



How number processing survives left occipito-temporal damage

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We investigated the neural systems that support number processing in a patient (JL) who had damage to the left ventral occipito-temporal cortex (LvOT). JL had severely impaired written word recognition but he was remarkably accurate in number tasks, albeit slower than normal. This suggests LvOT activation is necessary for efficient but not for accurate number decisions. Here we investigated how JL made accurate number decisions using fMRI; we compared JL's brain activation to that in healthy controls and in two patients with frontal lobe damage who, like JL, made slow but accurate responses in number tasks. For semantic relative to perceptual decisions on numbers, JL did not activate the left occipito-temporal area that was involved in all other subjects. However, JL had significantly increased activation in a left posterior middle temporal region. In addition, during semantic and perceptual decisions on numbers, JL showed increased activation in: (1) the right occipito-temporal cortex, (2) right caudate, and (3) bilateral frontal regions. These effects were unique to JL and cannot be explained in terms of abnormally long response times because they were not observed in the other patients who made slow but accurate number decisions. Together these results show that although the LvOT usually contributes to efficient number processing, activation in this region is not essential for accurate performance because (i) perceptual processing of numbers can be supported by right occipital, right caudate, and bilateral frontal activation and (ii) semantic processing of numbers can be supported by increased left posterior middle temporal activation associated with hand actions.

Keywords: Numbers; fMRI; Lesions; Left occipito-temporal; Parietal.

Many previous studies have shown that an area around the left ventral occipito-temporal cortex (LvOT hereafter) is activated during reading and object processing as well as during non-linguistic perceptual tasks (e.g., Cohen & Dehaene, 2000; Levy et al., 2008; Price & Mechelli, 2005; Simons, Koutstaal, Prince, Wagner, & Schacter, 2005; Vinckier et al., 2007; Wright et al., 2008). Recently, LvOT activation has also been observed in response to semantic tasks on Arabic numbers (Cappelletti, Lee, Freeman, & Price, 2010; see also

Figure 1A, B). This is interesting because, although patients with LvOT lesions have severe difficulty with object naming, reading aloud and semantic decisions on written words and speeded perceptual decisions, they are sometimes better at reading Arabic numbers and making magnitude judgments (e.g., Behrmann, Nelson, & Sekuler, 1998; Cohen & Dehaene, 1995; Cohen et al., 2003, 2004; Dejerine, 1892; Gaillard et al., 2006; Henry et al., 2005; Leff et al., 2001; McNeil & Warrington, 1994; Miozzo & Caramazza, 1998; Sekuler & Behrmann, 1996;

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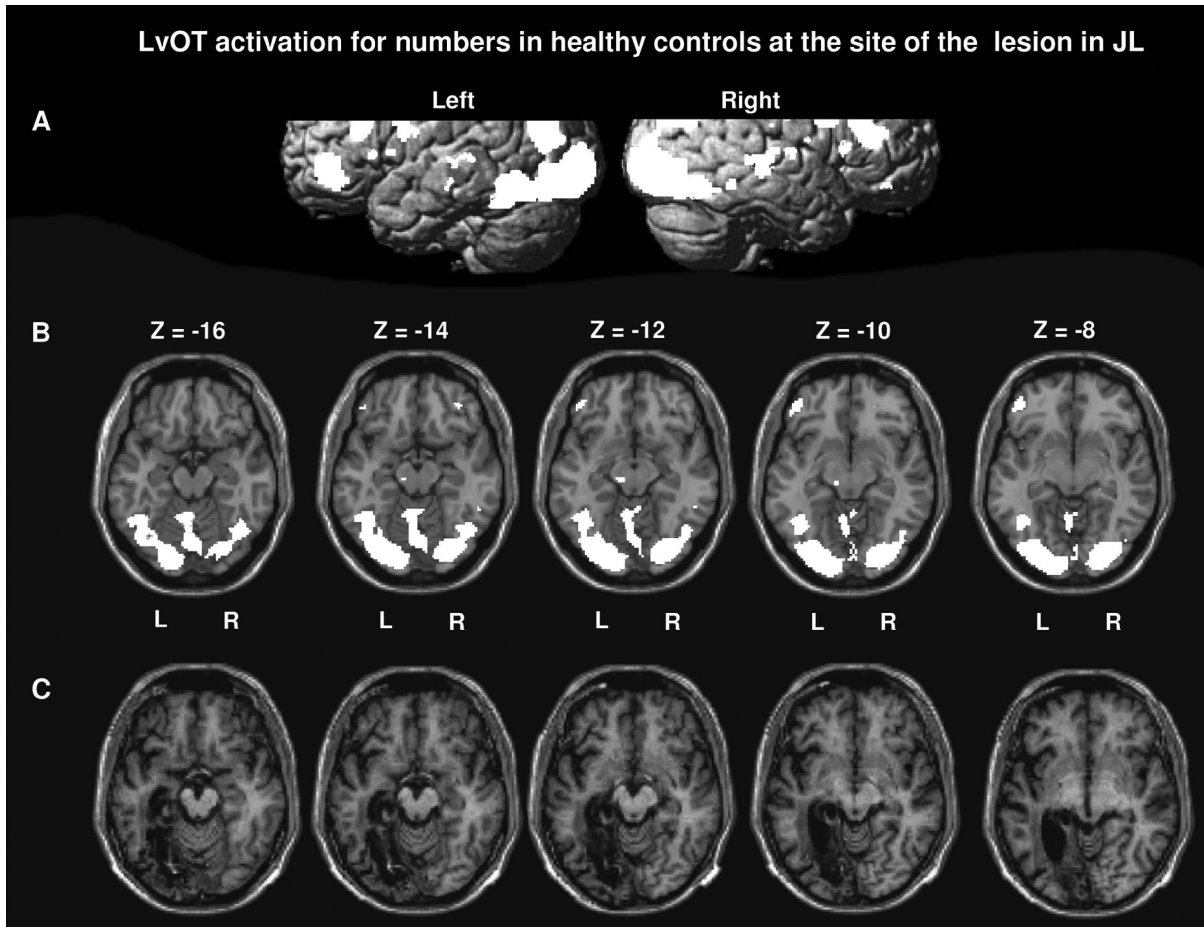


Figure 1. LvOT activation for numbers in healthy controls at the site of the lesion in JL. Controls' activations in LvOT regions on (A) a rendered brain, (B) sections, and (C) sections showing JL's lesion.

Starrfelt & Gerlach, 2007; Starrfelt, Habekost, & Leff, 2009; Trébuchon-Da Fonseca et al., 2009; Warrington & Shallice, 1980). This implies that LvOT activation is essential for rapid reading and object naming (e.g., Starrfelt et al., 2009) but is less essential for accurate number processing or perceptual categorization. We hypothesized that LvOT is normally required for efficient number processing but, following LvOT damage, numbers can be supported by alternative compensatory mechanisms that result in slow but accurate number performance. To examine this issue we conducted a functional imaging study in a patient who was able to make accurate semantic decisions on Arabic digits following an LvOT lesion. The observed effects were also investigated in two patients with frontal lobe damage who, like JL had slow but accurate performance on the number tasks. Below we examine the existing literature on preserved number processing following lesions to LvOT.

Number processing following LvOT lesions

Even the original observation of Dejerine's patient with alexia without agraphia following left occipitotemporal lesions revealed that the patient's ability to read Arabic numbers was much better preserved than his ability to read words (Dejerine, 1892). This observation has subsequently been confirmed and more patients with left occipitotemporal lesions have been reported with better number processing than word reading (e.g., Berhmann et al., 1998; Cohen & Dehaene, 1995; Leff et al., 2001; McNeil & Warrington, 1994; Miozzo & Caramazza, 1998; Starrfelt & Gerlach, 2007; Warrington & Shallice, 1980) although their number processing is abnormally slow (Starrfelt et al., 2009). The patients' performance with numerical stimuli is characterized by preserved reading of single-digit Arabic numbers with an increase in errors for multi-digit numbers, preserved ability

to compare the magnitude of both single and multi-digit numbers (e.g., Cohen & Dehaene, 1995; Leff et al., 2001; McNeil & Warrington, 1994; Miozzo & Caramazza, 1998; Starrfelt & Gerlach, 2007; Warrington & Shallice, 1980) and in some cases even preserved calculation (e.g., Cohen & Dehaene, 2000).

Two neurological explanations have been proposed to account for the residual number skills after LvOT lesions. One explanation, also referred to as 'the right hemisphere hypothesis', is the idea that right hemisphere areas may be sufficient to support serial number processing but parallel processing of character strings (words and multi-digit numbers) requires the LvOT (Cohen & Dehaene, 1995). Therefore, patients with LvOT lesions are able to read or compare single-digit Arabic numbers as these do not require parallel processing of character strings (Cohen & Dehaene, 1995). A second hypothesis suggests that residual functioning of the damaged left-hemisphere regions may be sufficient to support partially preserved numerical skills (Beeman & Chiarello, 1998; Blasi et al., 2002; Cohen & Dehaene, 1995; Gold & Kertesz, 2000). This would explain above chance performance in some tasks requiring, for example, a basic classification of stimuli, but would not be sufficient for reading aloud or for performing finer operations with visual stimuli (Bub & Arguin, 1995; Farah & Wallace, 1991).

Irrespective of which hemisphere is compensating, an explanatory theory needs to specify the processes that can support number processing (e.g., Leff et al., 2001; Warrington & Shallice, 1980). For example, if patients are able to recognize single digits or letters, then multi-item displays can be identified by serial assimilation of their individual components (Starrfelt et al., 2009). This is likely to be quicker and more successful for multi-digit number identification than reading letters because of (a) fewer possible items to select from (10 vs. 26), (b) more consistent shapes (letters have both lower case and upper case forms), and (c) the name associated with a number is consistent (1–10) whereas letters can be associated with their names or their sounds. Nevertheless, the importance of the LvOT for number processing is illustrated by the impact of LvOT damage on response times even when accuracy is preserved (Starrfelt et al., 2009).

The present study

Whether number processing is supported by right hemisphere compensatory mechanisms or residual

left hemisphere functioning has so far simply been inferred from the patients' lesion sites and behavioral performance. However, neuropsychological data do not characterize the specific neuronal mechanisms maintaining accurate performance. We therefore conducted a functional imaging study in a patient (JL) who was able to make accurate semantic decisions on numbers following an LvOT lesion. We aimed to: (1) identify the neural systems underlying accurate number processing in JL by looking for both activations in common with control subjects and activations that were significantly higher than the controls; and (2) characterize the systems supporting residual numerical skills in JL by examining whether they reflected compensatory strategies or other non stimulus-specific factors such as increased time on task. To this end we distinguished JL's activations that occurred within the normal number system from those that occurred in areas that were not observed in healthy control subjects or in two additional patients (T and B) who had frontal lobe lesions but no occipito-temporal damage. We were thereby able to determine whether accurate but slow numerical processing was a reflection of residual processing in the normal number processing system or compensatory activation in either the left or right hemisphere. We then discuss the activations related to numerical processing in our patient and control groups, and secondly relate the findings to previous studies that found activations in the same areas.

METHODS

Participants

Patient JL

JL is a right-handed English-speaking man who sustained a left hemisphere infarct in 2003 when he was 60 years old. An MRI-scan showed a lesion involving the left ventral occipito-temporal cortex, LvOT (see Figure 1C).

The patient undertook a neuropsychological assessment based on the Comprehensive Aphasia Test (CAT, Swinburn, Porter, & Howard, 2004). At the time of the experimental investigation, JL's scores were within the normal range for non-verbal general intelligence, verbal fluency, semantic associations, recognition memory, arithmetic and digit span. He was also within the normal range for auditory word and sentence comprehension, repetition of sentences as well as for copying and writing words to dictation. Abnormally low performance

TABLE 1
Results (number correct) of neuropsychological tests for patients JL, B, and T

| <i>Tasks performed</i> | <i>JL</i> | <i>Patient B</i> | <i>Patient T</i> |
|---|--------------|------------------|------------------|
| General cognitive tests | | | |
| 1. Progressive Matrices (<i>N</i> = 12) | 12 | Not tested | Not tested |
| 2. Verbal fluency | 19 | 33 | 23 |
| 3. Semantic associations (<i>N</i> = 10) | 10 | 10 | 10 |
| 4. Recognition memory (<i>N</i> = 10) | 10 | 10 | 10 |
| 5. Gesturing using objects (<i>N</i> = 12) | 8* | 12 | 12 |
| 6. Arithmetic (<i>N</i> = 6) | 6 | 6 | 6 |
| 7. Digit Span | 5 | 7 | 7 |
| Language specific tests | | | |
| 1. Comprehension | | | |
| (a) spoken words (<i>N</i> = 15) | 15 (26/30) | 15 (30/30) | 15 (30/30) |
| (b) spoken sentences (<i>N</i> = 16) | 15 (26/32) | 15 (30/32) | 16 (32/32) |
| (c) written words (<i>N</i> = 15) | 14 (26/30)* | 15 (30/30) | 15 (30/30) |
| (d) written sentences (<i>N</i> = 16) | 14 (17/32)* | 15 (30/32) | 15 (30/32) |
| 2. Repetition of | | | |
| (a) sentences (<i>N</i> = 6) | 6 (12/12) | 6 (12/12) | 6 (12/12) |
| (b) words (<i>N</i> = 16) | 15 (27/32) | 16 (32/32) | 16 (32/32) |
| 3. Object naming (<i>N</i> = 24) | 16 (25/48)* | 23 (46/48) | 24 (48/48) |
| 4. Reading | | | |
| (a) words (<i>N</i> = 24) | 18* (35/48)* | 24 (48/48) | 24 (48/48) |
| (b) complex words (<i>N</i> = 3) | 2 (3/6) | 3 (6/6) | 3 (6/6) |
| (c) function words (<i>N</i> = 3) | 3 (6/6) | 3 (6/6) | 3 (6/6) |
| (d) non-words (<i>N</i> = 5) | 3** (5/10)* | 5 (10/10) | 5 (10/10) |
| 5. Writing | | | |
| (a) copying (<i>N</i> = 27) | 27 | 27 | 27 |
| (b) to dictation (<i>N</i> = 28) | 25 | 28 | 28 |

Scores are adjusted (marks lost) when a correct response was made after self-correction, significant delay (i.e. over 5 seconds), or repetition of the stimulus.

*Denotes impairment; ● 2 items read letter-by-letter; ●● 3 items read letter-by-letter.

was recorded on tests of: (1) object naming; (2) written sentence comprehension; and (3) reading aloud words and non-words. When reading some words and nonwords, JL adopted a letter-by-letter strategy (see Table 1). This pattern of behavior, with impaired reading but preserved writing, is consistent with the definition of pure alexia or alexia without agraphia. On the in-scanner tasks, JL was unable to match written words, and his response times (RTs) were slower than controls (see Results). However, despite these difficulties, his accuracy performing number tasks under speeded presentation conditions was within the normal range.

Lesions to the LvOT are frequently associated with right hemianopia. Unfortunately, JL was not available for standardized assessment of his visual fields. However he did complete a perceptual task that compared his accuracy and response times to detect targets in the left and right visual fields. He was able to perform this task with no significant difference in the hemifield of the target on either accuracy or response times. Likewise, during scanning, JL showed no significant difference in his ability

to detect targets presented in the upper or lower hemifield. We also note that JL's performance on a line bisection task (part of the CAT assessment) was within the normal range. Therefore, although we cannot rule out the presence of a partial, right-sided hemianopia, we note that: (1) there was no evidence of a laterality effect for targets presented to left and right parafoveal vision; (2) there was no evidence of visual neglect; and (3) the stimuli in the fMRI task were presented to central vision above and below a fixation cross (Figure 3).

Control patients

Given JL's abnormally long RTs in the number tasks, we tested whether abnormal fMRI activation in JL was simply a consequence of abnormally long RTs. This was addressed by including data from two other patients (T and B) with frontal lobe damage who were selected for having abnormally slow response times on the number tasks, equivalent to those measured in JL. Neither patients T nor B had damage to LvOT.

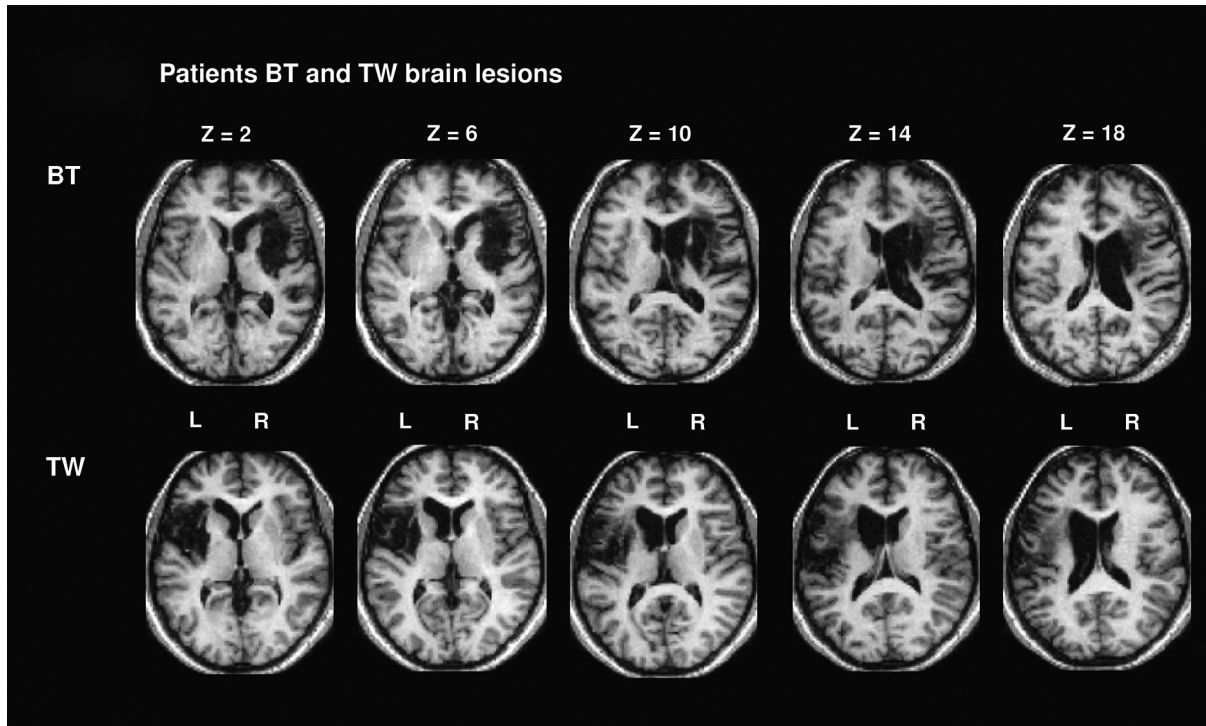


Figure 2. Patients B and T brain lesions.

Patient T is a right-handed English-speaking woman who sustained a left hemisphere infarct in 2000 when she was 36 years old. MRI identified damage to the left pars opercularis and ventral premotor cortex, insula, and subcortical structures (see Figure 2). Despite this large lesion, Patient T performed within the normal range on the Comprehensive Aphasia Tests (CAT, Swinburn et al., 2004; see Table 1). However, her RTs were significantly slower than normal during the number semantic tasks tested in the scanner (see Table 2).

Patient B is a right-handed English-speaking man who sustained a right hemisphere infarct in 2000 when he was 59 years old (see Figure 2). MRI identified damage to the right pars triangularis, pars opercularis, insula cortex, and superior temporal gyrus anterior to Heschl’s gyrus (i.e., the planum polare). Subcortically the white matter underlying the anterior parts of the inferior and middle frontal gyri are involved as are the putamen and globus pallidus, with the caudate spared. Despite this large lesion, Patient B (like Patient T) performed within the normal range on the Comprehensive Aphasia

TABLE 2
In scanner accuracy (percent correct) and response times (RTs with standard deviation)

| Tasks performed | Accuracy | | | | RTs (ms) | | | |
|---|----------|-------|-------|-------------|----------|---------|---------|------------------|
| | JL | T | B | Controls | JL | T | B | Controls |
| 1. Number quantity judgment (N = 144) | 87.5 | 94.40 | 93.06 | 93.65 (3.7) | 2159.65 | 2273.21 | 2107.11 | 1433.11 (219.85) |
| 2. Number non-quantity judgment (N = 144) | 85.4 | 90.30 | 86.11 | 86.11 (9) | 2620.26 | 2588.78 | 2368.78 | 1890.14 (262.89) |
| 3. Number color decision (N = 72) | 75 | 94.40 | 94.40 | 98.39 (2.1) | 2300.23 | 1218.6 | 628.24 | 751.37 (144.75) |
| 4. Object names quantity judgment (N = 144) | NT | 90.30 | 95.83 | 84.72 (6.8) | NT | 2416.79 | 2320.21 | 1686.59 (274.8) |
| 5. Object names non-quantity judgment (N = 144) | NT | 92.70 | 94.44 | 93.05 (3.1) | NT | 2276.64 | 2082.04 | 1418.48 (271.61) |
| 6. Object names color decision (N = 72) | 77.78 | 95.10 | 93.10 | 99.11 (1.4) | 2389.95 | 1214.93 | 664.97 | 710.85 (132.95) |

JL performed accurately on number semantic tasks (no significant difference with controls) and above chance in the number color-decision task. NT, not tested.

Tests (CAT, Swinburn et al., 2004), see Table 1. However, his RTs were significantly slower than normal during the number semantic tasks tested in the scanner (see Table 2).

Control subjects

Controls included eight right-handed healthy participants comprising three males with a mean age of 50.38 (range 22–69). Five participants were age-matched to JL (range = 58–69, mean age = 65.6). All control participants were neurologically normal native English speakers who gave informed consent and were screened prior to testing to ensure that they were MRI compatible with normal or corrected to normal vision. The study was approved by the Local Research Ethics Committee.

Experimental design

There were two tasks of interest for the analysis of JL's neurological brain activation during number processing. The first involved semantic decisions on number stimuli, the second was a perceptual color decision task that involved selecting one of two numerical stimuli on the basis of their color (see later for details). The number semantic task consisted of two subtasks: (i) a quantity task, which required a finger-press response to indicate the larger or smaller of two numbers; and (ii) a category task, which required a finger-press response to indicate which of two numbers corresponded to either a summer or winter date or a sleeping or working time (see Figure 3). Despite JL's reading being slow and inaccurate on standard assessments, he was able to follow the written instructions consisting of two words which were displayed on the screen for 2.7 seconds before the stimuli appeared and remained on the screen throughout each block of stimuli. JL was given extensive practice to familiarize himself with the tasks before being scanned. Accurate performance indicated that JL was able to understand the task instructions.

In addition to the semantic and perceptual tasks on numbers, the same semantic and perceptual instructions were presented with written object names. We do not report any functional imaging data from the written word conditions because JL's performance was not above chance, see Results in Table 2 for details. The difficulty that JL had with written object names was not due to these conditions being generally more difficult. This is demonstrated by a behavioral analysis of the control data only: Across tasks, there

| | | Experimental Design | |
|------------------------|----------------|---------------------|---|
| | | Numbers | Object names |
| Semantic quantity task | Larger number? | 23.07 + 10.02 | Larger object? Jacket + Flip flops |
| | Summer month? | 23.07 + 10.02 | Summer object? Jacket + Flip flops |
| Perceptual color task | Yellow item? | 23.07 + 10.02 | Yellow item? Jacket + Flip flops |

Figure 3. Experimental design. The same semantic (quantity and category tasks) and perceptual color decision tasks were used with pairs of Arabic numbers (left panel) and object names (right panel) which were presented in one of four possible colors (red, yellow, blue, green). In each trial, participants viewed pairs of stimuli presented one above the other with a fixation cross in the middle of the computer screen. Subjects were instructed to indicate with a button press which of the two stimuli was the correct response to a question consisting of two keywords presented above the upper stimulus before and during the stimulus display. For each task, one of two possible questions was presented in different blocks in counterbalanced order (i.e., quantity: 'larger/smaller' and 'more/less'; category: 'summer/winter' and 'working/sleeping' for the semantic tasks; 'red/yellow/blue/green item?' for the color-decision task, see Cappelletti et al., 2010 for more details). [To view this figure in color, please visit the online version of this Journal.]

was no main effect of stimulus type (numbers vs. object names) in either the accuracy or the response times, $F(1, 7) = 3.1$; $p = .09$ and $F(1, 7) = 4.9$; $p = .06$, respectively). Moreover, there was no difference in either accuracy and response times between numbers and object names in perceptual and semantic tasks (quantity and categorical collapsed; task-by-stimulus interaction, accuracy: $F(1, 7) = 2.7$, $p = .48$; RTs: $F(1, 7) = 1.04$, $p = .34$); t -test numbers vs. object names in semantic tasks, accuracy: $t(7) = 3.1$, $p = .085$; RTs: $t(7) = 2.22$, $p = .06$). The control data therefore suggest that tasks with numbers and object names were overall of similar difficulty. Further details of the data from neurologically healthy participants have been published in Cappelletti et al. (2010).

Experimental stimuli

A total of 144 Arabic numbers were used. Arabic numbers were presented as pairs of digits, each

separated by a dot, e.g., 23.07. They referred to a linear dimension of quantity, to dates (e.g., 23rd July) or to times (e.g., 7 minutes past eleven at night). In the scanner, the two stimuli were presented with one above and one below a central fixation point (see Figure 3). For more details about the stimuli used see Cappelletti et al. (2010).

Task instructions

Participants were told that they would see pairs of numbers (or object names) and that the instructions would be presented above the top stimulus in the form of a two-word question. These instructions were identical for tasks with numbers and object names. On every trial, participants were instructed to make a key press response to indicate which stimulus corresponded to the correct answer to the question. They were asked to press the upper key of a two-button keypad to select the upper stimulus and the lower key to select the lower stimulus. Trials where the correct answer was the upper or the lower stimulus were presented in equal proportion. JL was able to read the questions, as they stayed on the screen before and throughout a block of trials and he knew which words to expect.

For the number semantic tasks, participants were also told that the number stimuli could indicate either: (1) quantities, (2) dates, or (3) times. They were presented with four different questions for each type of task. For the quantity task, the questions were: (i) larger number? (ii) smaller number? (iii) more numbers? and (vi) less numbers. For the category task, the four questions were: (i) summer month? (ii) winter month? (iii) working time? and (vi) sleeping time? For the larger/smaller and more/less questions, participants were told that numbers referred to an amount and that they should choose the larger (or smaller) number in each pair irrespective of the wording of the question (i.e., 'larger' or 'more' and 'smaller' or 'less'). For summer/winter questions, participants were told that each number indicated either a summer or a winter month in the Northern hemisphere. They were told that summer months were 'June', 'July', and 'August' and winter months were 'December', 'January', and 'February' and that these months followed a day (1–31) separated with a dot (13.07) rather than the more familiar slash (13/07). They were instructed to select either the summer or the winter month in each pair of stimuli depending on the question. For the working/sleeping questions,

participants were told that working or sleeping times were in terms of a 24-hour clock; and that working times were between 8 am and 6 pm, and sleeping times were between 10 pm and 7 am. Participants were told not to consider jobs that include night shifts.

In the perceptual color decision task, participants selected the stimulus whose font was in one of 4 pre-defined possible colors (yellow, green, red, and blue).

Presentation parameters

The number tasks were presented in 36 blocks with six stimuli per block, 24 blocks of the number semantic tasks and 12 of the number color decision task. The 36 blocks were divided in 4 sessions (ABCD) in which 6 blocks of semantic tasks and 3 blocks of perceptual color decision tasks were presented in pseudo-random order in each session, counterbalanced with an equal proportion of written word stimuli (that JL did not respond to). There were four possible sequences of the sessions (ABCD, CADB, BDAC, and DCBA), with 2 participants randomly assigned to each sequence. Each block began with a question that appeared before the first trial for 2.7 seconds and remained on the screen for the duration of the block. Each pair of stimuli remained on the screen for four seconds, and was followed by an inter-stimulus interval of one second before the next pair appeared. A fixation lasting 16.2 seconds was then presented between blocks.

Data acquisition

A Siemens 1.5T Sonata scanner (Siemens Medical, Erlangen, Germany) was used to acquire both anatomical and functional images. Functional T2*-weighted echoplanar images with BOLD contrast comprised 30 axial slices of 2 mm thickness with 1-mm slice interval and 3 × 3 mm in-plane resolution. A total of 260 volumes were acquired per session, for a total of 1040 volume images across four sessions. Effective repetition time (TR) was 4.5 s/volume, with TR and Stimulus Onset Asynchrony not matching to allow for distributed sampling of slice acquisition across the experiment (Veltman, Mechelli, Friston, & Price, 2002). To avoid Nyquist ghost artifacts a generalized reconstruction algorithm was used for data processing.

Data analysis

Functional image analysis was performed using Statistical Parametric Mapping software (SPM5 software, Wellcome Trust Centre for Neuroimaging, London; <http://www.fil.ion.ucl.ac.uk/spm>) running under Matlab 7 (Mathworks, Sherbon, MA, USA).

The first six volumes of each fMRI session were discarded and the remaining 1016 (4 sessions \times 254) volumes were used for the analysis. Scans were realigned, unwarped and spatially normalized (Friston et al., 1995) to the Montreal Neurological Institute (MNI) standard space. The unified segmentation algorithm was chosen as this has the best performance for lesioned brains (Crinion et al., 2007). Functional images were then smoothed in the spatial domain with a Gaussian kernel of 6 mm FWHM to improve the signal to noise ratio. A high pass filter was used with a cut-off period of 128 seconds.

In a first level analysis activation for correct responses for each condition was compared to fixation according to the general linear model (Friston et al., 1995). Specifically, the functional data were modeled in an event related fashion with six regressors corresponding to the correct responses to each of the conditions (three tasks: quantity, category, i.e., semantic and perceptual color decision \times two stimuli: numbers and object names) and an extra regressor modeling all incorrect responses.

From the first level analysis we computed contrast images for semantic quantity decisions relative to fixation, semantic category decisions relative to fixation; perceptual color decisions on numbers relative to fixation; and semantic (category and quantity) relative to color decisions. These contrast images for each participant were used in a second level ANOVA to identify effects at the group level.

Second level analyses

We performed three second level analyses.

Analysis 1: Activations for number tasks in JL relative to healthy control subjects

This analysis included the contrast images for JL and each of the healthy controls for the semantic quantity task relative to fixation and the semantic categorization task relative to fixation. These images were factored with two groups (between subjects), and two conditions (within subjects), with a correction for non-sphericity on the within subject

factors. Statistical contrasts identified brain areas that were: (1) less activated in JL than control subjects, (2) more activated by JL than control subjects, and (3) activated by both JL and control subjects with no significant group differences. These contrasts were computed over both semantic tasks (quantity and category) and then we tested for the interaction between group task. For each contrast, we used the inclusive masking option in SPM to ensure that group differences were the result of activation relative to fixation rather than deactivation relative to fixation. Specifically, greater activation for controls than JL (contrast 1) was inclusively masked with activation for controls only; greater activation for JL than controls (contrast 2) was inclusively masked with activation for JL only. For contrast 3 we inclusively masked the main effect (JL plus controls) with controls only and JL only. The statistical threshold was set at $p < .05$ after family wise error correction for multiple comparisons (height or extent) for contrasts 1–3; and at $p < .001$ uncorrected for all inclusive masks.

Analysis 2: Activations for numbers versus color decisions in JL relative to control subjects

Here we focused only on activations for the number semantic tasks (category and quantity) after controlling for activations in the color decision task. This involved a two-sample t -test with two groups (JL and controls) and one contrast for each participant (category and quantity – color decision). The aim of this analysis was to identify activation that was greater for number semantics when written task instructions that remained on the screen during all conditions were controlled.

Analysis 3: Patients with response times similar to JL

This analysis included the two additional patients (T and B) who performed the number tasks accurately but with response times that were matched to those in JL and slower than those in controls. For each patient and each control subject, the contrast of interest was activation for the semantic category and semantic quantity task relative to fixation. The aim was to plot the effect size for each participant in the areas where JL over-activated in Analysis 2.

Behavioral data were analyzed following the Crawford and colleagues' approach (Crawford, Howell, & Garthwaite, 1998; Crawford & Garthwaite, 2002); specifically, we used a one-tailed significance test to compare JL with the

control groups. This test treats an individual patient as a sample, affording the comparison of the patient with the control group (Crawford et al., 1998; Crawford & Garthwaite, 2002).

RESULTS

Behavioral data

Accuracy

On the number semantic task, JL performed accurately (86.4% correct) and did not differ from controls ($t = -1.52, p = .085, ns$). Patient T and B also performed accurately in this task (92.3 and 89.6%, respectively), with no difference from controls (Patient T: $t = 1.07, p = .158, ns$; Patient B: $t = -0.14, p = .44, ns$; see Table 2).

On the perceptual color-decision task, JT's performance was significantly above 50% chance level (Binomial probability $p = .002$), although significantly less accurate than controls ($t = -8.2, p = .001$, see Table 2). Patient T and Patient B performance did not differ from controls in this task ($t = 0.76, p = .23, ns$, and $t = -0.09, p = .46, ns$, respectively, see Table 2).

Response times

JL and controls differ significantly across semantic and color-decision number tasks ($t = 4.581, p = .001$). Specifically, on the number semantic task, JL's response times were significantly slower than controls ($t = 2.844, p = .012$, see Table 2), similar to Patients T and B (Patient T: $t = 3.0, p = .01$, Patient B: $t = 2.25, p = .03$). Likewise, on the perceptual color-decision task, JL's response times were significantly slower than controls ($t = 11.2, p < .001$), similar to patient T ($t = 3.044, p = .009$); in contrast, patient B did not differ from controls ($t = -0.803, p = .22, ns$).

Functional imaging results

Analysis 1: Activations for number tasks in JL relative to control subjects

JL's under-activations. As expected, JL did not activate his damaged left occipito-temporal cortex in any condition. Specifically, activation was not identified in any LvOT voxels in or around JL's lesion even at the lowest statistical threshold of $p > .05$ uncorrected. This contrasted to the LvOT activation observed in controls during number tasks (see Figure 1A, B), see Table 3.

Neuronal systems that maintained JL's performance. The areas that JL activated during the number tasks could be divided into those that responded (A) normally during these tasks (i.e., no difference with controls); (B) in common but more than controls; and (C) only in JL but not in controls. All results are listed in Table 4. Here we focus on those that distinguished JL from controls (i.e., B and C). As these did not differ for the semantic category and semantic quantity task, all results are reported for the main effect of semantics (over category and quantity tasks).

JL showed increased activation in the right occipito-temporal areas that he and the controls activated for number tasks (see Table 4B and Figure 4, top panel). Moreover, JL but not controls activated the left posterior middle temporal cortex, the right head of caudate and the bilateral frontal regions (see Table 4C and Figure 4, lower panel).

Analysis 2: Activations for numbers versus color decisions in JL relative to control subjects

The only region that was activated in JL more than controls in semantic relative to color decision tasks with numbers was in the left posterior

TABLE 3
JL's under-activations and controls' activations

| Area | H | Coordinates | | | Controls > JL | Controls | |
|-----------|---|-------------|-----|-----|---------------|----------|---------------|
| | | x | y | z | Z scores | Z scores | No. of voxels |
| Occipital | | -28 | -84 | -12 | 3.9 | 4.8 | 958 |
| | L | -40 | -52 | -8 | 3.2 | 3.1 | |
| LvOT | | -36 | -56 | -10 | 3.1 | 3.2 | 143 |

H, Hemisphere; L, Left.

TABLE 4
Neuronal systems activated in JL and in controls and over-activated in JL

| Area | H | Coordinates | | | Z scores | | | No. of voxels |
|---------------------------|---|-------------|------------|-----------|------------|------------|------------|---------------|
| | | x | y | z | JL | Controls | JL > Ctrs | JL > Ctrs |
| (A) | | -38 | -4 | 38 | 3.3 | 4.3 | <i>ns</i> | |
| Dorsal Premotor | | -38 | 6 | 36 | 4.6 | 4.0 | <i>ns</i> | |
| | L | -52 | 4 | 48 | 4.9 | 4.0 | <i>ns</i> | |
| Intra parietal sulcus | | 28 | -66 | 48 | 3.7 | 3.3 | <i>ns</i> | |
| (B) | | 30 | -94 | 4 | 6.3 | 4.7 | 5.8 | 438 |
| | | 12 | -96 | 6 | 4.3 | <i>ns</i> | 4.1 | |
| Occipital | R | 28 | -96 | 12 | 6.4 | 4.3 | 5.9 | |
| | | 16 | -88 | 2 | 5.5 | <i>ns</i> | 5.6 | |
| | | 40 | -82 | -12 | 4.6 | 3.6 | 3.1 | 30 |
| Pars opercularis | L | -58 | 10 | 10 | 5.9 | <i>ns</i> | 5.8 | 143 |
| Occipito-temporal* | | 42 | -64 | -10 | 3.6 | <i>ns</i> | 3.1 | 21 |
| (C) | R | 64 | 4 | 18 | 5.4 | <i>ns</i> | 5.1 | 117 |
| Pars opercularis | | 62 | 4 | 6 | 5.2 | <i>ns</i> | 5.3 | |
| Caudate | | 10 | 12 | 10 | 5.1 | <i>ns</i> | 5.2 | 201 |
| | | -54 | -58 | 2 | 4.3 | <i>ns</i> | 4.3 | 231 |
| Posterior middle temporal | L | -50 | -64 | 6 | 4.7 | <i>ns</i> | 4.9 | |
| | | -44 | -62 | 10 | 3.8 | <i>ns</i> | 3.8 | |

Activations: (A) common to JL and controls; (B) stronger in JL than in controls (C) in JL but not in controls. H, Hemisphere; L, Left; R, Right; *ns*, not significant. *ROI.

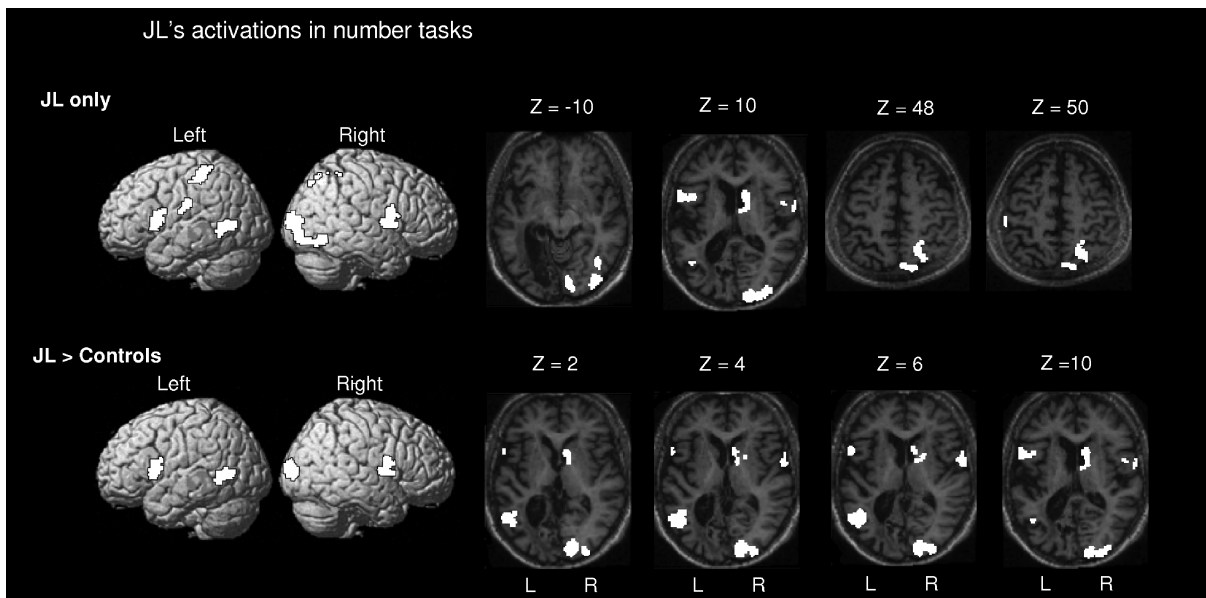


Figure 4. JL's activation in number tasks. JL's activations (top panel) and over-activations (bottom panel) during the number tasks on a rendered brain (left side) and on axial sections (right side) of JL's brain.

middle temporal cortex at: $x = -44$, $y = -62$, $z = 10$ ($Z = 4.3$, 94 voxels, significant at $p < .05$ corrected in extent). This enhanced left posterior middle temporal activation for number semantics cannot be explained in terms of prolonged reading of written task instructions because both the number semantic and number color decision tasks required attention to written task instructions. In contrast,

the comparison of semantic to color decisions did not identify significant activation in the other areas (e.g., right caudate) where JL showed abnormally high activation in the number tasks relative to fixation. Therefore we cannot rule out the possibility that activation in these areas was the result of JL reading the task instructions. Moreover, the enhanced left posterior middle temporal activation

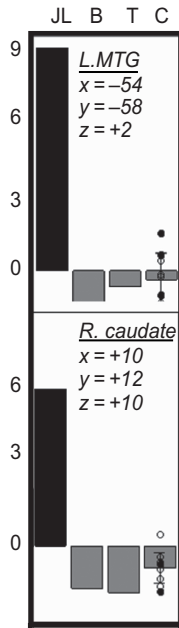


Figure 5. Activation in JL above all other participants. Plot of the parameter estimates in left middle temporal regions (MTG, top panel) and right caudate (bottom panel) showing stronger activation during number tasks in JL (black bars) relative to patients B and T with similar response times and to all controls (C; age-matched in filled circles).

during semantic tasks cannot be explained in terms of generic task difficulty which may result in prolonged response times. Indeed JL performed abnormally slowly on all the number tasks, i.e., the color decision and the semantic tasks, although the left

posterior middle temporal over-activation emerged only for number semantics. In brief, it is only the left posterior middle temporal area where activation was consistently abnormally high for number semantic processing in JL compared to controls.

Analysis 3: Patients with response times similar to JL

The results of this analysis confirmed that increased activation during the number tasks in JL could not be simply be attributed to longer reaction times because abnormally high activation in these areas was not observed in two other patients (T and B) who also performed the number tasks with abnormally long response times following frontal lobe damage (see Figure 5).

Finally, we note that abnormally high activation in JL during the number tasks was not an inevitable consequence of a single subject comparison to a normal group. We can demonstrate this using the fuzzy clustering algorithm proposed by Seghier, Friston, and Price (2008). The approach identifies atypical activation patterns in a quantitative and unsupervised manner by assessing the contribution of each subject to response profiles in voxels surviving a classical *F*-statistic criterion. The output (see Figure 6) identifies subjects whose activation is atypical across the whole neural system rather than at the voxel level. The results show that activation was most atypical in JL relative to all other subjects including patients B and T.

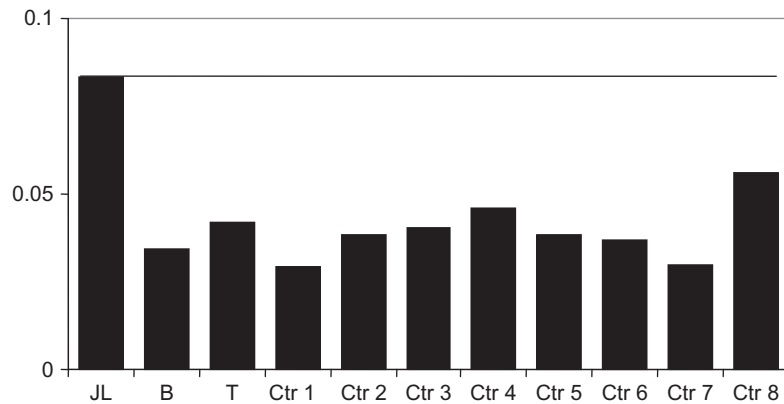


Figure 6. Atypical activation patterns in JL relative to patients B and T and to controls. Using the fuzzy clustering algorithm (Seghier, Friston & Price, 2007), atypical activation patterns are identified by assessing the contribution of each subject to response profiles in voxels that survive a classical *F*-statistic criterion. The output identifies subjects, like JL, who drive activation in voxels distributed across the whole neural system rather than at the voxel level. This showed that abnormally high activation in JL during the number tasks, indicated by the horizontal line, was not an inevitable consequence of a single subject comparison to a normal group.

DISCUSSION

This study investigated how a patient with a left ventral occipito-temporal damage was able to make semantic judgments on numbers. Previous studies have shown that the LvOT area is activated by control subjects during object recognition, reading, color naming and perceptual tasks, with greater activation for semantic than perceptual decisions on written and auditory words and pictures of objects (see Price and Devlin, 2003 for a review). LvOT activation has also been reported for calculations or number comparison on Arabic numbers (e.g., Cantlon et al., 2009; Cappelletti et al., 2010). However, LvOT damage typically impairs reading and object naming (Hillis et al., 2005) while leaving numerical processing and perceptual processing relatively preserved (Cohen & Dehaene, 1995; Damasio & Damasio, 1983; Dejerine, 1892; Leff et al., 2001; McNeil & Warrington, 1994; Miozzo & Caramazza, 1998; Starrfelt & Gerlach, 2007; Warrington & Shallice, 1980). Although patients can continue to make accurate numerical judgments, their response times are slower than normal (Starrfelt et al., 2009). This suggests that LvOT is required for efficient number processing but is not essential for accuracy. Preserved but inefficient numerical processing might be a reflection of residual processing in the normal number processing system. Alternatively it might require compensatory activation in either the left or right hemisphere. These residual and compensatory mechanisms have so far only been inferred from the patients' behavioral performance, as brain activity was not explored in previous investigations.

In this study we examined the pattern of brain activation that supported number processing in a patient (JL) who had extensive left occipito-temporal damage. We found that JL was able to make correct semantic decisions on numbers although his RTs were about 850 ms longer than any of our controls. The longer response times suggest that the left occipito-temporal cortex is normally required for efficient semantic decisions on numbers, consistent with previous studies (e.g., Starrfelt et al., 2009). The comparison of fMRI activation in JL and healthy controls indicated that JL's accurate numerical judgments were supported by abnormally high activation in (i) right occipital, right caudate and bilateral frontal areas that were activated during semantic as well as perceptual color decision tasks with numbers; and (ii) a

left posterior middle temporal region that was only activated by JL during number semantic tasks.

As JL was a highly qualified professional running his own business prior to his stroke, we assume that his slow response times were a consequence of the LvOT damage caused by his stroke. However, we needed to test whether increased activation was a direct consequence of LvOT damage or longer response times per se. We excluded the possibility that JL's increased activation were an inevitable consequence of increased response times because two other patients (B and T), with response times as slow as JL, did not show the same pattern of over-activation as JL (see Figure 5). Moreover, we excluded the possibility that enhanced activation in the left posterior middle temporal lobe could reflect prolonged reading of task instructions in JL as this region was more activated in semantic relative to color decision tasks with numbers, despite task instructions being displayed in both these tasks.

Two proposals have previously been put forward to account for the residual number performance in patients with LvOT lesions. One proposal, also named 'the right hemisphere hypothesis', suggests that the right hemisphere is capable of maintaining residual number processing (e.g., Cohen & Dehaene, 1995). The second proposal suggests that residual functioning of the lesioned left hemisphere areas may be sufficient to allow numerical processing (Beeman & Chiarello, 1998; Blasi et al., 2002; Cohen & Dehaene, 1995; Gold & Kertesz, 2000). A mechanistic account of how number identification can be better preserved than word identification was provided in Starrfelt et al. (2009). However, the neural systems that support number processing have not previously been investigated.

Our functional imaging study allows us to characterize the specific contribution of left and right hemisphere brain regions in supporting residual number performance. Specifically, our findings suggest that following left occipito-temporal damage, perceptual processing of numbers requires increased activation in right occipital, right caudate and bilateral frontal regions, but the semantic processing of numbers requires increased activation in the left posterior middle temporal cortex. Together these perceptual and semantic compensatory processes are able to support number tasks that involve both the ability to classify multi-digit numbers based on their magnitude as well as the ability to classify them according to other semantic criteria, for instance whether a number indicates a summer/winter date or a working/sleeping time.

These numerical tasks require the understanding of complex semantic associations and also involve parallel processing of multi-digit numerals; this latter task is possibly achieved using parsing strategies also employed by controls (e.g., Brysbaert, 2005). We suggest that these processes are supported by the combination of perceptual and semantic compensatory mechanisms implemented primarily in the right and left hemisphere respectively. JL's compensatory activations in the right hemisphere may support the idea that the right hemisphere is capable of some basic word or number processing, previously observed in alexic patients (e.g., Cohen & Dehaene, 1995; Coslett & Saffran, 1989). Moreover, the left posterior middle temporal area that was more activated in JL during number semantic processing has previously been associated with non-numerical semantic processing. Within this area there are two sub-parts: one that is commonly activated for all types of semantic decision, and one more posterior part that is associated with the retrieval of hand actions (e.g., Noppeney, Josephs, Kiebel, Friston, & Price, 2005). It was only the most posterior part of the middle temporal region that showed abnormally high activation in JL during semantic decisions relative to color decisions with numbers. Given the anatomical proximity of this left posterior middle temporal region to the parietal cortex, it is possible that, following occipital damage, connections to the parietal cortex became more reliant on left posterior middle temporal activation. This connection may enhance the well-known link between numerical processing and the representation of goal-directed hand actions as observed in many recent studies. For instance, numerical magnitude has been shown to influence the selection of hand grasping movements such that numerical information calibrates the judgment of action (e.g., Badets, Andres, Di Luca, & Pesenti, 2007) or its execution (e.g., Andres, Davare, Pesenti, Olivier, & Seron, 2004), and automatically primes grasping gestures (Moretto & Di Pellegrino, 2008). For example, small numerical values facilitate precision grip commonly used to grasp small objects, whereas large numerical values increase power grip typically used to grasp large objects (Moretto & Di Pellegrino, 2008). These and similar behavioral results together with neurophysiological and neuropsychological evidence of the connection between numbers and hand action, led to the proposal that numbers as well as other analogue magnitudes are represented by a generalized magnitude system dedicated to action (e.g.,

Andres et al., 2004; Andres, Olivier, & Badets, 2008; Badets et al., 2007; Castiello, 2005; Chiou, Chang, Tzeng, & Wu, 2009; Gobel & Rushworth, 2004; Jeannerod, Arbib, Rizzolatti, Sakata, 1995; Rossetti, Vighetto, & Pisella, 2003; Walsh, 2003).

Behaviourally, our results showing accurate but abnormally long numerical processing in JL are compatible with previous studies showing that number processing can be relatively preserved after LvOT lesions even when word processing is severely impaired (e.g., Cohen & Dehaene, 1995; Dejerine, 1892; Leff et al., 2001; McNeil & Warrington, 1994; Miozzo & Caramazza, 1998; Starrfelt & Gerlach, 2007; Starrfelt et al., 2009; Warrington & Shallice, 1980). However, our results have contributed to the understanding of how better accuracy with numbers can be achieved following LvOT lesions by showing which neurally instantiated compensatory mechanisms support residual performance.

In conclusion, this study investigated the compensatory mechanisms that maintained number processing in a patient with a LvOT lesion. We show that JL's performance in semantic tasks with Arabic numbers is supported by extensive compensatory activation in the left middle temporal cortex, in addition to right occipital, right caudate and bilateral frontal regions. Our results therefore suggest that following LvOT damage the right and left hemisphere play a different role in compensating for perceptual and semantic processing during numerical tasks. Our findings also have implications for understanding the neural systems that support number processing in the healthy brain. Specifically, we show that the left occipito-temporal cortex is normally involved in number processing. Without it, semantic decisions on numbers are less efficient. Nevertheless, this region is not essential for correct responses, perhaps because its role in number processing can be supported by the left posterior middle temporal cortex.

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