry study

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ABSTRACT

The number bisection tasks, whereby participants estimate the midpoint of a given number interval, is frequently used to explore the idea that numbers are spatially represented within the brain across a 'mental number line'. Some neuropsychological research supports the argument that number bisection is a spatial task, recruiting parietal brain regions, whereas other data suggest that number bisection is dissociable from spatial processing and is instead dependent on working memory in the prefrontal cortices. This study explored the anatomical correlates of deficits in the number bisection task, using voxel-based morphometry in a sample of 25 neuropsychological patients with both left and right hemisphere damage. Interestingly, impairments in number bisection were strongly associated with grey matter lesions in the left hemisphere including both frontal and prefrontal cortices, extending to inferior parietal cortex. Similar prefrontal and frontal grey matter areas were found to be associated with increased leftward deviations (underestimations of the midpoint), whereas no suprathreshold clusters were observed for rightward deviations from the midpoint. Analysis of white matter integrity revealed that lesions in the tracts connecting the parietal and frontal cortices (i.e. the superior longitudinal fasciculus) were highly associated with leftward deviation impairments in number bisection. The data suggest that there is a common parieto-frontal number processing network underlying performances on number bisection, with larger numbers represented on the left side.

1. Introduction

Number and space may rely on common functional and neural processes. The idea that people use spatial representations when they think about numbers dates back to early observational studies in the 1880s (Galton, 1880) which reported that participants consciously state that number processing involves visuo-spatial experiences. Subsequently, observations that participants are faster at responding to smaller numbers with their left hand and larger numbers with their right hand (Dehaene et al., 1993) has led to the idea that numbers are spatially represented within the brain across a horizontal 'mental number line'. This spatial representation of numbers is thought to be organised in a continuous, analogic format (Dehaene et al., 1990).

Some neuropsychological research with hemi-spatial neglect patients supports the spatial organisation of numbers. Zorzi et al. (2002) conducted research with four hemi-spatial neglect patients and found that these patients showed the same attentional biases on spatial and number tasks, suggesting that the underlying processes are related.

Typically, when asked to bisect the midpoint of a visually presented line, patients with left neglect following a right hemisphere lesion misperceive the midpoint as more towards the right. Furthermore, these patients tend to show a crossover effect for shorter lines — perceiving the midpoint to be towards the left side (Marshall and Halligan, 1989). Zorzi et al. (2002) observed that left neglect patients make this same pattern of errors on number bisection tasks; deviating towards the right when asked to indicate the midpoint number within a number interval (e.g. 1–7, response 6) and showing a crossover effect for shorter intervals (e.g. 1–3, response 1). These similarities in performance on the number and line bisection tasks in neglect patients suggest that numbers may be spatially represented within the brain. Zorzi et al. (2002) also found that, when number intervals were reversed (e.g. 7–1), left neglect patients still showed the same bias (i.e. a rightward bias towards larger numbers), consistent with the mental number line being canonically organised, with smaller numbers always represented on the left and larger numbers on the right, regardless of the order presented. These findings have since been replicated in other studies with the neglect population, including an individual with right neglect following left hemisphere lesions (Pia et al., 2009), supporting a functional relationship between representations of number and space (e.g. Zamarian et al., 2007; Cappelletti et al., 2009).

More recently Zorzi et al. (2012) found that this effect of spatial neglect on number processing can be modulated by task demands.

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They gave patients with right hemisphere damage a number bisection and an odd/even (parity) number judgement task. They found that neglect patients performed normally on the parity judgement task but when number magnitude was explicit, as in the number bisection task, they showed a rightward deviation. Zorzi et al. suggested that the explicit task exaggerated the number-space interaction causing this task specific impairment. They concluded that the spatial attention hypothesis remains 'the most viable' explanation for number bisection biases suggesting patients are unable to orient towards smaller magnitudes or disengage from larger magnitudes thus causing a rightward deviation when asked to bisect number intervals.

Some neurophysiological evidence supports this spatial-attention hypothesis finding that number processing relies on spatial processing areas within the brain, situated in the parietal lobes, including the posterior parietal cortex and the intraparietal sulcus (see Hubbard et al., 2005, for an overview). For example, research with repetitive transcranial magnetic stimulation (rTMS) with normal subjects has found that disrupting the right posterior parietal cortex produces neglect-like symptoms on both the line and number bisection tasks (Gobel et al., 2006), consistent with line and number bisection sharing common neural correlates within the parietal lobes. Pia et al. (2009) studied a right neglect patient who had a selective lesion to the posterior superior parietal region in the left hemisphere and a marked impairment on number bisection. They suggested that number bisection relies on regions of the posterior parietal cortex involved in spatial representation. The authors cautiously noted that "the functional association between the line and number bisection could be a consequence of damage to two different, although close, brain areas". Indeed, in a further study, Pia et al. (2012) failed to find a correlation between severity of left neglect and number bisection error in a group of 32 right-brain damaged patients with and without left neglect, suggesting that attentional systems involved in navigating across visual and numerical internal representations may involve distinct neuro-cognitive operations.

This contrasting account of functional independence of number and space was first proposed by Doricchi et al. (2005), who investigated line and number bisection performance in left neglect patients and found that bisection of these intervals was doubly dissociated, therefore suggesting they are not functionally related. Instead, they found that deviation in number bisection was associated with prefrontal damage and a spatial working memory deficit. This was corroborated by further research (Doricchi et al., 2009) observing a correlation between difficulties in maintaining verbal and spatial sequences in working memory and deviation on the number interval bisection task. In addition, other correlational studies investigating number and line bisection have failed to support a relationship (e.g. Rosetti et al., 2011; <0.1 correlation in 74 neglect patients). Furthermore, a recent study by Aiello et al. (2012) supports the idea of the 'mental number line' as a non-spatial entity. In this study, patients with left neglect were asked to indicate the midpoint hour of a given interval on a standard version of a clock face (with smaller numbers presented on the right side/larger numbers on the left) and a non-standard version, with larger numbers presented on the left side, congruent with the number bisection task. They found that the patients always deviated towards the higher numbers both on the standard and the non-standard versions of the task — that is, the numerical format won over spatial coding, with biases to the left produced by left-side larger numbers. In addition, there was no reliable correlation between neglect severity and a rightward bias on number bisection task.

Van Dijck et al. (2011) suggested that the neglect bias towards the right side of a number interval may be due to a position-based working memory deficit. Supporting this claim, they reported a patient with right neglect who showed a rightward deviation on number bisection, rather than a leftward deviation consistent with the pattern of neglect. The patient also had a working memory impairment for recalling the beginning of number sequences, which the authors

suggested led to more weight being given to the end of the number interval in the number bisection task. This observation suggests that different cognitive processes underlie the interval bisection and the line bisection task.

Anatomically, some research supports the alternative working memory hypothesis for number bisection whereby it is often the case that patients who are impaired on the number bisection task also have lesions that extend to prefrontal regions of cortex associated with working memory. For example, some of Zorzi et al.'s (2002) patients' had lesions extending into prefrontal cortex, however the patient's working memory abilities were not assessed. Doricchi et al. (2009) studied the anatomical correlates of rightward bias in the number bisection task. They found an anatomical dissociation between number interval and visual line bisection suggesting the tasks are unrelated. Furthermore, the rightward number bisection bias had maximal lesion overlap in right prefrontal areas frequently associated with number processing and working memory. Bongard and Nieder (2010) conducted single cell-recording experiments with primates and found more number specific neural activity in prefrontal than parietal cortex. Together, this research suggests a 'frontal' working memory account may provide a better explanation of number bisection deficits than the 'parietal' spatial number line account.

A more recent study by van Dijck et al. (2012) used Principle Component Analysis across a battery of tests to assess the functional relationship between different tasks and the effects on number bisection. They found that number bisection is complex and involves a number of components including both spatial and verbal working memory components, accounting for 78% of the variance among right brain damaged patients. This led them to suggest a unitary framework incorporating both the mental number line and working memory hypothesis to be more fitting in understanding the relation between numbers and space.

Number processing typically involves a distribution of brain areas including both parietal, spatial areas (e.g., the intraparietal sulcus/postcentral gyrus) and prefrontal, working memory areas (e.g., the inferior/dorsolateral prefrontal cortex; e.g. Chochon et al., 1999; Nieder and Dehaene, 2009). It may be, then, that impaired connectivity between spatial representations and working memory deficits causes the neglect-like symptoms which can be found in number bisection. Consistent with this proposal is evidence showing that increased activity in cortical regions associated with spatial attention is correlated with improved working memory performance (Lepsien et al., 2011). Furthermore, recent research using voxel-based lesion-symptom mapping with only right-hemisphere damaged patients, found a significant correlation between a rightward deviation on the number bisection task and frontal damage, along with lesions to dense white matter interconnections across parietal and frontal areas (Aiello et al., 2012). These data suggest that interactions between spatial, parietal regions and working memory-related prefrontal regions may support performance on the number bisection task.

To further our understanding of the neuroanatomy of number bisection issues, this study reports a voxelbased morphometry (VBM) analysis of the neural correlates of biased number bisection performance in a sample of neuropsychological patients which includes patients with left- hemisphere lesions as well as right-sided lesions. Patients presented behaviourally with various impairments (including neglect and working memory). High resolution structural MRI scans were taken for a consecutive sample of neuropsychological patients (selected neither for their lesion location nor their behavioural performance) and segmented into grey and white matter and entered in a general linear model, along with behavioural scores from the number bisection task. We ask whether biases in number bisection stem from lesions to parietal or prefrontal cortices, and also whether the deficits could relate to damage to regions of white matter associated with prefrontal–parietal connectivity supporting the 'number network' hypothesis.

2. Method

2.1. Participants

Twenty-five neuropsychological patients (21 male, 4 female) participated, aged 39–79 years (M = 65.36, SD = 11.35). The patients were volunteers from the University of Birmingham neuropsychological test panel. All the patients had acquired brain lesions (22 stroke, 2 anoxia, 1 encephalitis) and were in the chronic stage (>9 months). Full patient details are given in Table 1.

All patients provided written informed consent in agreement with ethics protocols at the School of Psychology and Birmingham University Imaging Centre (BUIC).

2.2. Behavioural assessment

The number bisection experiment was run using E-prime 2.0 software. The stimuli were presented on a 19″ LCD Samsung Sync Master 940 N monitor with a 1280×1024 pixel resolution. Participants were seated approximately 65 cm from the screen. The two numbers, representing a number interval, were presented centrally on a black background, in white font, size 1cmx1cm each and presented 1.5 cm apart (visual angle = 0.89°). Various number interval widths were included, ranging from three (e.g. 1–3), five (e.g. 1–5), seven (e.g. 1–7) to nine (e.g. 1–9). Each number interval was presented within one of the following magnitudes; units (1–9), tens (11–19) or twenties (21–29). The order was reversed across half the trials (e.g. 3–1) to investigate if patients produced the same pattern of errors in 'standard' and 'reversed' conditions. Overall, the experiment contained 3 blocks of 48 trials, totalling 144 trials, with 36 trials per interval width.

Patients were first presented with the instructions: 'Please tell me the midpoint number in the presented number intervals without making calculations'. Trials then started with presentation of a fixation cross for 1000 ms, followed by the two numbers presented in the centre of the screen for 5000 ms. Following this a question mark appeared on the screen indicating that the patient needed to make a response. The patient then verbally estimated the midpoint number and the experimenter entered this response using the numerical keypad. There was no timelimit set on the verbal responses of the patients, to not penalise patients who are generally slow in responding, or may have word finding problems

Average deviation from the midpoint was calculated for each patient in each condition.

2.3. Neuroimaging assessment

Patients were scanned at the Birmingham University Imaging Centre (BUIC) on a 3 T Philips Achieve MRI system with an 8-channel phased array Sense head coil. The anatomical scans were acquired using a sagittal T1-weighted sequence (sagittal orientation, TE/TR = 3.8/8.4 ms, voxel size 1×1×1mm)

2.4. Image pre-processing

T1 scans from patients were first converted and reoriented using MRIcro (Chris Rorden, Georgia Tech. Atlanta, GA, USA). Pre-processing of the scans was done in SPM5 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London, UK). Brain scans were transformed into the standard MNI space using the unified-segmentation procedure (Ashburner and Friston, 2005). This procedure involves tissue classification based on the signal intensity in each voxel and on a prior knowledge of the expected localisation of grey matter, white matter and cerebrospinal fluid in the brain. The tissues are iteratively segmented and warped onto standard space. To further improve tissue classification and spatial normalization of lesioned brains we used a modified segmentation procedure (Seghier et al., 2008). Following segmentation the scans were visually inspected to assess whether segmentation and normalisation were successful. Finally the segmented images were smoothed with 12 mm FWHM Gaussian filter to accommodate the assumption of random field theory used in the statistical analyses (Worsley, 2004). Pre-processed grey and white matter maps were then used in the analyses to determine voxel-by voxel relationships between brain damage and the number bisection scores. Previous analyses using these procedures with the patient population sampled here have been successful in establishing reliable structure-function links even with relatively small patient samples (Leff et al., 2009; Chechlacz et al., 2010; Sui et al., 2012).

Table 1
Patient overview: clinical and demographic details. TPL = time post lesion (in years), Lesion Side L = Left, R = Right, B = Bilateral.

ID	Sex	Age	Handedness	Aetiology	TPL	Lesion side	Lesion volume cm^3	% total error	Number bisection deviation	Interval 5,7,9 only bisection deviation
1	m	67	R	Stroke	2	R	70.79	7.16	−1.50	1.70
2	m	57	R	Anoxia	10	L	1.39	19.66	−16.49	−19.21
3	f	62	R	Stroke	13	B	25.77	16.50	−7.35	−14.43
4	m	76	R	Stroke	3	R	0.46	22.25	12.67	17.82
5	m	56	R	Stroke	4	R	29.94	13.10	−13.37	−15.97
6	m	79	R	Stroke	4	R	4.58	11.66	7.87	7.72
7	m	63	R	Stroke	3	R	0.53	1.67	0.12	0.15
8	m	78	L	Stroke	14	L	61.24	31.56	−37.04	−23.46
9	m	79	R	Stroke	3	L	16.90	8.99	−0.58	−1.70
10	f	54	R	Stroke	2	R	2.61	1.10	−0.98	−1.31
11	m	51	R	Stroke	5	R	3.34	4.13	2.49	1.47
12	m	63	L	Stroke	2	R	1.35	8.13	4.28	3.86
13	m	64	L	Stroke	12	R	70.53	21.20	21.64	18.67
14	m	77	L	Stroke	8	L	43.66	25.00	13.89	14.35
15	m	57	R	Stroke	5	R	30.73	3.38	2.95	3.94
16	m	45	R	Encephalitis	15	B	38.50	19.12	20.60	9.88
17	m	73	R	Stroke	8	R	72.92	6.25	8.39	9.34
18	m	77	R	Stroke	2	R	83.08	5.10	−4.28	−3.86
19	m	39	L	Stroke	10	L	27.17	21.21	−10.33	−24.88
20	m	22	L	Stroke	12	B	6.57	65.08	29.98	26.08
21	m	70	L	Stroke	4	B	36.00	96.86	12.76	−2.43
22	m	70	R	Stroke	4	L	8.91	4.74	−4.95	−6.60
23	m	85	R	Anoxia	13	R	0.59	54.87	15.05	13.58
24	f	76	R	Stroke	5	B	62.74	7.15	1.39	−1.85
25	f	66	L	Stroke	4	R	24.36	11.35	9.66	6.40

The lesion maps for all patients were automatically identified from T1-weighted scans using a modified unified segmentation and an outlier detection algorithm using default parameters (see Seghier et al., 2008 for details). This procedure identifies voxels that are different in the lesioned brains as compared to a set of healthy control brains (set of T1-weighted scans from 100 healthy controls; 55 males and 45 females, mean age 54.5 years, range 20–87) using normalized GM and WM segments. The GM and WM outlier voxels are next combined into a single outlier image and thresholded to generate a binary map of the lesion. The results of lesion reconstruction were verified against the patient's T1 scans and the binary lesion maps were used to calculate lesion volumes for each patient using Matlab 7.5 (The MathWorks, Natick, MA, USA).

2.5. Voxel based morphometry

Scans from the 25 patients, segmented into individual white matter and grey matter maps (see above for the pre-processing protocol) were used in the statistical analysis with SPM8. The voxel-by-voxel correlational relationship between the behavioural measures of number bisection and the damaged tissue was assessed separately for grey and white matter integrity. We used parametric statistics within the framework of the general linear model (Kiebel and Holmes, 2003). Three separate analyses will be reported, one on the overall number of errors made in the number bisection task. The second statistical model included covariates for average left deviation size and average right deviation size. Finally, in the third model, 4 covariates are contrasted: (i) average left deviation size when numbers were presented in normal order, (ii) when presented in reversed order, (iii) average right deviation size when presented in normal order and (iv) in reversed order. Including all four covariates in one analysis allows us to account for potential co-variation effects and to ensure we could test for dissociated neuronal substrates. Additionally, in each statistical model, we also included the calculated lesion volume per patient as well as other covariates of no interest: aetiology of brain damage, age, handedness and gender.

To be conservative, results were only documented if significant when cluster level corrected for multiple comparisons (family wise error corrected, FWE) at p<0.05 and with an extent threshold of 100 voxels. Brain coordinates are presented in the standardised MNI space. Anatomical localisation of the lesion sites is based on the anatomy toolbox (Tzourio-Mazoyer et al., 2002), the Duvernoy Human Brain Atlas

(Duvernoy et al., 1991) and the MRI Atlas of Human White Matter (Mori, 2005).

3. Results

3.1. Behavioural results: number bisection

Overall the percentage of errors ranged from 4.86% to 97.22% across the patients with a mean error of 39.18% (SD = 43.69). The overall error percentage values for each patient are given in the overview table, Table 1.

The average deviation from the midpoint was calculated per participant for each trial using the following formula (adapted from van Dijck et al., 2011):

$$Deviation = \frac{patient's\ estimate\ of\ midpoint - true\ midpoint}{true\ midpoint - 1} \times 100$$

The added "−1" in the denominator allows for a more true reflection of the bias in number bisections, with a 100% deviation being the end value of the numerical interval (as opposed to line bisections which start at value 0). A distribution of patients' deviation scores contrasting performance in the normal and the reversed order conditions is given in Fig. 1. A paired t-test on the reversed and normal order conditions revealed that these conditions did not differ significantly ($t(24) = -1.30$, p = .21), therefore the deviations were averaged across the two presentation conditions for all further analyses (see Table 1 for actual values per patient).

Given several reports of a directionally opposite bias on short 3-unit intervals (e.g. Zorzi et al., 2002), we also calculated the bisection bias on only the three larger number intervals (5,7,9). We did not find a difference between the two scores ($t(24) = 1.64$, p = .114) and they correlated highly (r = .910, p<.001). However, to ensure we do not underestimate the average bias per patient, we opted to use the bias across only the larger intervals as our covariate of interest for the VBM analysis.

Note that in the VBM analysis, scores were converted to absolute values, so that a larger value always represents a larger bias and two covariates rather than one were thus entered (Leftward and Rightward bias) — see Table 1 for values per patient.
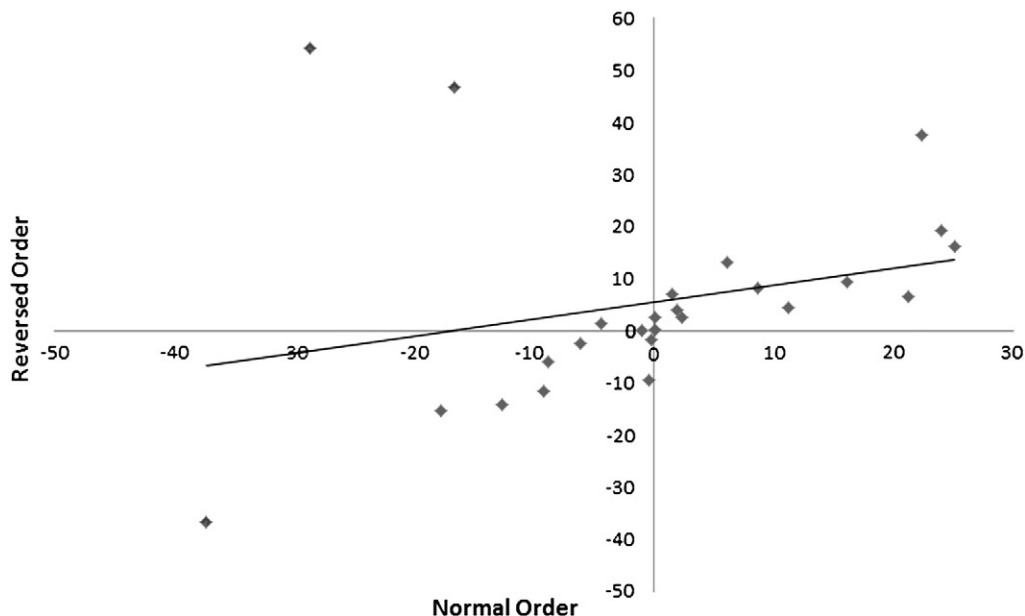

Fig. 1. Mean deviation scores (%) on the number bisection task for each patient in the normal (X) and reversed (Y) presentation conditions.
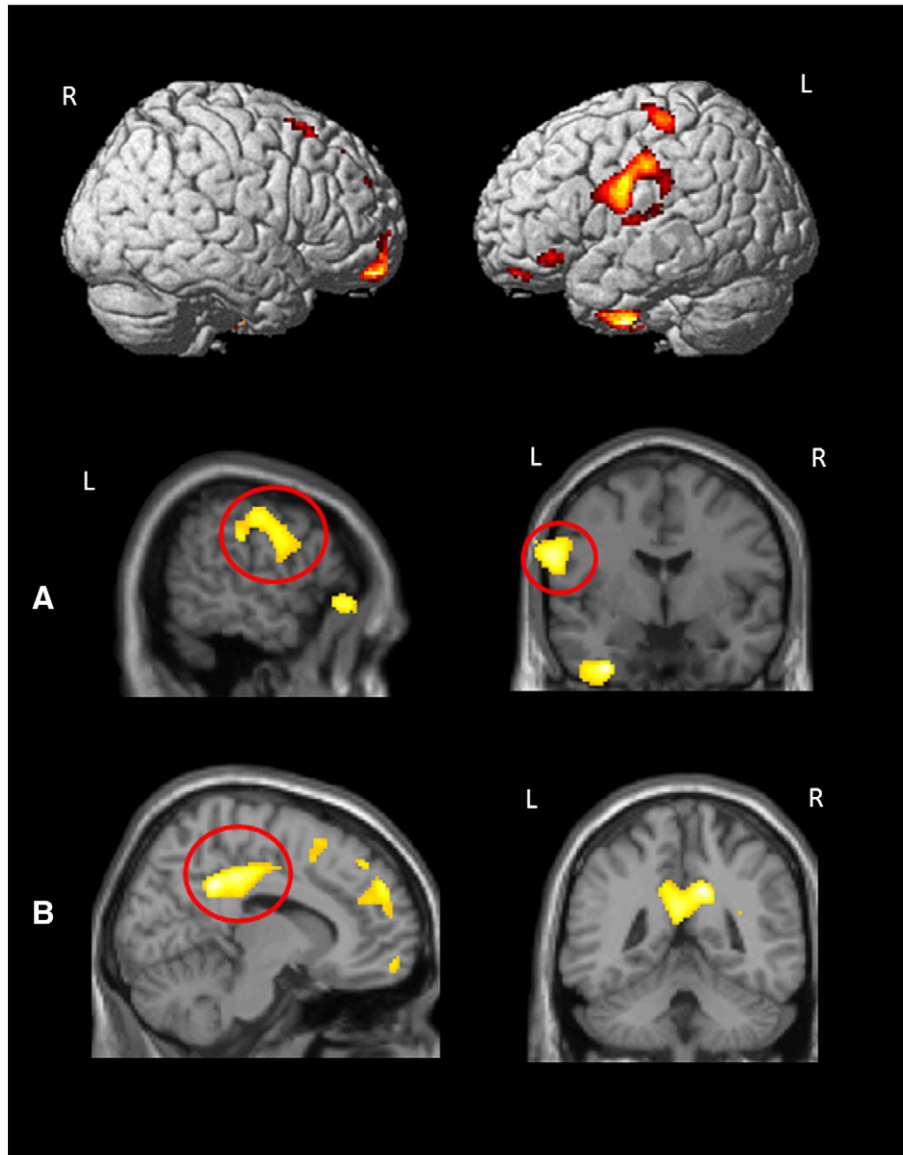
Fig. 2. Grey matter lesions associated with overall performance errors. Lesion areas that are brighter indicate a higher t-value. Top images show surface rendering of lesions. A.: damage involving the left inferior parietal cortex/postcentral gyrus, B.: Bilateral middle cingulate cortex (see Table 2). Each area has been circled on the image. L = left hemisphere, R = right hemisphere.

3.2. Voxel based morphometry results

Overall number of errors. A higher percentage of overall errors (no direction taken into account) on the number bisection task was associated with damage to a network of grey matter areas including the left postcentral gyrus extending to inferior parietal cortex, the left temporal fusiform gyrus and bilateral middle cingulate cortex (Fig. 2).

White matter analyses did not indicate any suprathreshold clusters. Table 2 indicates the full set of results for overall errors (p<0.05, FWE corrected at cluster level).

3.2.1. Number bisection deviation. When regarding average deviations from midpoint, rather than overall errors, a conjunction analysis of both leftward and rightward average deviations (across all interval

Table 2

The results reflect voxel-based correlations of voxel signal intensities for grey matter across the entire brains of 25 patients with contrasts assessing correlations specific for overall numbers of errors on the number bisection task. X, Y, and Z refer to the stereotaxic MNI coordinates of the peak of the cluster. The threshold for significance of the clusters reported here was set at a voxel-wise uncorrected p<.001 – whole brain – cluster level corrected for multiple comparisons (family wise error corrected, FWE) at p<0.05 and a spatial extent of 100 voxels.

		Cluster level		Voxel level	MNI coordinates				Area in
Analysis	Contrast	p (FWE)	Size	Z	x	y	z	Brain structure	Fig. 2
Grey matter	Overall errors	0.001	970	4.23	−66	−4	24	Left postcentral gyrus	A
					−58	−28	28	Left supramarginal gyrus	
		0.007	688	4.59	−34	−6	−40	Left temporal fusiform gyrus	
		0.0001	1631	4.44	1	−46	32	Bilateral middle cingulate gyrus	B
White matter	No suprathreshold clusters								

Table 3
Contrasts assessing correlations specific for average leftward and rightward bisection bias in the larger interval sizes. x, y, and z refer to the stereotaxic MNI coordinates of the peak of the cluster. The threshold for significance of the clusters reported here was set at a voxel-wise uncorrected p<.001 – whole brain – cluster level corrected for multiple comparisons (family wise error corrected, FWE) at p<0.05 and a spatial extent of 100 voxels.

| Analysis | Contrast | Cluster level | | Voxel level | MNI coordinates | | | Brain structure | Area in |
		p (FWE)	Size	Z	x	y	z		Fig. 3.
Grey matter	Left deviation	<0.001	2006	4.12	−48	28	4	Left inferior frontal gyrus/orbital gyrus	A
		0.031	487	4.11	−14	−8	12	Left Thalamus	
				3.94	−16	2	12	Left Putamen	
		0.012	624	3.83	−38	−34	52	Left postcentral gyrus	
				3.62	−48	−26	48	Left inferior parietal	
		0.041	451	3.58	−40	24	32	Left Mid. Frontal gyrus	
	Right deviation	No suprathreshold clusters							
White matter	Left deviation	0.020	248	3.49	−28	30	20	Left callosal body	B
								Left corticospinal tract	
		0.003	370	3.37	−22	0	32	Left superior longitudinal fasciculus	
	Right deviation	No Suprathreshold Clusters							
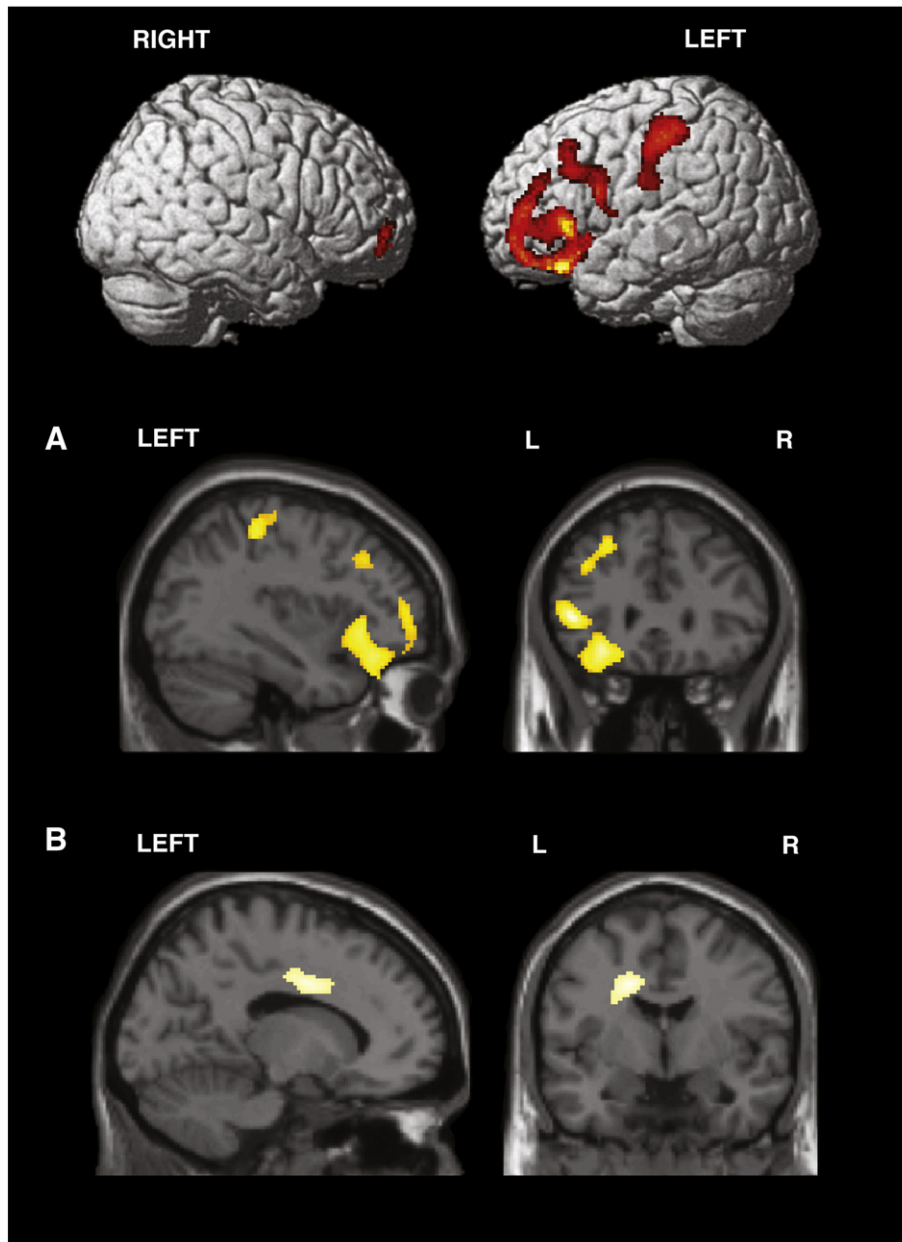
Fig. 3. Grey matter lesions associated with left deviation on the number bisection task, for the three larger interval sizes. Lesion areas that are brighter indicate a higher t-value. Top 3D images show surface rendering of lesions. A: Damage involving the left inferior frontal gyrus, and middle frontal gyrus (see Table 3). B: White matter lesions associated with left deviation on the number bisection task. Lesion areas that are brighter indicate a higher t-value. B. Damage to white matter tracts including the left callosal body and corticospinal tract. L=left hemisphere, R=right hemisphere. Each area has been circled on the image. L=left hemisphere, R=right hemisphere.

lengths) found no suprathreshold grey or white matter areas related to deviations (Table 3).

Leftward number bisection deviation (i.e. on average incorrectly responding with a smaller number than the midpoint number) was associated with damage to a large grey matter area spanning the left prefrontal/frontal to inferior parietal cortex. Specifically clusters surrounding the left inferior frontal gyrus and left postcentral gyrus were noted (Fig. 3). Deviating towards the right of the interval did not reveal any significant association with grey matter damage.

For the white matter analysis, leftward deviation was significantly associated with damage to white matter tracts including the left callosal body, the left corticospinal tract and the superior longitudinal fasciculus (Fig. 3). Deviating towards the right of the interval did not indicate any significant correlations with white matter lesions.

4. Discussion

This study is among the first to explore the brain lesions associated with impaired performance on the number bisection task using voxel based morphometry. We aimed to test which anatomical structures were necessary for accurate number bisection, and also whether spatial brain areas (parietal cortex), working memory areas (prefrontal cortex) or a combination of both related to performance in number bisection. Overall, we consistently found lesions in the left frontal and prefrontal cortices associated with poorer performance on the task. Importantly a significant white matter disconnection, including the left superior longitudinal fasciculus was found to be associated with leftward bias in bisecting numerical intervals. This white matter tract connects the parietal with the frontal areas within visuo-spatial attention networks (e.g. Bartolomeo et al., 2012). This tract has also been found to relate to deviation on the line bisection task (Thiebaut de Schotten et al., 2005, 2011). Surprisingly, we did not find any consistent grey or white matter regions related to overestimations of the midpoint. Aiello et al. (2012), in a study with only right hemisphere damage patients found that damage to this network in the right-hemisphere produces biases towards larger numbers and the current findings show that damage to the network in the left-hemisphere causes biases towards smaller numbers. The connections underlying this parieto-frontal network have been associated with other number processing domains, such as mental arithmetic and mathematical achievement (e.g. Emerson and Cantlon, 2011), consistent with the idea that both prefrontal and parietal regions contribute critically to number processing. These findings complement those of Aiello et al. (2012) and further our understanding of the number network across the two hemispheres. Importantly, this suggests that each hemisphere's number network is specialised towards different number magnitudes, with the left concerned with larger numbers and the right occupied by smaller numbers. Damage to this network in one hemisphere causes hypo-activation and possibly hyper-activation of the other hemisphere's network causing the patient to deviate from the midpoint of a numerical interval.

Our first analysis assessed the neural correlates of the overall number of errors on the number bisection task. The behavioural results indicated a wide range of abilities among the patients (SD = 43.69). Overall, the analysis revealed that error-prone performance was linked to grey matter damage around the left postcentral gyrus extending to left supramarginal gyrus as well as bilateral cingulate gyrus. Interestingly, the analysis also revealed lesions in anterior prefrontal areas which are commonly associated with planning and higher cognitive reasoning (Koechlin et al., 1999) thus also supporting the idea that prefrontal regions are crucial for this task (van Dijck et al., 2011).

Next we assessed the brain lesions associated with biased deviations to the left or right side of the number interval midpoint. In this analysis a greater leftward deviation (i.e. reporting the midpoint as smaller than the correct midpoint) was found to be associated with grey matter lesions in prefrontal areas, extending from the orbital gyrus, an area

implicated in decision making (Rogers et al., 1999), to middle frontal areas, associated with executive attention and working memory (Martin et al., 2009), supporting the argument for impairments in working memory contributing to performance. The white matter analysis revealed lesions in tracts connecting the parietal and frontal areas to be highly correlated with leftward deviation. Damage included the superior longitudinal fasciculus, a parieto-frontal tract previously found to be related to severity of neglect and spatial processing (He et al., 2007; Shinoura et al., 2009; Chechlacz et al., 2010). However, importantly, the frontal part of this tract contralaterally was found to support a bias to larger numbers, independent of and dissociated from any spatial bias (Aiello et al., 2012). Furthermore, studies using diffusion tensor imaging suggest that better arithmetic skills are associated with strength of this tract in a DTI study (Tsang et al., 2009), consistent with the suggestion that inter-connectivity within the parieto-frontal number processing network is required to support performance. Taking these results together we suggest that number bisection is dependent on a parieto-frontal number processing network, which codes larger numbers in the left hemisphere and smaller numbers to the right.

Overall, contrary to much of the previous literature on number bisection (e.g. Zorzi et al., 2002; van Dijck et al., 2011; Aiello et al., 2012), we did not find any significant associations between right hemisphere lesions and deficits on the number bisection task across any of the analyses. Note however that Aiello et al. (2012) found that neglect does not predict biases on the number bisection task and that rightwards number bisection was related to damage to the frontal components of the parietal-frontal number network. These results, along with our own finding of reliable correlations with left hemisphere damage, suggest that spatial attention is not as crucial as previously thought.

In summary, the current study has shown that lesions to frontal areas and the connections between these areas and the inferior parietal lobe in the left hemisphere relate to impaired performance on the number bisection task due to underestimations of the midpoint. 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). Aiello et al. (2012) found overestimations in number bisections to be related to right sided frontal injuries as well as fronto-parietal connections, while we found damage to contralateral regions to be associated with underestimations. Together, these studies support the above bilateral parietal-frontal network suggested, with small numbers represented on the right and larger numbers on the left.

Currently, we can only speculate on how these connections interact to facilitate performance on the number bisection task. Single cell recordings work in primates has found that, when the animals process number, there is early activation of parietal cortex followed by later activation of prefrontal areas (Nieder and Miller, 2004). Applying these findings to the number bisection task we can suggest that a parietal number specific representation of the numerical interval is activated first and then this is portrayed, via the superior longitudinal fasciculus pathway, to prefrontal regions which recode and manipulate the information in order to verbally estimate the midpoint. It would follow that lesions at both early, parietal and late, frontal stages, or equally to the white matter connections between these regions, cause impaired performance on the number bisection task, as found here.

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