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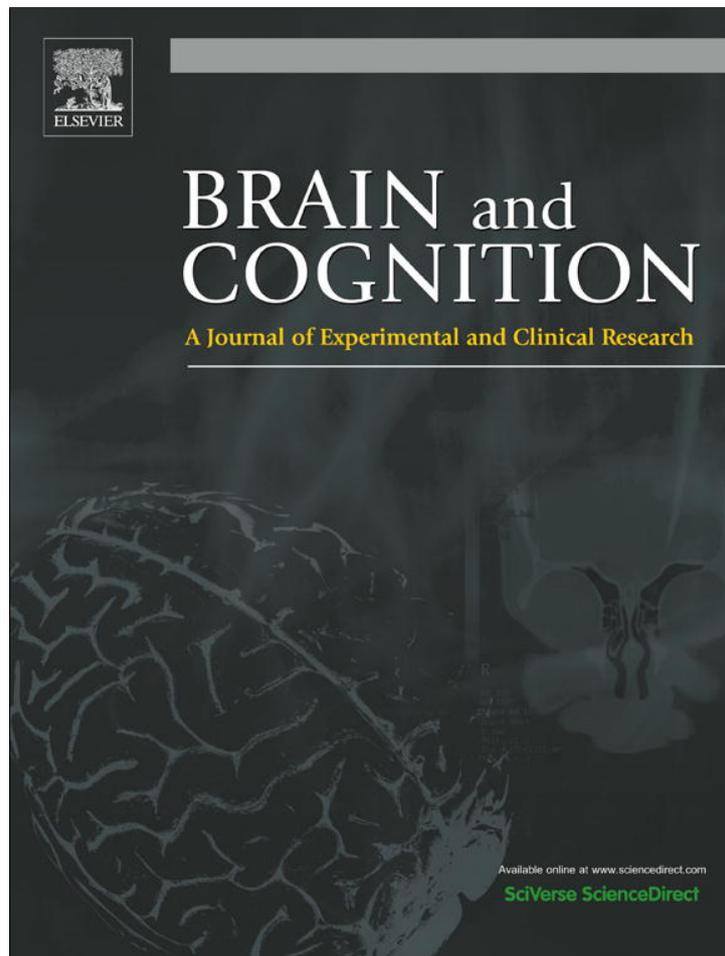
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## Differentiating core and co-opted mechanisms in calculation: The neuroimaging of calculation in aphasia



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## ARTICLE INFO

## Article history:

Accepted 30 April 2013

## Keywords:

fMRI  
Language  
Calculation  
Parietal cortex  
Aphasia

## ABSTRACT

The role of language in exact calculation is the subject of debate. Some behavioral and functional neuroimaging investigations of healthy participants suggest that calculation requires language resources. However, there are also reports of individuals with severe aphasic language impairment who retain calculation ability. One possibility in resolving these discordant findings is that the neural basis of calculation has undergone significant reorganization in aphasic calculators. Using fMRI, we examined brain activations associated with exact addition and subtraction in two patients with severe agrammatic aphasia and retained calculation ability. Behavior and brain activations during two-digit addition and subtraction were compared to those of a group of 11 healthy, age-matched controls. Behavioral results confirmed that both patients retained calculation ability. Imaging findings revealed individual differences in processing, but also a similar activation pattern across patients and controls in bilateral parietal cortices. Patients differed from controls in small areas of increased activation in peri-lesional regions, a shift from left fronto-temporal activation to the contralateral region, and increased activations in bilateral superior parietal regions. Our results suggest that bilateral parietal cortex represents the core of the calculation network and, while healthy controls may recruit language resources to support calculation, these mechanisms are not mandatory in adult cognition.

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### 1. Introduction

The role of language in other forms of thinking and reasoning is the subject of considerable debate. There are claims that language underpins and is necessary for many forms of higher order cognition such as theory of mind and mathematical reasoning (Siegal & Varley, 2002). Evidence in support of this view is drawn from various sources such as associations between developments in language and the emergence of new capabilities in other cognitive domains (e.g., de Villiers & Pyers, 2002); disruption of apparently non-linguistic cognition under conditions of verbal shadowing (e.g., Newton & de Villiers, 2007); and activation of left hemisphere perisylvian areas during behaviors such as calculation (e.g., Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999). However, other investigations indicate that activation of language zones does not

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always accompany higher order reasoning (Fedorenko, Behr, & Kanwisher, 2011; Monti, Parsons, & Osherson, 2009, 2012; Willems et al., 2010). With regard to verbal shadowing, when the cognitive demands of verbal and non-verbal shadowing are carefully matched, both forms of dual-tasking equally disrupt performance on secondary reasoning tasks (Bek, Blades, Siegal, & Varley, 2013; Dungan & Saxe, 2012). Furthermore, there are reports that people with severe aphasic language impairment can retain capability in domains for which language mediation is claimed as necessary (Bek, Blades, Siegal, & Varley 2010; Rossor, Warrington, & Cipolotti, 1995; Varley, Klessinger, Romanowski, & Siegal, 2005; Varley & Siegal, 2000; Willems, Benn, Hagoort, Toni, & Varley, 2011).

With regard to the evidence from severe aphasia, one possibility in accounting for residual capacity despite language impairment is that function is only possible because of significant reorganization of neurocognitive systems. For example, performance might be underpinned by activation of contralateral homologues, with this potentially less specialized mechanism being supported by increased prefrontal and anterior cingulate activation in order to pro-

vide additional strategic and attentional resources (e.g., [Duncan, 2001](#); [Park & Reuter-Lorenz, 2009](#); [Raboyeau et al., 2008](#)). The possibility that reorganization might have occurred is more likely where patients are studied in the chronic phase of recovery from neurological insult. All the patients with retained calculation reported by [Varley, Klessinger, Romanowski, and Siegal \(2005\)](#) had chronic aphasia in that they were tested at a minimum three years post-onset of their aphasic condition. If major reorganization has occurred, the insights that can be gained from the patterns of spared cognition in an aphasic mind might be limited, particularly with regard to their application to typical cognition. We explored this possibility in a functional neuroimaging study where the neural activations associated with exact calculation – the solution of two-digit addition and subtraction problems – was compared across healthy age-matched controls and two men with severe and chronic agrammatic aphasia but residual calculation ability.

The case for language involvement in exact calculation is supported by reports from bilingual behavior and functional neuroimaging. [Spelke and Tsivkin \(2001\)](#) trained Russian–English bilinguals on exact or approximate addition problems (e.g., is the product of  $13 + 15$  nearer to 20 or 40) in one of their languages. While approximation showed no advantage for the language of training, there was a transfer cost in exact calculation if problems were trained in one language and then tested in the second. With regard to neuroimaging evidence, [Dehaene et al. \(1999\)](#) reported that approximate calculation recruited both right and left parietal zones, while exact single-digit arithmetic elicited activation near to the left hemisphere language networks. Further functional neuroimaging studies of exact calculation in healthy adults have revealed a network of activation including the bilateral parietal gyri (BA 7, 40), bilateral middle frontal gyri (BA 9), and the left superior frontal gyrus (BA 6) ([Arsalidou & Taylor, 2011](#); [Benn, Zheng, Siegal, Wilkinson, & Varley, 2012](#)), as well as brain regions that are part of left hemisphere language networks and that are typically lesioned in severe aphasia. For example, activation of the left angular gyrus (LAG) and/or Broca's area has been observed in calculation ([Cowell, Egan, Code, Harasty, & Watson, 2000](#); [Delazer et al., 2003](#); [Grabner et al., 2009a](#); [Grabner et al., 2009b](#); [Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001](#); [Ischebeck, Zamarian, Egger, Schocke, & Delazer, 2007](#); [Menon, Rivera, White, Glover, & Reiss, 2000](#)). Furthermore, the degree of involvement of linguistic systems appears to vary across mathematical operations. Typically, addition and multiplication evoke more language-related activation in healthy participants, potentially reflecting the retrieval of verbally-encoded information in support of these operations ([Benn et al., 2012](#); [Kawashima et al., 2004](#); [Kazui, Kitagaki, & Mori, 2000](#); [Kong et al., 2005](#); [Kuo, Yeh, Chen, Liang, & Chen, 2008](#)).

However other neuroimaging studies have reported findings that indicate some autonomy between exact calculation and language. A number of investigators propose a key role in calculation for regions of bilateral parietal cortex that are also linked to visuospatial processing ([Benn et al., 2012](#); [Zago et al., 2001](#); [Zago et al., 2008](#)). Furthermore, [Fedorenko et al. \(2011\)](#) were able to identify distinct language- versus calculation-related activation within the traditional language zones such as Broca's area (BA 44/45). Similarly, [Maruyama, Pallier, Jobert, Sigman, and Dehaene \(2012\)](#), report activation linked to syntactic structure of mathematical expressions that is outside of language areas, and instead located in bilateral occipital–temporal ventral visual pathways. Transcranial Magnetic Stimulation (TMS) investigations also reveal the importance of parietal cortex in calculation, with impaired calculation efficiency following stimulation of the right intra-parietal sulcus ([Andres, Pelgrims, Michaux, Olivier, & Pesenti, 2011](#); [Salillas, Semenza, Basso, Vecchi, & Siegal, 2012](#)). Observations of retained calculation behavior in individuals with severe aphasia and extensive lesion of the perisylvian language network are consistent with

such reports ([Rossor, Warrington, & Cipolotti, 1995](#); [Varley et al., 2005](#)). The broad network of neural sites linked to numerical tasks may suggest that different brain regions are recruited for specific subcomponents of number processing and calculation. While numerosity may be represented within the inferior parietal sulcus ([Dehaene & Cohen, 1995](#)), calculation recruits regions such as the precuneus, superior and inferior parietal regions ([Arsalidou & Taylor, 2011](#); [Benn et al., 2012](#)).

In the present study, we examined the neural activations elicited by exact calculation in two men, JCB and PR, with chronic and severe agrammatic aphasia. PR was one of three patients studied by [Varley et al. \(2005\)](#), while JCB is a new case. Both patients showed residual comprehension and production of number forms and retained calculation ability across all four mathematical operations.

Structural brain scans for both patients revealed extensive damage to left hemisphere perisylvian regions ([Figs. 1 and 2](#)). Areas of damage included regions such as the inferior parietal region and Broca's area that have been claimed to be central to exact calculation in healthy participants. Both PR and JCB showed ischemic lesions of the left inferior parietal region with damage to angular and supramarginal gyri. Damage extended to inferior frontal cortex with extensive lesion of Broca's region in PR's case. JCB had damage to sub-fields of Broca's area including the pars opercularis and some partial involvement of the pars triangularis.

The brain activation patterns of the patients during calculation were compared to those of a group of age- and education-matched healthy participants. If the retained calculation ability in the aphasic cases is due to post-lesional neuroplasticity and widespread reorganization of function ([Elbert & Rockstroh, 2004](#); [Levin, 2006](#)), activation maps for patients would show markedly different patterns in terms of lateralization and/or intrahemispheric localization than those of healthy participants. However, if left perisylvian zones (Broca's area, angular and supramarginal gyri) are not core to exact calculation, then damage may not trigger whole-scale reorganization. In this case, activation patterns might be similar between patients and healthy controls. We explored activations across addition and subtraction operations. Addition typically involves more language-mediation than subtraction in healthy participants, particularly if simple additions are performed (e.g.,  $2 + 2 = 4$ ) as such problems may be stored as rote-learned facts in a verbally encoded format ([Dehaene, Piazza, Pinel, & Cohen, 2003](#)). Our aim was not to investigate the recall of verbally-encoded information in aphasia, but to examine the integrity of calculation routines. Therefore we examined performance on two-digit addition and subtraction problems, which are less likely to be dependent upon stored solutions.

## 2. Methods

### 2.1. Participants

Two patients with severe aphasia, JCB and PR, took part in the study. Both gave informed consent to participation, and ethical approval for the study was granted by the North Sheffield Local Research Ethics Committee (08/H1308/32). The control group consisted of 11 healthy right-handed males, aged between 57 and 79 years ( $M = 68.75$ ,  $SD = 6.63$ ). All were native English speakers who had completed a minimum of 10 years in formal education, and were competent in simple mathematics. Participants had normal, or corrected-to-normal vision, and were screened for neurological and psychiatric illnesses.

JCB is a right-handed, 60-year-old former welder with 15 years of formal education. Four years prior to taking part in the study, he developed severe agrammatic aphasia following a large left hemi-

sphere vascular lesion in left middle cerebral artery territory. The anatomical scan for JCB (Fig. 1) revealed damage to the whole of the superior temporal gyrus, the majority of the middle temporal gyrus, the inferior parietal lobule including the supramarginal and angular gyri, the inferior portion of the postcentral gyrus, the opercular region of the inferior frontal gyrus, the entirety of the inferior frontal gyrus posterior to the ascending ramus of the Sylvian fissure, the pars opercularis and some partial involvement of the pars triangularis, the posterior third of the middle frontal gyrus, and the inferior aspect of the precentral gyrus (including the face area). Within deep structure, there was destruction of the entire insula cortex, and significant loss of white matter within the anterior portion of the corona radiata adjacent to the anterior one third of the lateral ventricle. The posterior portion of the corona radiata was partially involved, but the middle fibres appeared spared. In the right hemisphere, there was a small lacunar infarct in the right thalamus (anterior nuclear group).

PR, a 64-year-old former retail manager with 15 years of formal education, was nine years post-onset of a large left-hemisphere vascular lesion in left middle cerebral artery territory. Although PR was pre-morbidly left-handed, the presence of severe aphasia following left-hemisphere lesion indicates that he was one of the majority of left-handers who are left-hemisphere dominant for language. The anatomical scan for PR (Fig. 2) indicated damage to the whole of the superior and middle temporal gyri, the posterior upper bank of the inferior temporal gyrus, the whole of the inferior parietal lobule involving supramarginal and angular gyri, the lateral occipital gyrus, the inferior aspect of the postcentral gyrus, the whole of the opercular region (pars orbitalis, pars triangularis and pars opercularis), the posterior-most portions of the inferior frontal gyrus, and the inferior aspect of the precentral gyrus. Within deep structures, there was a complete destruction of the insula cortex, almost complete destruction of the lenticular nucleus involving the posterior portion of the putamen, all of the globus

pallidus with sparing only of the anterior portion of the putamen and head of caudate nucleus. The infarct extended to the ventricular surface with involvement of most of the corona radiata.

Both patients presented with stable behavioral deficits and, consistent with their extensive left perisylvian pathology, they both displayed severe agrammatic aphasia. Profiling of language, number and basic calculation abilities was completed prior to the fMRI study.

## 2.2. Evaluation of lexical and grammatical processing

Language assessments were completed by both patients to determine the extent of residual lexical and grammatical processing. Tests were taken from the Action for Dysphasic Adults (ADAs) Auditory Comprehension Battery (Franklin, Turner, & Ellis, 1992), the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA, Kay, Lesser, & Coltheart, 1992), or were devised for the purpose of this study.

*Lexical processing* was assessed in comprehension and production in both spoken and written modalities. Comprehension was assessed by spoken and written word-picture matching and synonym judgment tests (Franklin et al., 1992), with the latter permitting evaluation of lower-imageability non-picturable words. Word-picture matching tests required a stimulus word (spoken or written) to be matched to a corresponding picture in the presence of visual, phonological/orthographic and semantic distracters. Synonym judgment tests involved a Yes/No decision as to whether two words (spoken or written) had similar meanings. *Lexical retrieval* was assessed through spoken and written picture naming tests (PALPA 54, Kay et al., 1992).

*Grammatical processing* was evaluated by comprehension of reversible spoken and written sentences, a written grammaticality judgment test, and collection of samples of spontaneous and elicited spoken and written output. The reversible sentence compre-

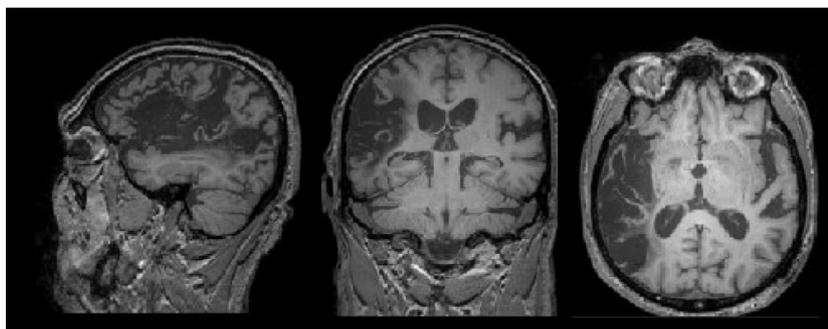


Fig. 1. MRI scan for JCB.

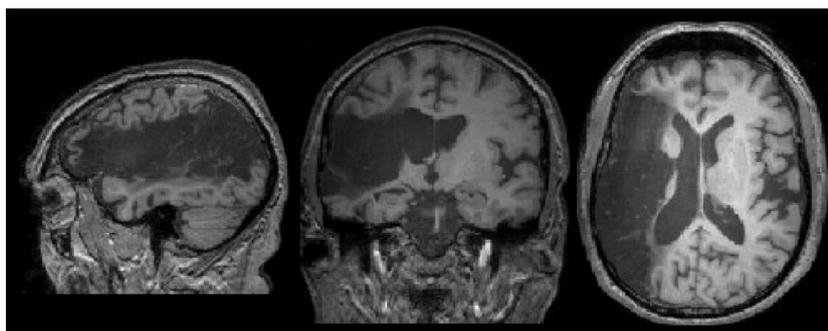


Fig. 2. MRI scan for PR.

hension tests (unpublished) required matching of a spoken or written sentence to the corresponding pictured event in the presence of a distracter picture showing the reversed roles of the protagonists (e.g., the man killed the lion/the lion killed the man). The stimulus sentences included equal numbers (40 each) of active and passive sentences to prevent use of an order-of-mention strategy in decoding the sentence (e.g., “assume that the first mentioned noun is the Subject of the sentence”). The grammaticality judgments test required the patient to decide whether a written sentence is grammatical. Ungrammatical stimuli contained gross violations of English syntactic structure (e.g., ‘sentences’ with no verbs). This task was not performed in the phonological modality to avoid prosodic cues influencing grammaticality judgments.

Patients' *short-term phonological memory capacity* was determined by a digit span test (PALPA 13, Kay et al., 1992). Span was established in a recognition paradigm in order to eliminate speech production problems from the task. The patient decided whether two auditorially presented strings of numbers were the same or different.

Both patients displayed some residual lexical comprehension ability (Table 1), particularly for concrete vocabulary tested in word-picture matching tests. JCB's word comprehension scores were lower than those of PR, but they both scored significantly above chance on the spoken and written word-picture matching. Synonym verification was more impaired, although both patients scored at above chance level on written synonym judgment. PR also scored above chance on the spoken synonym judgment task. On the picture naming tasks, JCB and PR displayed severely

impaired lexical production in the spoken modality (JCB: 8/60, PR: 0/60). Errors were typically no responses or neologisms. JCB performed better in the written modality (37/60), but PR remained severely impaired (2/60).

In contrast to some residual lexical comprehension ability, both patients showed severe impairment in grammatical comprehension. They performed no greater than chance level on understanding reversible sentences in both spoken (JCB: 38/80; PR: 29/80) and written (JCB: 43/80; PR: 34/80) modalities. They also performed at chance level on a written grammaticality judgments test. Phonological digit span was reduced in both patients from the average span for recognition in an age-control group of eight items (unpublished data).

With regard to language production, speech output consisted of social forms (*Yes/Bye*), high frequency, fully lexicalised utterances (e.g., *I know that*) and sentence connectives (e.g., *and, but*). Production was supported by occasional written words and gestures.

### 2.3. Evaluation of number processing and calculation

Both JCB and PR showed residual comprehension and production of numbers between zero and twenty. Numbers were understood when expressed in spoken and written number words, or digits in a task involving selecting counters to match a number form (Table 2). The test of number production involved labeling a quantity of counters with a spoken or written word, or numeral. Results indicated that both patients had relatively intact digit and spoken number production. More problems were evident with orthographic number words, particularly in the case of JCB. Spoken number naming was somewhat atypical in that patients employed count-up strategies to assist number word retrieval, and counted up in series, stopping when the required value was reached. Tests of calculation across all four mathematical operations including small and large number problems (e.g.,  $3 \times 7$ ;  $14 \times 18$ ), revealed residual calculation ability in both patients.

### 2.4. Imaging study stimuli

Following the procedure described in Benn et al. (2012), patients and healthy participants completed two-digit plus/minus two-digit problems, always involving the same digits across addition and subtraction ( $56 + 32$ ;  $56 - 32$ ) in order to match problem size and to control for phonological length of numbers across operations. Problems had no ties, i.e., no shared units ( $25 + 45$ ), shared decades ( $42 + 43$ ), or both ( $22 + 44$ ), as the solution for such problems is more likely to be retrieved than calculated. Use of 1 or 9 as units was excluded to avoid round up/down strategies. As part of a larger study of calculation, participants also performed addition and subtraction problems involving shapes rather than numbers (for details and results, see Benn et al., 2012). Here we report results from number tasks only.

Participants were presented with a stimulus problem that remained on the presentation screen while they calculated an answer and also during the response phase. When they were ready to respond, they pressed a button to display a probe item. They then indicated whether the probe matched their solution through a Yes/No button press response. Half the probes were correct and half were incorrect. Incorrect probes were wrong either in units (e.g.,  $36 - 17 = 17$ ) or decades ( $36 + 17 = 63$ ), with half having wrong units and half wrong decades. The wrong unit probes involved change by two to avoid parity checking strategies during response selection. False decade probes involved change by 10 to make estimation strategies more challenging.

A control task was designed that allowed for subtraction of semantic and visual processing of numbers, and the motor responses associated with pressing a correct/incorrect button.

**Table 1**  
Scores on lexical and grammatical processing tests.

	Chance score	JCB	PR
<i>Lexical processing</i>			
ADA Spoken Word Picture Matching	16.5	58/66*	61/66*
ADA written word picture matching	16.5	60/66*	66/66*
ADA spoken synonym matching	80	80/160	121/160*
ADA written synonym matching	80	137/160*	145/160*
PALPA 54 spoken picture naming	–	8/60	0/60
PALPA 54 written picture naming	–	37/60	2/60
<i>Grammatical processing</i>			
Comprehension of spoken reversible sentences	40	38/80	29/80
Comprehension of written reversible sentences	40	43/80	34/80
Written grammaticality judgements	20	19/40	21/40
PALPA 13 digit span (recognition)	–	2 items	4 items

\* Scores significantly above chance at the  $p < 0.01$  level.

**Table 2**  
Scores on number and calculation tests.

	JCB	PR
<i>Task: Comprehension: selecting the matching number of counters in response to a number form</i>		
Phonological	21/21	20/21
Orthographic	21/21	21/21
Digits	21/21	21/21
<i>Task: Production: labeling a quantity of counters with a spoken or written word, or numeral</i>		
Phonological	19/21	20/21
Orthographic	11/21	19/21
Digits	20/21	21/21
<i>Task: Calculation across operations: small and large number problems</i>		
Addition	20/20	20/20
Subtraction	17/20	19/20
Multiplication	18/20	17/20
Division	16/20	16/20

The task involved viewing an array of four digits in horizontal alignment. When participants were ready to respond, they pressed a button to view a probe digit and they were required to indicate whether the probe was identical to one in the stimulus array by pressing a Yes/No button. The original stimulus array again remained visible during the response phase.

### 2.5. Procedure and apparatus

To synchronize stimulus presentation with fMRI acquisition and to facilitate the recording of response time and accuracy, the stimuli were presented using E-prime. (2002) enhanced with Eloquence/IFIS (2006) software for paradigm development. Subjects were scanned in an MR system operating at 3T (Achieva, Philips Healthcare, Best, The Netherlands) with an 8-channel radiofrequency-receive-only head coil.

Calculation problems were presented visually on a monitor positioned above the head coil of the scanner, and the participant was instructed to calculate the result. When a participant was ready to answer, he pressed the button under the left thumb on a 5-button response box. A probe item was then displayed on the screen below the stimulus slide. The original problem remained visible on the monitor in order to reduce working memory demands. Participants then indicated whether the probe answer was correct by pressing the “correct button” (left index finger) or the “incorrect button” (left middle finger). Response accuracy and timing were recorded. The structure of the control task was similar. Participants viewed an array of digits and pressed the left thumb button when ready to view the probe item. The stimulus string remained visible while the participant viewed the probe item and correct/incorrect responses were made via the same buttons as the calculation task.

The time participants took to view the stimulus slide was labeled “calculation time” (or “observation time” in the case of the control tasks), whereas the time participants took to make a correct/incorrect judgment on the probe item was labeled “verification time”.

### 2.6. Training

In order to familiarize the patients with the format of the experiment and the position of the response buttons, both patients participated in four training sessions of 45 min each in the four week period prior to the fMRI experiment (one per week).

The first session included practice using paper examples. The following three training sessions began with a practice of the paper version. Then a laptop version of the experiment was introduced that was also used to familiarize healthy participants with the tasks prior to their scanning session. Patients were exposed to ten examples of addition and subtraction problems, none of which were used during the experiment.

### 2.7. Scanning procedure

Data were acquired over four separate runs of 8 min and 18 s each. Each run was made up of 16 blocks of 30 s, and two instruction blocks of 9 s. A 30-s fixation-block began each run and was repeated between the shape and the number tasks. The fixation period was followed by an instruction slide that indicated the nature of the upcoming task (shapes or numbers). The slide was displayed for 9-s and flashed in order to alert the participant to the stimulus set ahead. Addition and subtraction problems and control tasks were presented in blocks and no indication was given as to the nature of the calculation required in the upcoming block (i.e., addition or subtraction) or a change of task (calculation or control).

The first problem of the next condition appeared after the last problem of the previous condition was completed.

Each task was repeated twice in every run. Shape and number tasks were grouped so that all shape tasks appeared consecutively, followed by the blocks of number tasks or vice versa. Items in each block were fully randomized. The order of blocks varied between the runs. Half the runs started with shape blocks and half with number blocks. The number of stimuli in each condition was participant-driven, as the next stimulus appeared on the screen as soon as the participant made a judgment to a given probe.

### 2.8. Data acquisition

Cerebral vascular response to task was recorded using Blood Oxygen Level-Dependent (BOLD) fMRI. A time series of 175 scans was performed with a repetition time of 3.0 s. At each scan “time point,” 35 contiguous, transaxial slices parallel to a line bisecting the AC–PC were acquired using a T2\* weighted, gradient-echo, single-shot Echo Planar Imaging (EPI)-based technique (Echo Time = 35 ms, Repetition Time = 3000 ms, sensitivity encoding factor = 1.5). Each slice had an in-plane reconstructed pixel size of 1.8 mm × 1.8 mm and a slice thickness of 4 mm.

### 2.9. Data processing

All image data analysis was performed using Statistical Parametric Mapping software (SPM5, <http://www.fil.ion.ucl.ac.uk/spm>). Images were time adjusted and realigned to correct for head movements between scans. The realigned scans were then spatially normalized to the size and shape of an EPI template of SPM5. After normalization, images were smoothed using an 8 mm Full Width Half Maximum (FWHM) Gaussian filter. To determine brain BOLD-response activation, the following steps were performed. After specifying the design matrix for each of the participants, the hemodynamic responses induced by the different conditions were assessed for each individual using the general linear model and the theory of Gaussian fields (Friston et al., 1995) to form the task-contrast images. Second level analysis of the healthy control group was carried out using a one-sample *t*-test for each contrast with the appropriate contrast images from each individual in a random effects model. Activation maps of task versus control were superimposed onto the mean spatially normalized EPI image to determine the location of activations. In the case of the healthy controls, images and contrasts were constructed using uncorrected values but with a very conservative threshold of  $p < 0.0001$  and a minimum cluster size of 10. This approach was adopted, as interpretation based on structures smaller than 10 voxels in uncorrected group data is less reliable. This analytical approach is common in fMRI analysis (Wood et al., 2008; Dehaene et al., 2010). For analyses of patient data, images and contrasts were constructed using a height threshold  $t = 4.7979$  ( $p < 0.05$  (FWE)), with a minimum cluster size of 0 voxel, in order to allow for even slight re-organization to become apparent. Given the unusual structure of the patients' brains, the exact locations of activations were manually confirmed.

SPM was used to determine whether the patients' activation patterns were significantly different from those of the control group using Individual Case Analysis (ICA). ICA is a form of second level analysis that allows identification of significant differences between groups (each of 1 or more subjects) performing the same task, while accounting for any behavioral or other confounds such as brain abnormalities. For each patient, a first-level analysis with factorial design was defined with three factors: group (patient and healthy-controls), subject (11 in the control group and one patient), and task (task 1: number addition > control and task 2: number subtraction > control). The *t*-contrast examined the inter-

action between Group and Task. The analysis included calculation time as a covariate, to eliminate group differences due to differences in performance patterns.

### 3. Results

#### 3.1. Behavioral results

The patients showed a high level of accuracy in both addition and subtraction with scores above or close to healthy control means (Table 3). Independent sample *t*-tests indicated that the differences between patient and control scores were not significant.

With regard to response times, PR's performance did not significantly differ from that of the control group. JCB's responses were significantly (or near significantly) slower (calculation time: addition –  $t(2) = -2.927$ ,  $p = 0.015$ ; subtraction –  $t(2) = -2.063$ ,  $p = 0.066$ ; verification time: addition –  $t(2) = -2.562$ ,  $p = 0.028$ ; subtraction –  $t(2) = -3.512$ ,  $p = 0.006$ ).

Comparison of performance across mathematical operations revealed that healthy controls were significantly more accurate on addition than subtraction,  $t(10) = 2.492$ ,  $p = 0.032$ , and took significantly longer to calculate subtraction problems,  $t(10) = -4.345$ ,  $p = 0.001$ . However, neither of the patients showed significant differences between addition and subtraction.

#### 3.2. fMRI results

Fig. 3 displays activation maps of addition and subtraction for JCB, PR, and the healthy controls.

##### 3.2.1. Healthy control group

During addition, significant increases in activations were observed in the left middle occipital gyrus, left anterior cingulate, medial and superior frontal gyri (BA 6, 24, and 32), left precentral and inferior frontal gyri (Broca's area, BA 44 and 45), bilateral subgyral temporal regions, and right fronto-parietal sub-gyral regions. Subtraction evoked a larger network of activation than addition and included the right inferior and middle frontal gyri, right supra-marginal gyrus and inferior parietal lobule, bilateral anterior cingulate and medial frontal gyri, left inferior, superior, medial and middle frontal gyri, left precentral (BA 6, 13, 32, and 44), angular

**Table 3**

Accuracy level and response times for patients and the healthy control group.

	JCB	PR	Healthy (SD)
<i>Accuracy scores (%)</i>			
Addition	95	100	91 (4.7)
Subtraction	85	93	86 (7.7)
Control task	82	99	93 (3.1)
<i>Calculation time (ms)</i>			
Addition	8028	4206	4061 (1297)
Subtraction	7575	3879	4785 (1294)
Control task	5185	1299	1443 (450)
<i>Verification time (ms)</i>			
Addition	4051	3043	1655 (895)
Subtraction	5644	3275	1744 (1063)
Control task	2465	1528	1152 (1655)

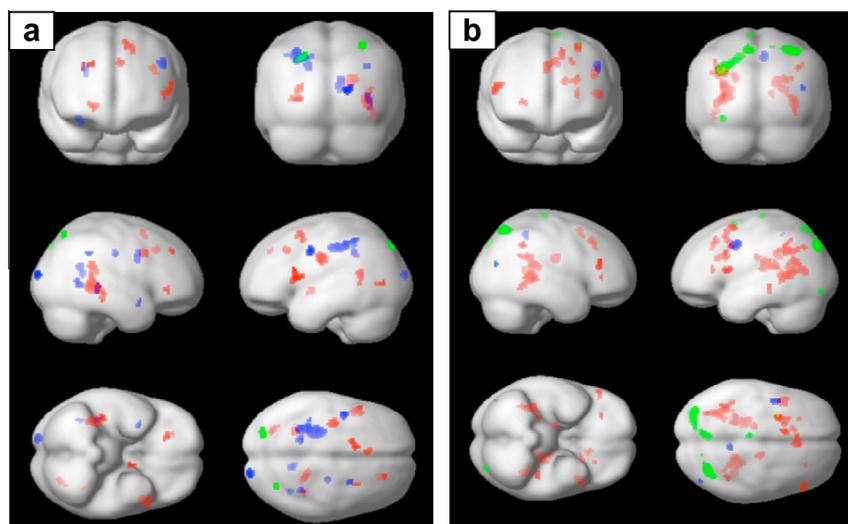
and supramarginal gyri, and left inferior parietal lobule and precuneus (BA 19, 39, and 40) (Benn et al., 2012). The increased left fronto-temporal activity in addition compared to subtraction may reflect retrieval of linguistically-encoded information to offset calculation demands.

In addition to the usual functional analysis, we also conducted an ICA to determine whether activation patterns for JCB and PR were significantly different from those of the control group. In comparing patient brain activations to normative patterns, data from individuals are compared to a group average. Large areas of markedly different activation from those of the healthy group might indicate post-lesional shift as a result of neurofunctional reorganization.

##### 3.2.2. Patients

###### 3.2.2.1. JCB.

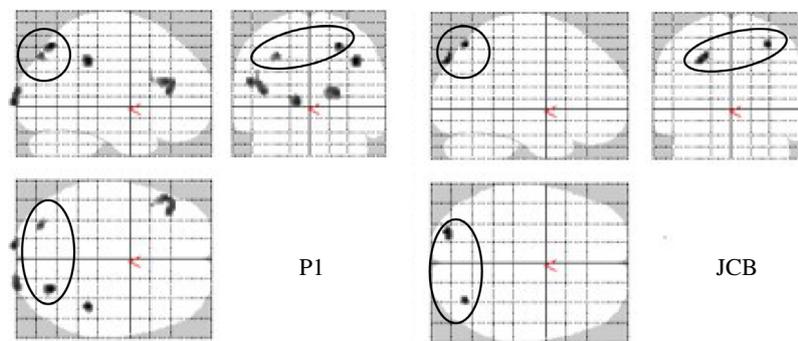
**3.2.2.1.1. Addition.** JCB's activation map during addition revealed strong bilateral parietal activity (Table 4). This pattern of activation appeared different from that observed in the healthy control group, who demonstrated strong left lateralized fronto-temporal and weak parietal activation during addition. However, the parietal activations in addition were similar to those observed in the control group during subtraction, in that they both involved activation of the left precuneus. This pattern suggests that, while the healthy controls may utilize the language system for retrieval of verbally



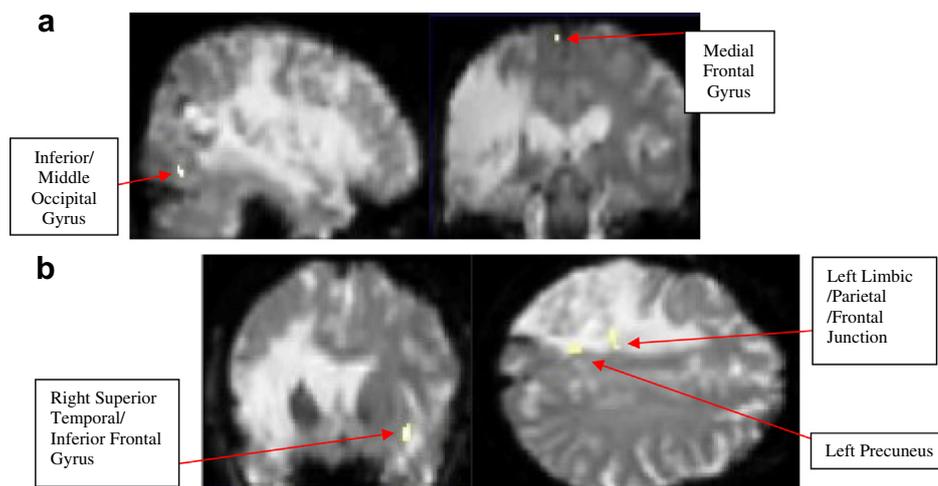
**Fig. 3.** Brain activations during: (a) addition > control and (b) subtraction > control. JCB (green) and PR (blue) FWE corrected;  $p = 0.05$ , cluster size threshold = 0; healthy control (red): un-corrected,  $p = 0.0001$ ; cluster size threshold: 10. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 4**  
Foci of fMRI signal for JCB during addition > control and subtraction > control, FWE corrected;  $p = 0.05$ , cluster size threshold = 0.

Region		BA	Max coordinates (MNI)			Z score	Cluster size (Voxels)
Lobe	Anatomical localization of cluster		x	y	z		
<i>Addition</i>							
<i>Right</i>							
Parietal	Superior parietal lobule	7	32	-70	56	5.3	22
<i>Left</i>							
Parietal	Precuneus	7/19	-26	-86	42	5.37	30
<i>Subtraction</i>							
<i>Right</i>							
Parietal	Superior parietal lobule	7	34	-70	56	6.26	132
<i>Left</i>							
Frontal	Medial frontal gyrus	6	-6	-26	72	5.29	19
Parietal	Precuneus/superior parietal lobule	7	-8	-76	56	5.54	54
Occipital/parietal	Superior occipital gyrus/cuneus/precuneus	7/19	-30	-86	40	6.88	130
Occipital	Inferior occipital gyrus	18	-32	-88	-14	5.36	14



**Fig. 4.** Glass brain activation during number addition > control for P1, (left panel) and JCB (right panel). Circles show similar activations of the bilateral superior parietal region.



**Fig. 5.** Increased activation in patients compared to healthy controls: (a) JCB during subtraction; (b) PR during addition.

**Table 5**  
Foci of fMRI signal during JCB subtraction > healthy subtraction FWE corrected;  $p = 0.05$ , cluster size threshold = 0.

Region		BA	Max Coordinates (MNI)			Z score	Cluster size (Voxels)
Lobe	Anatomical localization of cluster		x	y	z		
<i>Left</i>							
Frontal	Medial frontal gyrus	-	-6	-26	74	4.91	2
Occipital	Inferior/middle occipital gyrus	19	-42	-72	-12	5.38	8

encoded results in solving these relatively simple addition problems, JCB utilized a more “pure” calculation strategy that was centred in superior parietal regions.

ICA revealed that differences between JCB’s and the controls’ activation maps during addition were not significant. However, given that the activation maps appear to show differences between JCB and the averaged pattern for the healthy control group, we examined individual maps for control participants to determine if JCB’s profile was within the normal range. The pattern of increased activation during addition in parietal cortex evident in

JCB was also apparent in some healthy participants. For example, Participant 1 (P1, a 66 year old healthy participant) showed similar neural activations to JCB in parietal regions and indicates that the patient profile was within the normal range (Fig. 4).

3.2.2.1.2. *Subtraction.* The activation map for subtraction in JCB appeared similar to that of addition, but with increased intensity in the bilateral superior parietal region and extending to areas around the left frontal and occipital regions. Although activations were similar to those observed in the healthy group, ICA revealed some significant increase of activation in left medial frontal and inferior

**Table 6**

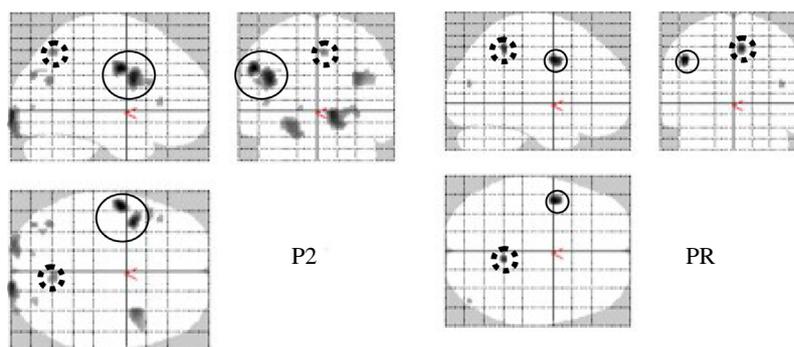
Foci of fMRI signal for PR during addition > control and subtraction > control. FWE corrected;  $p = 0.05$ , cluster size threshold = 0.

Region		BA	Max coordinates (MNI)			Z score	Cluster size (Voxels)
Lobe	Anatomical localization of cluster		x	y	z		
<i>Addition &gt; Control not same format as Table 3</i>							
<i>Right</i>							
Frontal	Sub-gyral	–	24	–18	34	5.06	16
		–	26	6	32	5.46	31
Frontal/temporal/limbic	Parahippocampal/superior temporal/inferior frontal gyrus	13/38	32	6	–18	5.05	14
Limbic/	Posterior cingulate	–	12	–54	20	5.57	59
Parietal	Supramarginal gyrus/sub-gyral	40	36	–44	36	4.98	15
Temporal	Sub-gyral	–	40	–36	0	4.96	14
	Middle temporal gyrus/sub-gyral	–	38	–56	2	5.22	27
Occipital	Middle occipital gyrus/cuneus	18	18	–98	12	5.42	38
<i>Left</i>							
Frontal	Precentral/inferior/middle frontal gyrus	6	–46	–2	38	5.75	49
Limbic/Parietal/Frontal	Cingulate Gyrus/precuneus/sub-gyral	31	–18	–46	36	5.09	47
		–	–30	–38	46	5.7	230
<i>Subtraction &gt; control</i>							
<i>Right</i>							
Parietal	Precuneus	7	8	–46	50	5.89	29
Temporal	Middle temporal gyrus	–	46	–78	18	4.97	6
<i>Left</i>							
Frontal	Precentral/inferior/middle frontal gyrus	6/9	–46	0	40	6.20	65

**Table 7**

Foci of fMRI signal during PR addition > healthy addition FWE corrected;  $p = 0.05$ , cluster size threshold = 0.

Region		BA	Max Coordinates (MNI)			Z score	Cluster size (Voxels)
Lobe	Anatomical localization of Cluster		x	y	z		
<i>Right</i>							
Limbic	Posterior cingulate/cingulate gyrus/extra-nuclear	–	8	–36	22	5.42	21
Temporal/frontal	Superior temporal/inferior frontal gyrus	13/38	36	8	–16	5.67	31
<i>Left</i>							
Limbic/parietal/frontal	Sub gyral/cingulate gyrus	–	–28	–32	44	5.48	41
Parietal	Precuneus	–	–18	–54	38	5.3	25



**Fig. 6.** Glass brain activation during number addition > control of P2, (left panel) and PR (right panel). Circles show similar activations of the right precuneus (dotted line) and the left middle frontal gyrus.

and middle occipital gyri in JCB compared to controls (Fig. 5 and Table 5).

In summary, there were few significant differences in activation between JCB and controls. There was little evidence of large-scale re-organization of function in order to support calculation. Moreover, it appears that the system has narrowed to a core mechanism around the bilateral superior parietal region, which subserves both addition and subtraction.

### 3.2.2.2. PR.

**3.2.2.2.1. Addition.** Addition resulted in a large, mostly right sub-cortical activation together with activation of spared tissue in the left frontal area and the bilateral parietal (BA 40) region (Table 6).

ICA analysis revealed significant differences between PR and controls during addition. This was manifested in significant increase of activation in peri-lesional areas including the left precuneus and the left fronto-parietal junction (Fig. 5 and Table 7). Increased activation was also observed in the right fronto-temporal area, extending to sub-cortical regions. The increases in activation for PR are sparse, diffuse, and mostly bordering damaged tissue. These results suggest that the differences may reflect individual variation in localization, together with a slight shift of activation to nearby undamaged tissue.

**3.2.2.2.2. Subtraction.** Subtraction recruited the same region as addition of spared left frontal tissue, as well as the right precuneus (BA7) and the right middle temporal gyrus (Table 6). ICA analysis revealed no significant differences between PR and the controls during subtraction. Furthermore, activation of the right precuneus and the left middle cerebral gyrus observed in PR were within the normal range, in that this pattern was found in at least one healthy control (P2, a 70-year-old healthy control (Fig. 6).

Overall, activations of the left precuneus (addition) and right BA7 (subtraction) were similar to those of JCB, while activations of the left frontal region (BA 6/9) in both operations, and the right sub-gyral temporal regions and right BA40 during addition appeared similar to those observed in the healthy controls. These activation patterns suggest efficient utilization of spared tissue neighboring damaged regions, as well as of spared parietal regions. In sum, there was little evidence of large-scale re-organization.

**3.2.2.2.3. Individual Case Analysis of healthy controls.** Given that the ICA analysis revealed some significant differences between patients and controls, there are two possibilities in interpreting such differences. One is that the differences represent abnormality in that they lie outside of the normal range of processing, and hence may reflect functional-anatomical reorganization in the patients. The other is that these differences lie within normal variability, and hence represent differences in processing between an individual and a group average. To explore these possibilities, we conducted similar ICA analysis for each healthy participant compared to the other 10 participants in the control group. Eight of the eleven healthy participants showed significant differences from the group (see sup materials1). This indicates that a higher cognitive function such as calculation is no different from other cognitive domains such as language in that individual differences in the neural substrates of processing can be identified (Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, & Kanwisher, 2010; Fedorenko, Nieto-Castañón, & Kanwisher, 2012; Nieto-Castañón & Fedorenko, 2012).

## 4. Discussion

The results of this study reveal that exact addition and subtraction can be retained in the face of severe aphasia. The accuracy of two aphasic patients on 2-digit plus/minus 2-digit problems was comparable to that of healthy controls and, in the case of PR, re-

sponse times were also similar to those of controls. The behavioral results suggest that there is considerable autonomy between the processes of calculation and those of language. This finding replicates earlier reports of dissociation between language and math in the established (adult) cognitive system (Maruyama et al., 2012; Rossor et al., 1995; Varley et al., 2005). Furthermore, by combining neuroimaging techniques and lesion studies, the findings of this study extend beyond dissociation at a cognitive-behavioral level and report the neural mechanisms underpinning residual cognitive function in aphasia. While imaging studies of healthy participants might reveal activations associated with a behavior, in combination with patient functional imaging results, findings show activations that may be necessary for that behavior (Rorden & Karnath, 2004). The functional neuroimaging results reveal that, in the aphasic case, there was little evidence of wide-scale reorganization of function in order to support calculation. For example, neither patient displayed large-scale recruitment of prefrontal mechanisms that might have been required if automatic calculation routines had been disrupted, requiring the allocation of increased attention and strategic resources to support performance (Duncan, 2001; Park & Reuter-Lorenz, 2009). If language was a core mechanism in calculation, as opposed to an ancillary system that can support aspects of calculation performance, more marked activation shifts in patients would have been expected. This finding stands in contrast to evidence of altered patterns of activation that are evident when aphasic patients process linguistic information. In the latter case, damage to the core processing mechanisms of language results in both intra- and inter-hemispheric shifts in activations (e.g., Leff et al., 2002; Saur et al., 2006). Of the two patients, PR displayed during addition some peri-lesional shift anterior to Broca's area in the left hemisphere and some activation of the right fronto-temporal homologue. This finding was somewhat similar to the results of healthy controls who also showed activations in language regions during addition. PR was pre-morbidly left-handed, but also clearly pre-morbidly left hemisphere dominant for language given that his left hemisphere lesion resulted in a severe and long-lasting aphasia. In PR's case, the peri-lesional and homologous activations might reflect an ability to access some residual verbally-encoded calculation facts, with the atypical lateralization reflecting his left-handedness.

The finding of retained exact calculation despite severe aphasia and the absence of major reorganization of the neural substrates of calculation supports a view that bilateral superior parietal regions represent the core not only of a simple numerosity mechanism which is common to humans and other non-human species (Dehaene, Molko, Cohen, & Wilson, 2004), but also the processing of exact number representations in humans. This region is also central to higher order numeric functions such as exact calculation, and the integration of a bilaterally organized system in humans may be important in the emergence of higher order numeric capacities. Both patients displayed significant activation of bilateral parietal areas during both addition and subtraction, indicating that undamaged tissue in the bilateral precuneus and superior parietal regions (BA7) is likely to be the core neural substrate for exact calculation. The healthy control group showed some differences in performance across subtraction and addition problems that potentially reflected greater language involvement in addition. Addition and subtraction differ in the availability of stored results, with greater dependency on retrieval in addition than subtraction (Dehaene, 1992; Dehaene & Cohen 1995). The activation of the left perisylvian network that is often observed in studies of healthy participants may reflect access to verbally encoded information. However, residual calculation ability in the two patients, and the absence of a behavioral difference on addition and subtraction, indicates that this mechanism is an adjunct to the calculation core. The adjunct functions of language in calculation include not only

offsetting demands for computation through access to stored mathematic facts encoded in verbal format, but also short-term retention of intermediate products of calculation through encoding into phonological form and maintenance within phonological working mechanisms. However, in the instance of simple mathematics, calculation can be successfully completed without access to such resources.

The role of the LAG in calculation has attracted considerable attention in investigations of the neural basis of calculation. Increased activation in this region has been observed in expert calculators (Menon et al., 2000), and in the early stages of training calculation problems (Ischebeck et al., 2007). These activations may reflect encoding and retrieval of information in verbal memory. For both PR and JCB, the LAG was lesioned, although the superior part was spared in JCB. Nevertheless, behaviorally, both performed within the range of healthy participants. These results indicate that the LAG may mediate between left hemisphere linguistic and right hemisphere visuo-spatial processes (Benn et al., 2012). Calculation can be retained despite damage to this structure with dependence upon core mechanisms and without recruitment of language or need for integration of the two forms of representation.

With regard to the role of language in other domains of cognition, our results support the view that linguistic resources are valuable in supporting performance in intrinsically non-linguistic domains. However, the residual competence of some people with severe aphasia in domains such as calculation, theory of mind (Varley & Siegal, 2000), generating and understanding communicative intentions (Willems et al., 2011) and spatial re-orientation (Bek et al., 2010) indicates that the resources of the language faculty can be removed without collapse of performance. We have shown here that residual capacity in aphasia is not a consequence of massive and extraordinary adaptation of a processing network and, in the case of calculation, inferences can be made from aphasic performance to the function and structure of calculation in the healthy state.

## Acknowledgments

We thank JCB, PR and their families for their willing involvement in this research. This paper is dedicated to the memory of our colleague Michael Siegal who died in February 2012.

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