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Neural correlates of training-induced improvements of calculation skills in patients with brain lesions

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Abstract.
Purpose: The loss of calculation skills due to brain lesions leads to a major reduction in the quality of life and is often associated with difficulties of returning to work and a normal life. Very little is known about the neural mechanisms underlying performance improvement due to calculation training during rehabilitation. The current study investigates the neural basis of training-induced changes in patients with acalculia following ischemic stroke or traumatic brain lesions.
Methods: Functional hemodynamic responses (fMRI) were recorded in seven patients during calculation and perceptual tasks both before and after acalculia training.
Results: Despite the heterogeneity of brain lesions associated with acalculia in our patient sample, a common pattern of training-induced changes emerged. Performance improvements were associated with widespread deactivations in the prefrontal cortex. These deactivations were calculation-specific and only observed in patients exhibiting a considerable improvement after training.
Conclusion: These findings suggest that the training-induced changes in our patients rely on an increase of frontal processing efficiency.

Keywords: Acalculia, training-induced activity changes, fMRI, calculation training

1. Introduction

Calculation is generally considered to be an important cognitive skill, and the ability to deal with numbers is of essential importance in daily life. Neuroimaging studies investigating these topics have proposed that number processing and arithmetic operations are performed by virtue of an interplay of frontal and inferior parietal brain regions (Dehaene and Cohen, 1995; Dehaene et al., 1996; Kiefer and Dehaene, 1997; Pinel and Dehaene, 2010; Rueckert et al., 1996). According to the triple code model (Cohen and Dehaene, 1995; Dehaene and Cohen, 1997), quantity manipulations required for subtraction are performed in the bilateral intraparietal sulci, whereas addition and multiplication are represented in the left hemisphere. Neuroimaging studies have thus far provided conflicting evidence. A recent study found that all arithmetic operations, with the exception of addition, elicited systematic activation of the left posterior intraparietal sulcus and deactivations in the right posterior angular gyrus. Multiplication and addition were both

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proposed to be subserved by the cognitive process of fact retrieval. However, multiplication was found to be associated with higher hemodynamic activity in the posterior intraparietal sulcus, prefrontal cortex, and lingual and fusiform gyri of the right hemisphere. Lastly, compared to multiplication, subtraction elicited a different pattern of activations in the right hemisphere (Rosenberg-Lee et al., 2011).

Lesion studies have furnished an account of arithmetic skills and their neural underpinnings partially consistent with neuroimaging evidence. The bilateral IPS, as well as the left angular and supramarginal gyrus, have received much attention, as several studies have shown that lesions in these areas impair arithmetic calculation and the internal representation of quantities (Cipolotti et al., 1991; Dehaene and Cohen, 1997; Dehaene et al., 2003). Lesions in the inferior parietal area of the language dominant hemisphere has been shown to impair reading, the naming of numbers, calculating (Cipolotti et al., 1991). However, the deficit can also be selective for calculation, with reading, writing, spoken recognition and production of arabic digits as well as number words remaining unaffected (Dehaene and Cohen, 1997; Warrington, 1982). In parallel with the neuroimaging evidence, there also appears to be some heterogeneity in the deficits caused by inferior parietal lesions. This suggests that although this region plays a central role (Simon et al., 2002), it may not be the only area involved in calculation and number processing.

Presently it is generally agreed that a wide network of brain areas is involved in different facets of calculation, including language-based retrieval of arithmetic facts, rote arithmetic memory, quantity processing oriented to an internal number line, and the spatial layout of multi-digit calculations (Dehaene et al., 2004). Unsurprisingly, acalculia can stem from a variety of lesion locations, from parietal lesions causing disorganization of the semantic representation of numerical quantities (Dehaene and Cohen, 1997), to disruptions within the frontoparietal network affecting calculation or reasoning processes (Arsalidou and Taylor, 2011; Dehaene and Cohen, 1995).

An important question concerns the impact training can have on the above-described network. Following training, the response time and accuracy during the solving of complex arithmetic problems have improved significantly, with participants performing much faster and more accurately (Ischebeck et al., 2006). These behavioral improvements are associated with a shift in activation distribution from frontal to parietal brain areas, which has been suggested to reflect an increase of arithmetic competence (Delazer et al., 2003). Furthermore, within the parietal lobe, a shift of activation from the intraparietal sulci to the left angular gyrus which otherwise responds selectively to multiplication training (Ischebeck et al., 2006) has also been reported (see (Zamarian et al., 2009) for review).

Several studies have also examined training procedures, but with the goal of reducing acalculia symptoms (for a recent overview see (Cappa et al., 2011)). Most of these studies have attempted to reestablish simple arithmetic facts that could be improved through extensive drill or rote training (Domahs et al., 2004; Domahs et al., 2008; Girelli et al., 1996; Hittmair-Delazer et al., 1994; Kashiwagi et al., 1987; Whetstone, 1998). Another acalculia rehabilitation training method refers to the transfer of procedural knowledge and solution strategies based on individual residual knowledge and the re-teaching of basic arithmetic principles. These single-subject studies (Domahs et al., 2003; Girelli et al., 2002; Miceli and Capasso, 1991) yielded improved patient performance, and showed that these effects are more flexible and sustainable relative to those acquired through pure drill learning procedures.

A straightforward method used in rehabilitation consists of the employment of computer-based training programs. At a behavioral level it has been convincingly shown that such programs increase patient performance (Claros-Salinas, 2003). However, not much is known about the neural correlates of such training-induced improvements in calculation performance among patients with lesions. One study aimed at investigating this issue in one patient with acalculia following a left subcortical lesion performed fMRI before and after calculation training (Zaunmüller et al., 2009). After training, the patient could solve trained and untrained items not only faster, but also with apparently altered calculation strategies. Specifically, instead of time-consuming back-up strategies, he increased direct retrieval of multiplication facts from long-term memory. In fMRI significant foci of activation were observed in the angular gyrus of the right hemisphere, with different subregions being activated during trained and untrained conditions. For trained items of multiplication, the main activation was found in the anterior aspect of the right angular gyrus, whereas activations for the untrained condition were observed in a more posterior aspect. However, whether this pattern of findings would generalize to other patients remains unknown.

The goal of the current study was to investigate the neural basis of training-induced improvements not only in single subjects, but also in a group of patients with acalculia. Because the neural correlates of calculation are expected to be different between normal subjects and patient groups with lesions, we forego testing in normal participants. Instead, our approach, included all patients that presented the clinical signs of acalculia following strokes or traumas regardless of the location of the lesions. The standardized computer-based training was performed using the Acalculia Rehabilitation Program (ARP), which retrains addition, subtraction, multiplication and division operations normally solved without a pocket calculator (Acalculia Rehabilitation Program/ARP, cf. Claros-Salinas 2003). fMRI was acquired before and after training as patients either solved mixed calculation problems or compared the size of two circles presented on the screen. The perceptual task served to assess whether the changes reflected improvements in calculation processing per se, or more general processing improvements that would also be observed in the size comparison task. Consistent with previous work we expected improvements at the behavioral level. At the neural level we expected these behavioral improvements to be associated with changes in hemodynamic activity levels in frontal and parietal regions, especially in the IPS and the angular and supramarginal gyri.

2. Methods

2.1. Patients

We tested a total of seven patients with traumatic or ischemic lesions who presented with symptoms of acalculia. The demographic data of the patients are shown in Table 1. Interestingly, the localization of the lesions revealed their distribution to be very heterogeneous across patients. In two patients (BH and GT) the calculation problems emerged following a traumatic brain injury. Patient GT exhibited a left parieto-temporal lesion while Patient BH had right fronto-polar morphological changes (see Fig. 1). BH's neuropsychological testing revealed attentional, memorial and dysexecutive problems: his cognitive processing speed was severely reduced; memory performance and planning skills were moderately impaired. GT's neuropsychological tests revealed a slightly decreased ability to learn, impairment of divided attention performance and cognitive flexibility, and significant limitations in cognitive endurance. GT showed more residual symptoms of aphasia with references to alexia and agraphia. In particular, he noticed a weakness in mental arithmetic abilities. Three (JL, ST, UN) of the five remaining patients had subcortical lesions in the left basal ganglia. JL's neuropsychological test results showed an almost standard learning and attention performance as well as average logical-deductive thinking abilities. JL described difficulties in mental calculation, which he considered a severe handicap. ST initially presented with a right-sided hemiparesis, visual hemispatial neglect, learning and long-term retention deficits, especially for verbal material, and moderate aphasia, primarily in word retrieval. At the time of our calculation training, the hemiparetic and neglect symptoms had mostly resolved. However, his calculation abilities were severely reduced and he reported to be insecure whenever he had to deal with numbers. UN presented with a right-sided hemiparesis, moderately reduced memory function, and moderate limitations in cognitive endurance and residual aphasia.

The remaining two patients (XC, NL) had cortical lesions in the left temporal, parietal and occipital cortex. Patient XC presented with a right-sided hemiparesis, right-sided homonymous hemianopia and

Table 1
The table shows a short summary of the demographic and clinical data of the patients

Patients					
Patient	Gender	Age	Aetiology	Localisation	Time post onset/months
BH	m	27	TBI	right, fronto-polar	12
JL	m	52	basal ganglia hemorrhage	left, subcortical	48
GT	m	48	TBI	left, temporo-parietal	7
XC	m	47	stroke	left, temporo-parieto-occipital	16
NL	m	57	stroke	left, fronto-temporal	32
ST	m	52	basal ganglia hemorrhage	left, subcortical	41
UN	m	50	basal ganglia hemorrhage	left, subcortical	12

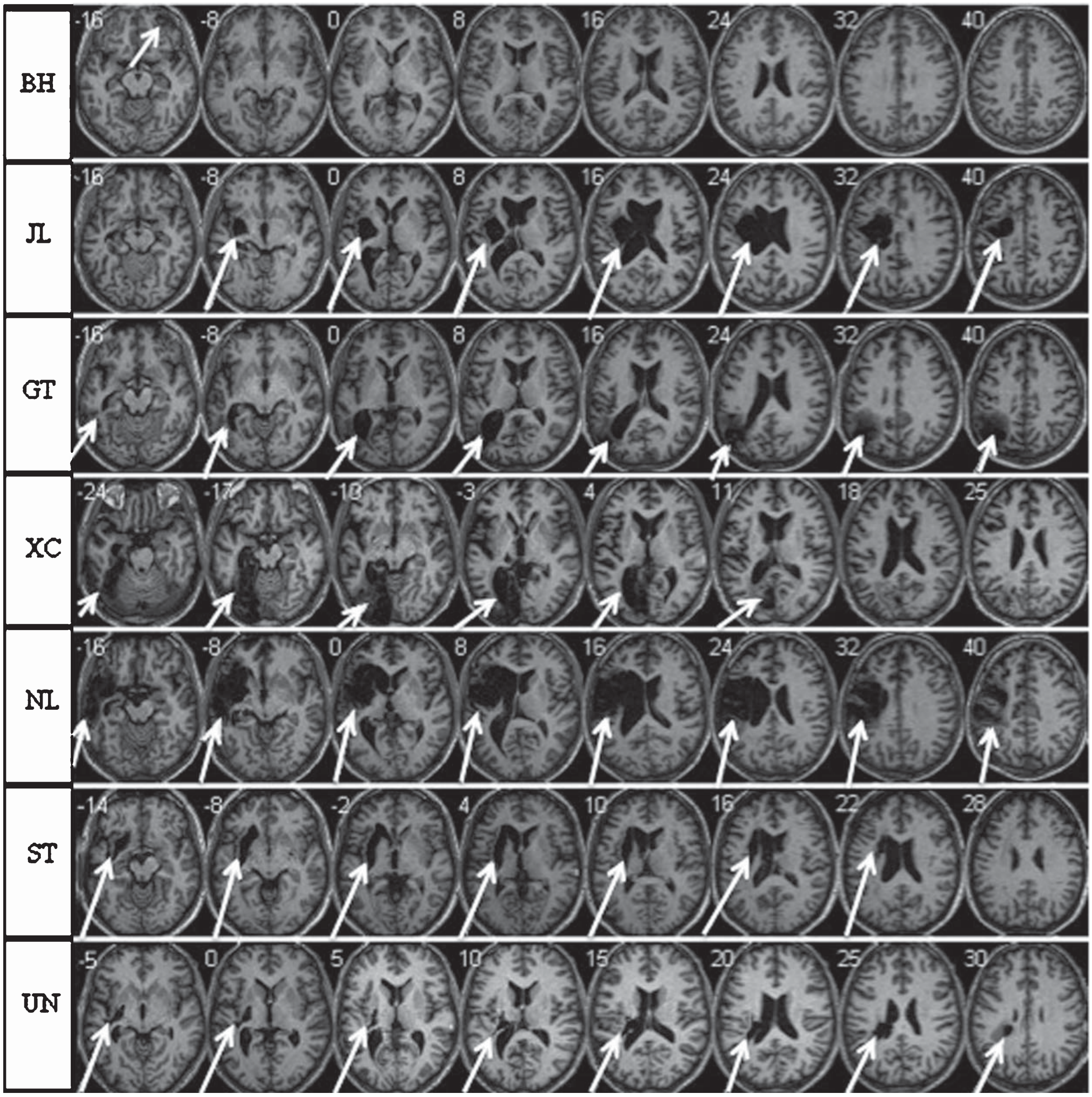

Fig. 1. The figure shows the structural MRI images of the patients. A white arrow indicates the site of the main lesion. Note the heterogeneity of the lesion locations giving rise to the clinical signs of acalculia.

aphasia. At the time of our computer training, the functioning of the right arm was still restricted, the right-sided homonymous hemianopia persisted, and language skills, especially spontaneous speech, had recovered, but were still considerably reduced in terms of word retrieval, naming and written language. Besides slightly reduced alertness, there were no further cognitive impairments observable according to neuropsychological tests results. Patient NL presented with a right-sided hemiparesis and global aphasia that persisted when calculation training started. Importantly, neuropsychological examinations did not reveal any cognitive impairment independent from NL´s language problems. It is also worth noting that only one patient within our sample (BH) had a right hemisphere lesion.

2.2. Training

A computer-based rehabilitation program (Acalculia Rehabilitation Program/ARP, cf. Claros-Salinas 2003) was employed for training in which calculation problems (all four basic calculation operations according to individual needs) were presented on a computer monitor and had to be solved by the patient. The correct response to the problem had to be typed in via keyboard as fast as possible after which the patient received feedback. The duration of a training session was 20 minutes, during which different behavioral variables such as the ratio between correct and incorrect answers, reaction time for each basic calculation operation and the average solution time were recorded. Error patterns and solving behavior were analyzed afterward and communicated to the patients, giving them hints for future training sessions.

In order to measure not only simple training effects but also the transfer to untrained problems, the ARP provides a mixed calculation problems section that was presented at the onset of training (t1), after five sessions of individual training (t2) and at the end, after another five sessions (t3). The entire training regimen consisted of 14 sessions completed within four weeks. Details on this training procedure have been reported previously (Claros-Salinas, 2003).

2.3. fMRI Task

The stimuli were presented in white color (150 cd/cm2) on a black screen (0.5 cd/cm^2) about 2° above a central fixation cross (1° X 1°). They consisted of a mixed calculation problem with a solution (e.g. 15 + 34 = 85) that was correct in 50% of the cases superimposed on two circles located next to each other to the left and right of the fixation cross. The size of the numbers was about 1.5° while the size of the circles varied between 3° and 5°. The calculation problems were two parallelized sets of mixed problems (one for the scanning session before and the other after training). Each set comprised 120 problems (30 problems each per type of basic calculation-addition, subtraction, multiplication, and division – presented in a pseudo-randomized order). Addition and subtraction tasks were more complex than multiplication and division tasks. The difficulty in reference to the training was medium, with numbers being single- and double-digit values. The patients were assigned to either the calculation or circle comparison task on a run-by-run basis. For the calculation task, they were asked to perform the calculation and execute a response via button press with either the index finger or middle finger indicating whether the equation was correct or incorrect, respectively. In the size comparison task the patients had to indicate which circle was bigger by pressing a button with the index for the left circle and another button with the middle finger for the right circle. For both tasks the response time window was limited to 6 seconds. The difficulty of the tasks was roughly equated but not perfectly adapted to the individual performance level of each patient.

2.4. MRI

2.4.1. Structural MRI

The MRI data were acquired with a 1.5 Tesla Philips Gyroscan NT (Philips Medical System). A T1 weighted volume (21 axial slices of 5 mm thickness with 1 mm gap, FOV 250 × 250 mm, 512 × 512 matrix, TR 134.46 ms, TE 2.1 ms, flip angle 80°) was acquired for each patient before the functional imaging experiment.

2.4.2. fMRI

Blood oxygen level-dependent contrast was measured with a T2* sensitive gradient-echo echo-planar imaging sequence (23 axial slices with a voxel size of 3.1 mm and a slice thickness of 5 mm, interleaved slice acquisition, field of view of 200 × 200 × 137, 64 × 64 matrix, TR of 2 sec, TE of 40 ms and a flip angle of 80°). A total of 230 volumes were acquired during each run. The experiment was carried out in 4 runs with a short break in between each session. Data analysis was performed with the SPM 5 software package. The volumes were realigned to the first image, normalized to the SPM 5 EPI template and smoothed using a Gaussian kernel of 8 mm full-width at half maximum. The time series in each voxel were high pass filtered with a cutoff at 1/128 Hz to remove low frequency confounds.

3. Results

3.1. Behavioral results

Prior to training, patients had trouble solving mixed calculation problems contained in the ARP (e.g. 27+15 or 56/7). The average solution time was between 8 and

Table 2
Mixed calculation: error rates (%) and average solution times (sec.) for the fMRI task (pre and post training) and for the computer based training ARP tasks (t1: start, t2: after five sessions, t3: end)

			ARP training / mixed calculation																									
	fMRT pre		**t1**								**t2**								**t3**								**fMRT post**	
	% error	time	% error				time				% error				time				% error				time				% error	time
BH	**15,6**	4,5	**14,4**				7,7				**18,3**				6,4				**7,4**				7,8				**18,7**	4,1
			+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:		
			18,2	**33,3**	**2,7**	**5,4**	11,2	12,2	2,7	5,2	**32,4**	**21,2**	**2,9**	**15,8**	10,6	6,7	2,9	4,9	**21,7**	**11,1**	**0**	**0**	12	9,8	4,3	5,8		
JL	**20,3**	3,9	**19,4**				14				**17,4**				13,7				**13,2**				12,4				**21,9**	3,9
			+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:		
			27,3	**20**	**0**	**25**	15,2	19,5	5,2	15,7	**11,8**	**44,4**	**0**	**11,8**	15,5	25,7	3,1	10,1	**29,4**	**18,8**	**0**	**5,6**	16	22,7	3,8	8,1		
GT	**20,3**	5,2	**13**				19,5				**6,6**				13,4				**11,4**				14				**18,7**	5,2
			+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:		
			9,1	**36,4**	**0**	**7,7**	18,4	37,3	7,9	15,1	**17,4**	**4,8**	**0**	**4,2**	18,1	16,9	6	12,9	**13,6**	**4**	**0**	**29,6**	14,1	16,5	7,1	15,4		
XC	**14,1**	6,1	**10**				18,7				**10**				13,8				**6,6**				14,7				**9,4**	6,4
			+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:		
			11,8	**7,1**	**0**	**18,8**	20,8	23	10,6	19,3	**16,7**	**5,6**	**4,3**	**18,2**	12,8	17,3	7,6	17,6	**23,5**	**11,1**	**0**	**0**	16,9	17,3	8,9	16,3		
NL	**29,7**	2,7	**10**				8				**5,6**				8,3				**3,6**				8,7				**23,4**	2,9
			+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:		
			5,7	**15**	**11,1**	**7,7**	10,6	10,1	5,5	5,5	**12,8**	**2,9**	**2,6**	**3,2**	9,7	9,6	7,5	5,8	**0**	**5,9**	**9,4**	**0**	9,2	9,5	9,2	7,1		
ST	**54,7**	4,6	**17,4**				8,9				**14,3**				8,9				**3,7**				10,7				**45,3**	4,3
			+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:		
			3,6	**37**	**3,3**	**26,7**	10,5	14	5,7	5,9	**6,9**	**3,6**	**12**	**33,3**	10	13,2	7,5	4,8	**0**	**4,8**	**4,8**	**4,8**	10,8	12,7	9,4	10,1		
UN	**18,7**	6,8	**11,9**				8,8				**1,2**				12,5				**0**				7,4				**7,8**	4,8
			+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:	+	-	x	:		
			12,5	**28**	**0**	**8**	10,5	13,9	2,9	8,3	**0**	**0**	**0**	**5**	18,4	17,4	3,9	11,3	**0**	**0**	**0**	**0**	10,7	8,5	2,9	7,1		

20 seconds and the error rate was at least 10 %. The values of each patient are shown in Table 2.

In order to measure improvements we developed an improvement index, in which the quality of the calculation had a higher weight than the speed. The formula for the index was 2 * (error rate before training – error rate after training) + (time before training – time after training). The mixed calculation test-session following the completion of training showed that all patients improved their performance (black bars in Fig. 2). It should be noted that this test, unlike the task completed during MRI measurements, did not put any time pressure on the patients, who were instructed to perform the calculation and give the correct result for which the time was measured. In the scanner maximum response time window of 6 seconds made the task more difficult than during the training sessions, forcing subjects to engage in a speed-accuracy tradeoff. Thus, improvements compared to the first measurement in the scanner were observed in only 5 of the patients (white bars in Fig. 2). The performance improvements were also evident in the control task, in which the size of two circles had to be compared. Remarkably, the two patients (BH and JL) who failed to improve in the calculation task also showed a drop in performance in the perceptual control task (grey bars in Fig. 2) suggesting that the additional time pressure in the scanner resulted in a generalized decrement in performance.

3.2. fMRI results

As expected the different locations of the lesions led to different patterns of neural activity for calculation, and to some extent for the size comparison condition (data not shown), which eliminated the possibility of a group analysis. Since we were interested in investigating the neural correlates of training-induced changes, we contrasted the individual hemodynamic activation patterns before and after training for the calculation and for the size comparison condition within each subject. The results of these contrasts (increases of activity in red, decreases of activity in blue) reflecting training-induced changes of hemodynamic activity are shown in Fig. 3.

Increases of activity were observed in four of the patients. However, no common pattern emerged,

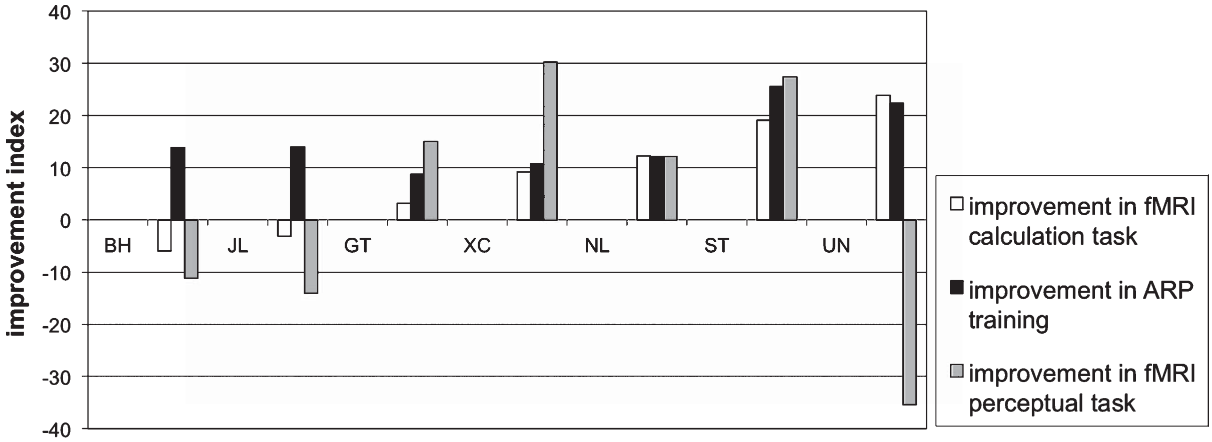

Fig. 2. Improvement index for calculation (fMRI and ARP training) and circle comparison task (fMRI). In the index the veracity of the calculation had a higher weight than the speed. The formula for the index was 2 * (error rate before training – error rate after training) + (time before training – time after training). Note that during the training all patients improved their performance (black bars). In the fMRI task (under time pressure) improvements were only observed in 5 of the patients (white bars). Performance improvements were also observed in the perceptual task (grey bars). Two patients (BH and JL) failed to show improvement across sessions in all tasks, presumably due to the added time pressure in the scanner.

especially with regard to the distinction between the patients who showed improved performance in the scanner task (GT, XC, NL, ST, UN) and those who did not (BH, JL). A very different picture emerged for the decreases of activity. Strikingly, all patients with performance improvements in the task exhibited deactivations in the frontal cortex while the two patients without performance increases (BH, JL) did not. While these deactivations were quite widespread, the prefrontal cortex (middle and superior frontal gyrus) was deactivated in all patients who improved their performance in the task (GT, XC, NL, ST, UN). It is important to note that this common prefrontal deactivation was exclusively observed for the calculation condition. No common pattern was observed for the size comparison condition.

4. Discussion

The present study employed fMRI with a calculation task in order to study the neural basis of training-induced changes in patients with acalculia following ischemia or traumatic brain lesions. The main finding was that despite the heterogeneity of brain lesions associated with acalculia in our small sample of seven patients, a common pattern of training-induced changes emerged. Improvements in performance were associated with widespread deactivations in the prefrontal cortex, especially in the middle frontal gyrus. The deactivations were specific for calculation processes, and only observed in patients exhibiting considerable improvement after training. These findings suggest that the observed training-induced changes rely on an increased efficiency of frontal processing.

Typically, training in a cognitive task leads to a decrease of hemodynamic activity in the brain areas in which task-relevant processing is performed (Erickson et al., 2007; Landau et al., 2004; McKiernan et al., 2003). This decrease of activity has been attributed to more efficient processing as a result of training. It is therefore not surprising that training-induced changes of activity were reflected by the common pattern of activity decreases observed in our patients. Importantly, the common pattern of activity decreases was observed in frontal areas, which at first glance might appear to be in contradiction to previous studies. In contrast to the present findings, the majority of previous studies, mostly performed in healthy subjects, found activity increases in parietal regions and postulated a special role of the angular gyrus in mental calculation. One study compared different arithmetic learning effects in healthy young adults using fMRI (Ischebeck et al., 2006). In multiplication, an increased activation of the angular gyrus was interpreted as a switch of cognitive processes from quantity-based processing (supported by activations in areas along the

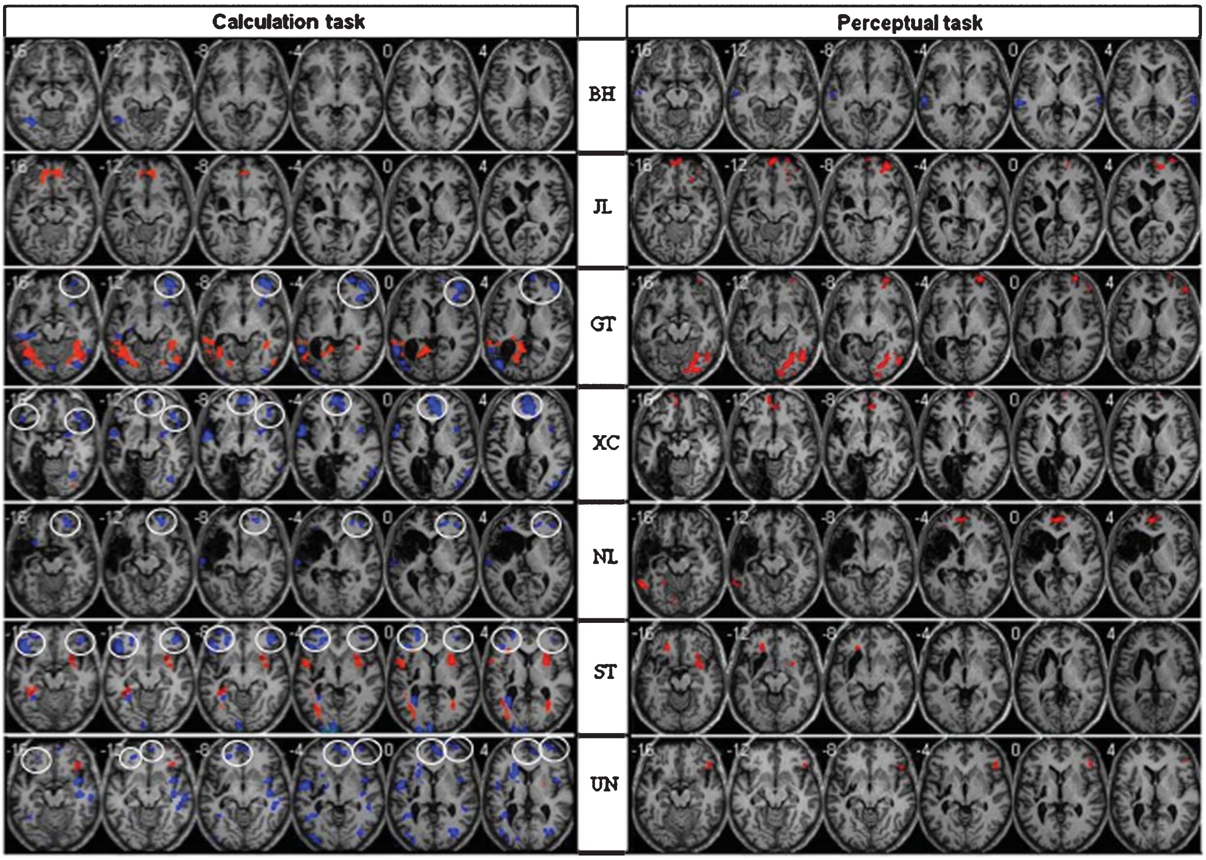

Fig. 3. The figure shows the results of the fMRI contrasts of the individual hemodynamic activation patterns before and after training for the calculation and for the size comparison tasks in each patient. Increases of activations are shown in red, decreases in blue. The white circles point to the common pattern of activity decreases reflecting training-induced changes of hemodynamic activity that was evident for the calculation task but not for the perceptual task.

intraparietal sulci at the beginning of the training) to more automatic retrieval (supported by activity in the left angular gyrus at the end of the training).

Furthermore, (Ischebeck et al., 2009) argued that the angular gyrus is not only involved in retrieval processes of arithmetic fact knowledge, but also in the transfer between different arithmetic operations. Transfer procedures were also required in our task, as the behavioral training focused individually on the four basic arithmetic operations, whereas the behavioral tests and fMRI task required subjects to solve mixed calculation problems. We did not observe training-induced changes of activity in the angular gyrus, at least not as a common pattern across subjects. This was a bit surprising, given that the only study that investigated neural correlates of training-induced changes of calculation skills in a patient with brain damage presenting acalculia reported activity changes in the angular gyrus (Zaunmüller et al., 2009). In this particular study, trained items (simple multiplication) elicited activity increases in the anterior aspects, whereas activity for the untrained condition was found in a more posterior portion of the right angular gyrus. It appears unlikely that this finding would generalize to other patients. In our study neither a marked activation of right hemispheric areas nor pronounced differentiation of angular gyrus structures as a general pattern of training-induced changes was observed.

Instead, we observed frontal activity decreases as a more general pattern associated with training-induced improvement across five patients. These frontal decreases were found during the calculation but not during the perceptual task, and only occurred when the patients showed improved fMRI task performance. Zaunmüller and colleagues also observed such training-related activity decreases in prefrontal regions in a study (Zaunmüller et al., 2009). The authors interpreted these decreases in terms of the application of back-up strategies, which presumably decreased after training. In principle, this aligns well with our interpretation of an increased processing efficiency in the prefrontal cortex due to training. In other studies, training-induced decreases of activity in the middle and inferior frontal gyrus were found to index increased efficiency of working memory performance (Hempel et al., 2004; Olesen et al., 2004; Schneiders et al., 2012). In our view, working memory performance is a key component in mentally resolving mixed calculation problems. In our perceptual task, which did not require working memory, we didn't observe any decreases of hemodynamic activity in frontal regions from the first to the second measurement. Therefore we believe that the observed decreases of hemodynamic activity in the frontal cortex indeed reflect increased processing efficiency related to working memory.

The frontal cortex is an important area for calculation. In children as well as adults, the gain of arithmetic competence is manifested as a shift of activation from frontal brain areas to parietal areas thought to subserve arithmetic processing (Zamarian et al., 2009). In our patients, this shift does not appear to take place, at least not during the four weeks of training. Training-induced activity changes were exclusively observed in the frontal cortex, which appears to correspond to the initial stages of regaining arithmetic competence. Whether the shift of activity towards parietal regions occurs at a later time is still to be determined. A recent meta-analysis (Arsalidou and Taylor, 2011) examining 53 imaging studies proposed an update of the long-standing triple code model (Dehaene et al., 2003). The authors observed that the prefrontal cortex was one of the most commonly activated regions within the network of areas involved in calculation. They suggest that although the function of these regions appears to be generic (working memory processes), their contribution to mental arithmetic needs to be represented in a neurofunctional model. These findings are well in line with the present results, in which modulations of hemodynamic activity in the prefrontal cortex were observed in all patients with brain lesions after successful calculation training.

It is important to note that at a behavioral level, all patients of our sample improved their calculation skills with ARP training. This was indexed by a considerable reduction of the errors observed in all patients, as well as by a slight reduction of the time needed to solve the problems in about half of the patients (see Table 2). Nevertheless, the shortest average time to solve a problem was 7.3 seconds (UN), after the training, which shows that the patients were still impaired in their calculation ability. Due to time constraints related to the scanning procedure, the fMRI task required a limited response time window of 6 seconds. This put time pressure on the patients and consequently not all patients were able to improve their performance from the first to the second measurement. Importantly, only those patients who improved their performance under the time pressure in the scanner exhibited the common pattern of activity decreases in the frontal cortex. The two patients (BH and JL) who failed to improve in the calculation task also showed a drop in performance in the perceptual control task (grey bars in Fig. 2) suggesting that these two patients had problems with the time pressure in particular.

The results of the current study suggest that calculation training-induced changes in patients with brain damage exhibiting the clinical signs of acalculia rely on an increase of frontal processing efficiency. Furthermore, the independence of the observed training-induced changes in the prefrontal cortex from the variety of locations of the brain lesions suggests a wide applicability of such training procedures in patients with acalculia.

References

Arsalidou, M., & Taylor, M.J. (2011). Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. *Neuroimage*, *54*, 2382-2393.

Cappa, S.F., Benke, T., Clarke, S., Rossi, B., Stemmer, B., & van Heugten, C.M. (2011). Cognitive Rehabilitation. In: Gilhus, N.E.B., M.P.; Brainin M. (Ed.), European Handbook of Neurological Management. Blackwell Publishing Ltd., New York, pp. 545-567.

Cipolotti, L., Butterworth, B., & Denes, G. (1991). A specific deficit for numbers in a case of dense acalculia. *Brain*, *114*(Pt 6), 2619-2637.

Claros-Salinas, D. (2003). Therapie von Zahlenverarbeitung und Rechnen nach Hirnschädigung. *Aphasie und verwandte Gebiete*, *17*, 43-60.

Cohen, L., & Dehaene, S. (1995). Towards an anatomical and functional model of number processing. *Mathematical Cognition*, *1*, 83-120.

Cohen, L., & Dehaene, S. (1997). Cerebral pathways for calculation: Double dissociation between rote verbal and quantitative knowledge of arithmetic. *Cortex*, *33*, 219-250.

Dehaene, S., Molko, N., Cohen, L., & Wilson, A.J. (2004). Arithmetic and the brain. *Curr Opin Neurobiol*, *14*, 218-224.

Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cogn Neuropsychol*, *20*, 487-506.

Dehaene, S., Tzourio, N., Frak, V., Raynaud, L., Cohen, L., Mehler, J., & Mazoyer, B. (1996). Cerebral activations during number multiplication and comparison: A PET study. *Neuropsychologia*, *34*, 1097-1106.

Delazer, M., Domahs, F., Bartha, L., Brenneis, C., Lochy, A., Trieb, T., & Benke, T. (2003). Learning complex arithmetic–an fMRI study. *Brain Res Cogn Brain Res*, *18*, 76-88.

Domahs, F., Bartha, L., & Delazer, M. (2003). Rehabilitation of arithmetic abilities: Different intervention strategies for multiplication. *Brain and Language*, *87*, 165-166.

Domahs, F., Lochy, A., Eibl, G., & Delazer, M. (2004). Adding colour to multiplication: Rehabilitation of arithmetic fact retrieval in a case of traumatic brain injury Neuropsychol *Rehabil*, *14*, 303-328.

Domahs, F., Zamarian, L., & Delazer, M. (2008). Sound arithmetic: Auditory cues in the rehabilitation of impaired fact retrieval. *Neuropsychol Rehabil*, *18*, 160-181.

Erickson, K.I., Colcombe, S.J., Wadhwa, R., Bherer, L., Peterson, M.S., Scalf, P.E., Kim, J.S., Alvarado, M., & Kramer, A.F. (2007). Training-induced functional activation changes in dual-task processing: An FMRI study. *Cereb Cortex*, *17*, 192-204.

Girelli, L., Bartha, L., & Delazer, M. (2002). Strategic learning in the rehabilitation of semantic knowledge. *Neuropsychol Rehabil*, *12*, 41-61.

Girelli, L., Delazer, M., Semenza, C., & Denes, G. (1996). The representation of arithmetical facts: Evidence from two rehabilitation studies. *Cortex*, *32*, 49-66.

Hempel, A., Giesel, F.L., Garcia Caraballo, N.M., Amann, M., Meyer, H., Wustenberg, T., Essig, M., & Schroder, J. (2004). Plasticity of cortical activation related to working memory during training. *Am J Psychiatry*, *161*, 745-747.

Hittmair-Delazer, M., Semenza, C., & Denes, G. (1994). Concepts and facts in calculation. *Brain*, *117*(Pt 4), 715-728.

Ischebeck, A., Schocke, M., & Delazer, M. (2009). The processing and representation of fractions within the brain: An fMRI investigation. *Neuroimage*, *47*, 403-413.

Ischebeck, A., Zamarian, L., Siedentopf, C., Koppelstatter, F., Benke, T., Felber, S., & Delazer, M. (2006). How specifically do we learn? Imaging the learning of multiplication and subtraction. *Neuroimage*, *30*, 1365-1375.

Kashiwagi, A., Kashiwagi, T., & Hasegawa, T. (1987). Improvement of deficits in mnemonic rhyme for multiplication in Japanese aphasics. *Neuropsychologia*, *25*, 443-447.

Kiefer, M., & Dehaene, S. (1997). The time course of parietal activation in single-digit multiplication: Evidence from event-related potentials. *Mathematical Cognition*, *3*, 1-30.

Landau, S.M., Schumacher, E.H., Garavan, H., Druzgal, T.J., & D'Esposito, M. (2004). A functional MRI study of the influence of practice on component processes of working memory. *Neuroimage*, *22*, 211-221.

McKiernan, K.A., Kaufman, J.N., Kucera-Thompson, J., & Binder, J.R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci*, *15*, 394-408.

Miceli, G., & Capasso, R. (1991). I disturbi del calcolo, Diagnosi e riabilitazione. Masson, Milano.

Olesen, P.J., Westerberg, H., & Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. *Nat Neurosci*, *7*, 75-79.

Pinel, P., & Dehaene, S. (2010). Beyond hemispheric dominance: Brain regions underlying the joint lateralization of language and arithmetic to the left hemisphere. *J Cogn Neurosci*, *22*, 48-66.

Rosenberg-Lee, M., Chang, T.T., Young, C.B., Wu, S., & Menon, V. (2011). Functional dissociations between four basic arithmetic operations in the human posterior parietal cortex: A cytoarchitectonic mapping study. *Neuropsychologia*, *49*, 2592-2608.

Rueckert, L., Lange, N., Partiot, A., Appollonio, I., Litvan, I., Le Bihan, D., & Grafman, J. (1996). Visualizing cortical activation during mental calculation with functional MRI. *Neuroimage*, *3*, 97-103.

Schneiders, J.A., Opitz, B., Tang, H., Deng, Y., Xie, C., Li, H., & Mecklinger, A. (2012). The impact of auditory working memory training on the fronto-parietal working memory network. *Front Hum Neurosci*, *6*, 173.

Simon, O., Mangin, J.F., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron*, *33*, 475-487.

Warrington, E.K. (1982). The fractionation of arithmetical skills: A single case study. *Q J Exp Psychol A*, *34*, 31-51.

Whetstone, T. (1998). The representation of arithmetic facts in memory: Results from retraining a brain-damaged patient. *Brain Cogn*, *36*, 290-309.

Zamarian, L., Ischebeck, A., & Delazer, M. (2009). Neuroscience of learning arithmetic–evidence from brain imaging studies. *Neurosci Biobehav Rev*, *33*, 909-925.

Zaunmüller, L., Domahs, F., Dressel, K., Lonnemann, J., Klein, E., Ischebeck, A., & Willmes, K. (2009). Rehabilitation of arithmetic fact retrieval via extensive practice: A combined fMRI and behavioural case-study. *Neuropsychol Rehabil*, *19*, 422-443.