CEREBRAL PATHWAYS FOR CALCULATION: DOUBLE DISSOCIATION BETWEEN ROTE VERBAL AND QUANTITATIVE KNOWLEDGE OF ARITHMETIC

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Abstract

We describe two acalculic patients, one with a left subcortical lesion and the other with a right inferior parietal lesion and Gerstmann's syndrome. Both suffered from "pure anarithmetia": they could read arabic numerals and write them to dictation, but experienced a pronounced calculation deficit. On closer analysis, however, distinct deficits were found. The subcortical case suffered from a selective deficit of rote verbal knowledge, including but not limited to arithmetic tables, while her semantic knowledge of numerical quantities was intact. Conversely the inferior parietal case suffered from a category-specific impairment of quantitative numerical knowledge, particularly salient in subtraction and number bissection tasks, with preserved knowledge of rote arithmetic facts. This double dissociation suggests that numerical knowledge is processed in different formats within distinct cerebral pathways. We suggest that a left subcortical network contributes to the storage and retrieval of rote verbal arithmetic facts, while a bilateral inferior parietal network is dedicated to the mental manipulation of numerical quantities.

Introduction

Acalculia, or an acquired deficit of calculation, is often observed following brain damage. The most frequent lesions yielding acalculia involve the left inferior parietal area or the left parieto-occipito-temporal junction (e.g. Henschen, 1919, 1920; McCarthy and Warrington, 1988; Takayama, Sugishita, Akiguchi et al., 1994; Warrington, 1982). However calculation deficits have also been observed following left subcortical (Corbett, McCusker and Davidson, 1988; Hittmair-Delazer, Semenza and Denes, 1994; Whitaker, Habiger and Ivers, 1985), left medial frontal (Lucchelli and De Renzi, 1993), left and right frontal (Fasotti, Eling and Bremer, 1992; Luria, 1966), right posterior (Hécaen, Angelergues and Houillier, 1961) or left ventral temporo-occipital lesions (Cohen and Dehaene, 1995). In the present paper, we clarify the functional deficits underlying these various neurological conditions. In particular, we show that different lesion sites can be associated with different functional impairments in the numerical domain that are predictable from a cognitive neuro-anatomical model of number processing.

It has often been noted that not all of calculation deficits should be considered as genuine acalculias (e.g. Hécaen et al., 1961). Right posterior lesions may yield visuo-spatial deficits that affect calculation inasmuch as the patient becomes

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unable to align digits properly on the page. In some patients with frontal damage, the calculation deficit mostly concerns complex multi-step arithmetic problems and may be related to a general deficit of planning (Luria, 1966). In left ventral temporo-occipital cases, calculation is impaired only when the operands are presented visually, not when they are presented auditorily (Cohen and Dehaene, 1995; see also McNeil and Warrington, 1994). Hence, the deficit concerns the visuo-verbal identification of digit and letter strings rather than calculation per se.

This still leaves us, however, with two main categories of calculation deficits to be accounted for:

- the classical acalculia, sometimes called anarithmetia, which is observed in cases of left inferior parietal lesion, and is frequently but not necessarily associated with agraphia, finger agnosia, and left-right confusion in a tetrad of deficits called "Gerstmann's syndrome" (Benton, 1961, 1987, 1992; Gerstmann, 1940);
- the less frequent acalculia which has been reported in cases of isolated left subcortical damage (Corbett et al., 1988; Hittmair-Delazer et al., 1994; Whitaker et al., 1985).

Clinically, both types of deficits involve an inability to compute simple operations such as 6×7 or 11-3, often with preserved ability to read numbers and to write them down to dictation. Both have been described as resulting from an impaired memory for stored tables of arithmetic facts (Grafman, 1988; Hittmair-Delazer et al., 1994; McCarthy and Warrington, 1988; Warrington, 1982). This interpretation, however, leaves unexplained why two very different lesions sites should both affect the same function, and why one site does not take over when the other is lesioned. Hence, the nature of the number knowledge encoded in left inferior parietal and left subcortical circuits remains unclear. As a matter of fact, the very concept of Gerstmann's syndrome has been strongly criticized (e.g. Benton, 1961, 1987, 1992). Furthermore, only rarely have in-depth cognitive analyses of single cases of calculation deficits been performed (but see e.g. Cipolotti, Butterworth and Denes, 1991; Dagenbach and McCloskey, 1992; Hittmair-Delazer, Semenza and Denes, 1994; Hittmair-Delazer, Sailer and Benke, 1995; Warrington, 1982). Hence, no distinct type of calculation deficit has yet emerged from the published cases of either Gerstmann's syndrome or of subcortical acalculia.

In the present paper, we tentatively suggest a partial resolution of this question. We have recently proposed a general model of the cognitive and neuro-anatomical architectures for number processing (Dehaene, 1992; Dehaene and Cohen, 1995; Cohen and Dehaene, 1995, 1996). Our "triple-code model" postulates three main representations of numbers (Figure 1):

- a visual arabic code, localized to the left and right inferior ventral occipito-temporal areas, and in which numbers are represented as identified strings of digits. This representation subserves multidigit operations and parity judgements (e.g. knowing that 12 is even because the ones digit is a 2);
- an analogical quantity or magnitude code, subserved by the left and right

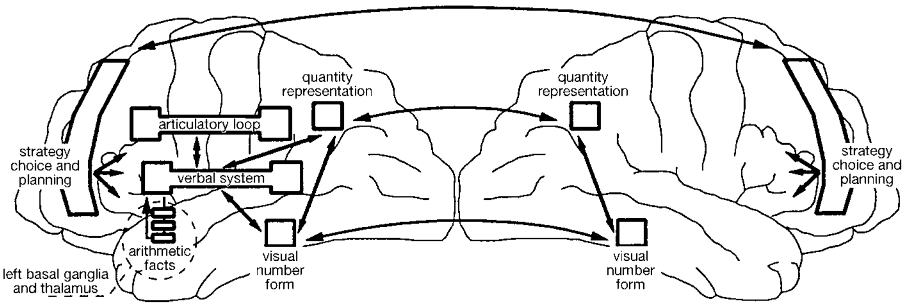

Fig. 1 – *Schematic anatomical and functional depiction of the triple-code model (adapted from Dehaene and Cohen, 1995).*

inferior parietal areas, and in which numbers are represented as distributions of activation on an oriented number line (Restle, 1970). This representation subserves semantic knowledge about numerical quantities, including proximity (e.g. 9 close to 10) and larger-smaller relations (e.g. 9 smaller than 10);

– a verbal code, subserved by left-hemispheric perisylvian areas, and in which numbers are represented as a parsed sequence of words. This representation is the primary code for accessing a rote verbal memory of arithmetic facts (e.g. “nine times nine, eighty-one”).

According to this model, there are two basic routes through which simple single-digit arithmetic problems can be solved. In the direct route, the operands of the problem (for instance, 2 × 4) are transcoded into a verbal representation of the problem (“two times four”) which is then used to trigger completion of this word sequence using rote verbal memory (“two times four, eight”). The critical components of this direct route are visual identification, visuo-verbal transcoding, and verbal sequence completion. In the triple-code model, the latter process is assumed to involve a left cortico-subcortical loop through the basal ganglia and thalamus, a circuit known to be involved in the control of sequence execution (e.g. Houk and Wise, 1995). Note that this direct route is blind to the meaning of the numbers it manipulates. In essence, it is simply “reading out” 2 × 4 as “eight”. We assume that the direct route is the normal route for overlearned calculations such as single-digit addition and multiplication problems, at least in countries such as France or Japan where the verbal recitation of addition and multiplication tables is used as a teaching method in elementary schools. We also assume that it is not available for complex operations such as 13 + 5 or for simple subtraction or division problems that are not normally acquired by rote verbal learning.

In the second, indirect semantic route, the operands are encoded as quantity representations held in the left and right inferior parietal areas. Semantically meaningful manipulations can then be performed on these internal quantities, and the resulting quantity can eventually be transmitted from the left inferior parietal cortex to the left-hemispheric perisylvian language network for naming. For the operation 5 – 2, for instance, starting from a mental representation of quantity 5, and decrementing this quantity twice, one reaches quantity 4 and then quantity 3. The latter result can then be named by the verbal system. We assume that this indirect semantic route is used whenever rote verbal knowledge of the operation result is lacking, most typically for subtraction problems.

In fact, many operations probably involve the simultaneous operation of both the direct and indirect routes. In single-digit addition and multiplication, we assume that the number line is mostly used to guide rote memory retrieval by the direct route, a process that we have termed "semantic elaboration" (Dehaene and Cohen, 1995). For instance, if the result of "nine times four" is not available in verbal memory, the magnitude representation can be used to compare the operands and to re-order the problems as 4×9, a new problem which can then be retrieved from rote memory. The semantic route is also assumed to be useful when monitoring the plausibility of a result retrieved by the direct route. If, for instance, the direct route mistakenly names the operands and comes out with "twenty-four" in response to 2×4 (Campbell, 1994), the incompatibility between the small magnitude of the operands and the large magnitude of the purported result may be detected using an approximate quantitative evaluation of the operation (Ashcraft and Stazyk, 1981; Dehaene and Cohen, 1991).

Clearly, the exact processes that are presently assumed to underlie the indirect semantic route are diverse and will require further specification. In past studies, we have emphasized the availability of an approximate representation of number magnitudes and its dissociability from exact fact retrieval (Dehaene and Cohen, 1991). In addition to approximate magnitude knowledge, however, different types of exact categorical knowledge of numerical quantities seem to be needed from the operations that we regroup under the heading of "semantic elaboration". Consider for instance the complex example of solving 9×4 by recoding it as $4 \times 10 - 4$, a frequent strategy (LeFevre, Bisanz, Daley et al., 1996). This example calls for larger-smaller knowledge (to recode 9×4 into 4×9), but also exact distance knowledge on the number line (to notice that 9 is one unit below 10), knowledge of the distributivity of multiplication [to notice that $4 \times 9 = 4 \times (10 - 1) = 4 \times 10 - 4 \times 1$], and knowledge of the rule $a \times 1 = a$ (to reduce 4×1 to 4). In its present form, the triple-code model lumps together all of these forms of semantic numerical knowledge, though they are potentially dissociable (Hittmair-Delazer et al., 1994; Hittmair-Delazer, Sailer and Benke, 1995), and it opposes them to rote verbal knowledge.

According to the triple-code model, then, two major sets of brain areas should be critical for calculation: the bilateral inferior parietal areas, because they hold semantic knowledge about numerical quantities, and the left cortico-pallido-thalamic loop, because it is involved in the storage of the rote verbal sequences of number words that correspond to simple arithmetic facts. The model makes contrasted predictions about the impact of lesions to these areas. Inferior parietal acalculia should be characterized by its *domain-specificity* (if the deficit is confined to semantic number knowledge, it should not affect other non-numerical areas of verbal or semantic knowledge), the *sparing of automatized facts* (simple addition and multiplication, which are leamed by rote, should be spared), and the presence of *numerical impairments outside calculation per se* (e.g. in number comparison or in deciding which number falls between 2 and 4). Conversely, left subcortical acalculia should be characterized by its *domain-nonspecificity* (non-numerical rote verbal knowledge such as poems, prayers or song lyrics may be affected), the *loss of automatized arithmetic facts* (multiplication should be particularly impaired), and the *sparing of semantic number knowledge*, including conceptual knowledge about the impaired operations.

These predictions were examined in two single-case studies of patients with acalculia, one of each type. Patient MAR suffered from a localized inferior parietal lesion, while patient BOO suffered from a left subcortical infarct.

Clinical Description

Patient MAR

Patient MAR was a 68-year-old left-handed painter and engraver, with a long-standing history of coronary failure. Following surgery for a coronary bypass, he complained of unusual writing difficulties. Two weeks after surgery, writing was almost normalized, with only mild residual clumsiness. However, closer examination revealed that the patient suffered from clear-cut acalculia. He also had minimal finger agnosia and left-right confusion, as well as some difficulties in imitating arbitrary hand postures and in simulating the use of familiar objects. There was no sensory or motor deficit, no aphasia (see Table I), no spatial neglect. CT-scan showed an infarct affecting the right inferior parietal lobule (see Figure 2).

In summary, patient MAR displayed all the defining clinical features of Gerstmann's syndrome. Lesion localization in the inferior parietal lobule was also typical of this syndrome. The remarkable fact that the lesion affected the right-hemisphere should be linked to the patient's strong left-handedness. He used his left hand for all skilled gestures, including painting and engraving. He had only been taught to write with his right hand, although he would occasionally use his left hand too. In the following, we postulate that language and calculation processes were cross-lateralized in patient MAR, such that his cerebral organization prior to the stroke was the mirror image of the one depicted on Figure 1. His unilateral right-sided lesion induced deficits that are typical of an homologous left-sided lesion in patients with a standard hemispheric specialization.

Patient BOO

Patient BOO was a 60-year-old right-handed retired school teacher. Three years before testing, she had suffered a left-hemispheric capsulo-lenticular haemorrage responsible for an initial coma, right-sided hemiplegia, and aphasia. Over the following months, the cognitive, sensory, and motor deficits receded almost entirely. When the present study was carried out, the patient showed minimal right-sided motor deficit, and chronic pain in the right half of her body. She scored at ceiling level in almost all subtests of the Boston Diagnostic Aphasia

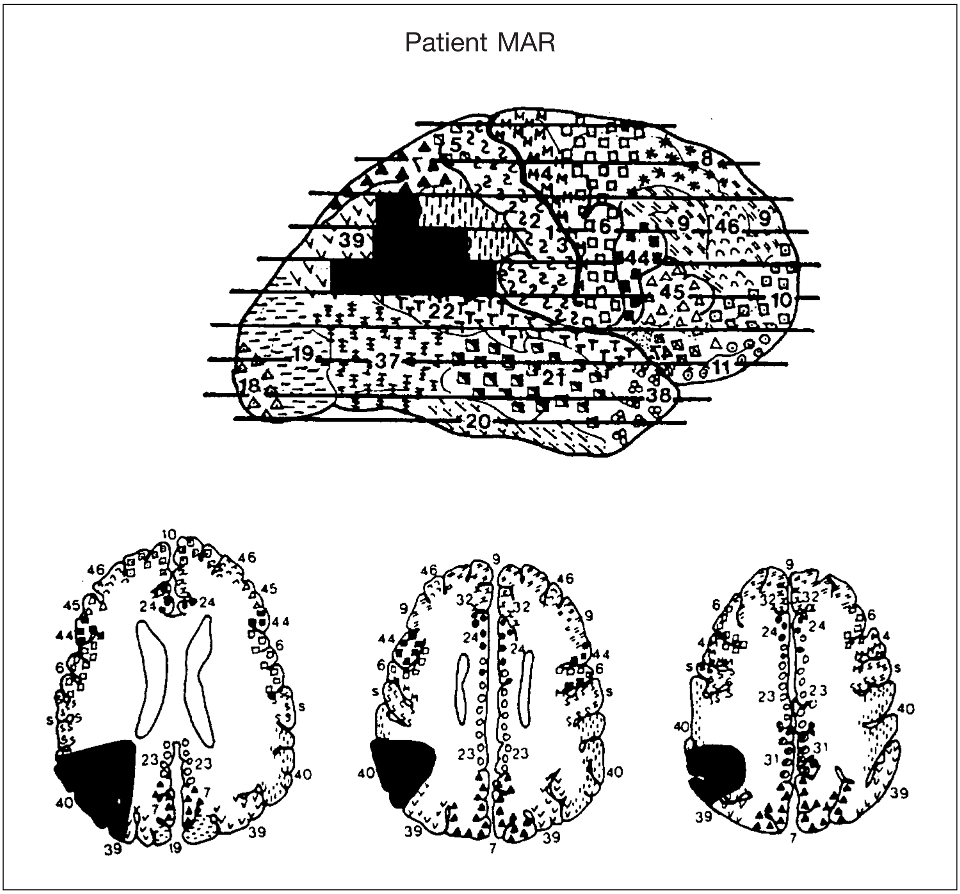

Fig. 2 – *Outline of patient MAR's lesion as plotted on Damasio and Damasio's (1989) templates. The left hemisphere appears on the right-hand side of axial sections. Profiles show the projection of the lesion on the lateral aspect of the brain.*

Examination (see Table I). However, her speech was somewhat slowed and hypophonic, with a reduced verbal fluency and occasional word-finding difficulties. The patient complained that verbal production was abnormally effortful, especially when complex utterances were required. She also complained of acalculia. CT-scan showed a hypodense slit affecting the left lenticular nucleus, head of the caudate, internal capsule, and insula (see Figure 3).

Initial Assessment of Number Processing

Both patients were initially submitted to a number processing battery comprising a digit span task, arabic numeral dictation (10 numbers ranging from 6 to 5300), arabic numeral naming (21 numbers ranging from 1 to 6005), and a short written calculation test comprising both single-digit and multi-digit addition, multiplication and subtraction problems (the number and type of problems are described below).

Patient MAR

Patient MAR's digit span was 5 forward and 2 backward (his backward letter span was also 2). In a block tapping test of spatial span, he scored 4 forward and 2 backward. Naming numerals and writing numerals to dictation were perfect. Simple mental calculation was tested with arabic problems in horizontal formal (e.g. 3 + 5 =), to which the patient was asked to write down the answer. In calculation, MAR made 26.7% (4/15) errors in simple mental addition of 1-digit and 2-digit numerals (e.g. 3 + 5, 5 + 13), 40% (8/20) errors in mental multiplication of single digits (e.g. 9×9, 5×4), and 70% (7/10) errors in simple mental subtraction of l-digit and 2-digit numerals (e.g. 40 – 30, 18 – 1, 6 – 1). The subtraction test was stopped after the patient failed on the tenth problem,

TABLE I
Boston Diagnostic Aphasia Examination

	MAR	BOO
Fluency		
Articulation rating	7/7	6/7
Phrase length	7/7	7/7
Verbal agility	14/14	11/14
Automatic speech		
Automatized sequences	9/9	9/9
Reciting	2/2	2/2
Repetition		
Words	10/10	10/10
High-probability sentences	8/8	8/8
Low-probability sentences	8/8	7/8
Writing		
Mechanics	3/3	2/3
Serial writing	47/47	32/47
Primer-level dictation	15/15	15/15
Spelling to dictation	8/19	10/10
Written confrontation naming	9/10	10/10
Sentences to dictation	12/12	11/12
Narrative writing	4/4	3/4
Auditory comprehension		
Body-part identification	19/20	20/20
Word discrimination	72/72	72/72
Commands	11/15	15/15
Complex ideational material	8/12	12/12
Naming		
Responsive naming	30/30	30/30
Naming of body-parts	30/30	30/30
Confrontation naming	105/105	105/105
Fluency in controlled association	23/23	18/23
Reading		
Word reading	30/30	30/30
Sentence reading	10/10	10/10
Reading comprehension		
Word-picture matching	10/10	10/10
Sentences and paragraphs	6/10	10/10
Oral spelling	2/8	4/8
Word recognition	8/8	8/8
Symbol discrimination	8/10	10/10

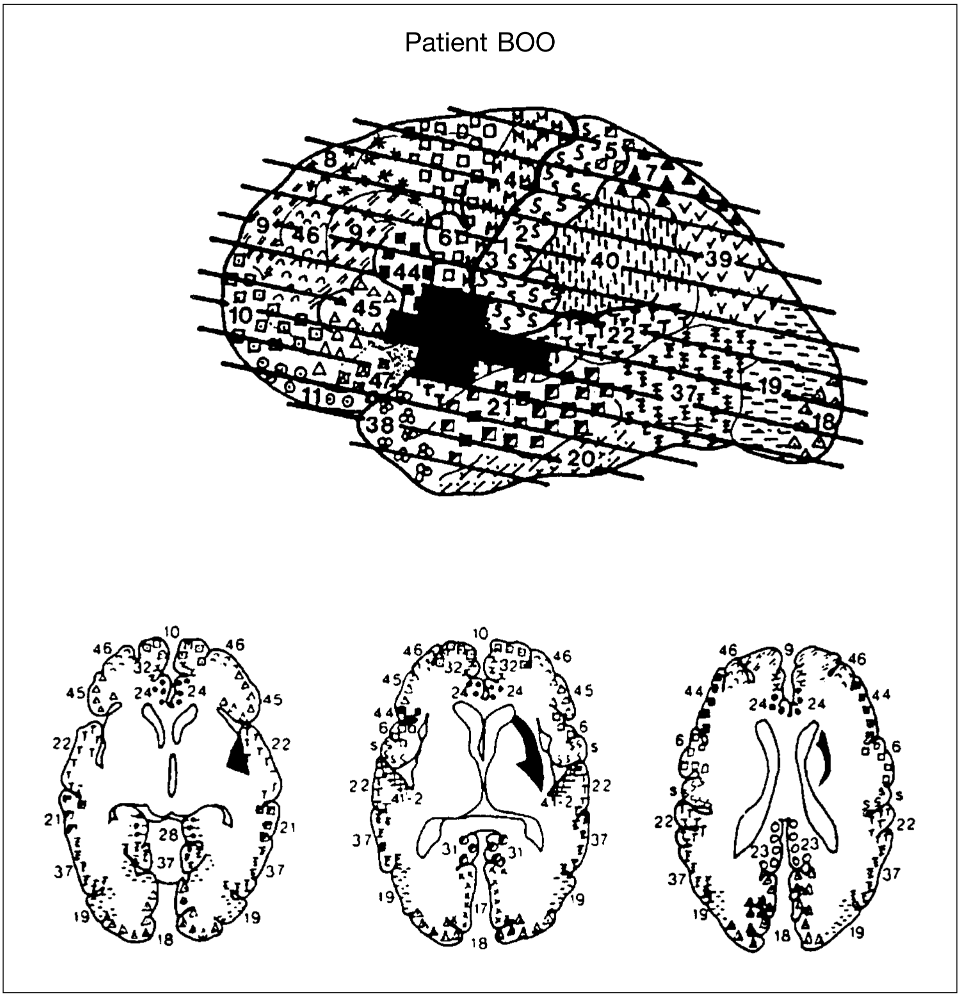

Fig. 3 – *Outline of patient BOO's lesion (same legend as Figure 2).*

which was 3 – 1. As for more complex calculation procedures, four multidigit addition problems and four multidigit subtraction problems, presented in the usual vertical format, were solved using the appropriate sequence of operations, but with many errors on intermediate single-digit problems. Carrying was correct in addition, but impossible in subtraction problems. In four multidigit multiplication problems, the procedure for multiplying a multidigit numeral by a single digit was well preserved, but multiplying by a multidigit numeral was nearly impossible, both because of errors in fact retrieval and because of a failure to properly arrange the intermediate results spatially.

Patient BOO

Patient BOO's digit span was 4 forward and 3 backwards. Naming numerals and writing numerals to dictation were perfect. In simple written calculation (same problems as MAR), BOO made 5% (1/20) errors in addition, 20% (4/20) errors in multiplication, and 10% (2/20) errors in subtraction. Although the patient often reached the correct result, she was extremely slow and resorted to indirect strategies (e.g. $9 \times 8 = (10 \times 8) - 8$). On the same multidigit problems as patient MAR, BOO's procedures for multidigit addition, multiplication and subtraction were found to be perfect except for a single carrying error in subtraction. However she often made errors on intermediate single-digit multiplication problems within multi-digit multiplication problems (4/11 = 36.4% errors).

Discussion

Both patients were perfect in naming arabic numerals and in writing arabic numerals to dictation, and both suffered from difficulties in simple calculation. Hence, both would be classified as suffering from "pure anarithmetia" according to the terminology set forth by Hécaen, Angelergues and Houillier (1961). The patients seemed to differ, however, in the extent of their difficulties with specific arithmetic operations: multiplication was the most impaired arithmetical operation for patient BOO, whereas subtraction was the most impaired operation for patient MAR. At this point, this observation must be taken with caution because the arithmetic problems in our screening battery were few and were not matched in complexity. In the remnant of this paper, we describe more stringent tests of calculation and number processing abilities. These tests basically confirmed the original clinical findings, and indicated that MAR and BOO suffered from calculation deficits of very different origins.

Single-digit Calculation

Patient MAR

Over several sessions, patient MAR was tested on a list of mixed single-digit addition, subtraction, multiplication and division problems. The list comprised all 81 additions and all 81 multiplications problems with digits 1-9; all 36 subtraction problems with digits l-9 whose result also fell in the range 1-9; and all 26 division problems with a numerator smaller than 20 and a divisor in the interval 2-9. The problems were written in arabic numerals, with the appropriate operation sign. They were simultaneously presented visually and read aloud by the experimenter. Patient MAR responded orally. Since he often hesitated and muttered to himself, no attempt was made to record his response time.

Overall, patient MAR made 27.2% errors in multiplications, 32.1% in addition, 53.8% in division and 75.0% in subtraction problems. Multiple χ^2 tests indicated that subtraction and division were significantly more impaired than either addition or multiplication. Note that some of the addition and multiplication problems involved large operands that were not used in corresponding subtraction or division problems. When performance was compared across problems of comparable difficulty, however, the dissociations were equally or even more significant. Thus, when multiplication and division problems were matched on the underlying operation involved (e.g. 20/5 or 20/4 vs 5 × 4 or 4 × 5), MAR's error rate was only 3,8% in multiplication versus 53,8% in division (p <0.0001). Likewise, when addition and subtraction problems were matched on the operation involved (e.g. 6 – 2 or 6 – 4 vs 2 + 4 or 4 + 2), MAR's error rate was only 22.2% in addition versus 75.0% in subtraction (p <0.0001). Finally when problems were matched by operand size (e.g. 9 – 5 vs 9 + 5 vs 9 × 5), MAR still failed on 75.0% of subtraction problems as compared to only 41.7% addition problems (p = 0.004) and 22.2% multiplication problems (p <0.0001). The four operations were then analyzed separately.

Multiplication: Four of the 22 errors were "don't know" responses. Of the remaining 18, 6 were later self-corrected. Three could be interpreted as operation errors (1 × 1 = 2, 5 × 1 = 6 and 6 × 6 = 12). Errors affected mostly large multiplication problems (Figure 4). In 17/18 errors, the response was the correct answer to another multiplication problem, and in 15 cases it was within the correct row or column of the multiplication table.

Addition: Two of the 26 errors were "don't know" responses. Of the remaining 24, 5 were later self-corrected. Two were putative operation errors (2 + 3 = 6, 4 + 2 = 8). Errors were often close to the correct sum (Figure 4). Interestingly, patient MAR made few errors when the sum was 9 or lower (8/36 = 22.2% errors), no error at all when the sum was 10 (0/9 errors), and many errors when the sum was 11 or higher (18/36 = 50% errors). No error was observed for ties (e.g. 2 + 2, 5 + 5; 0/9 errors).

Division: Although only one of the 14 errors was a "don't know" response, patient MAR was quite at a loss with division problems. The vast majority of errors consisted in repeating the divisor (e.g. 8/4 = 4; 12/6 = 6). This curious error most likely reflected an attempt at retrieving the corresponding multiplication fact. Indeed, on 4 error trials, the patient stated the appropriate multiplication fact but then mistook the divisor for the result. For instance when faced with 15/3 the patient said "fifteen... three times five, fifteen... then it must be three". Three additional trials in which the patient merely stated the relevant multiplication fact were scored as correct (e.g. for 12/4 the patient said "four times three, twelve"). Note that even the simplest division problems were impaired (e.g. 4/2, 6/2, and 6/3). If anything, larger problems tended to be correct more often than smaller ones (Figure 4).

Subtraction: Three of the 27 errors were "don't know" responses. Among the remaining ones, only 3 were self-corrected. Patient MAR complained of being utterly unable to subtract, although in his own words "it should have been easy". Searching for clues as to the origin of errors, we found that 3 errors consisted in repeating the first operand, and 4 in repeated the second operand. In four cases, the patient added rather than subtracted. In three cases, he seemed to have used an automatic series (8 – 7 = 6; 9 – 8 = 7; 8 – 6 = 4). The patient seemed to have little sense of numerical plausibility, since in 7 cases he proposed a result that was greater than or equal to the first operand (e.g. 6 – 3 = 7).

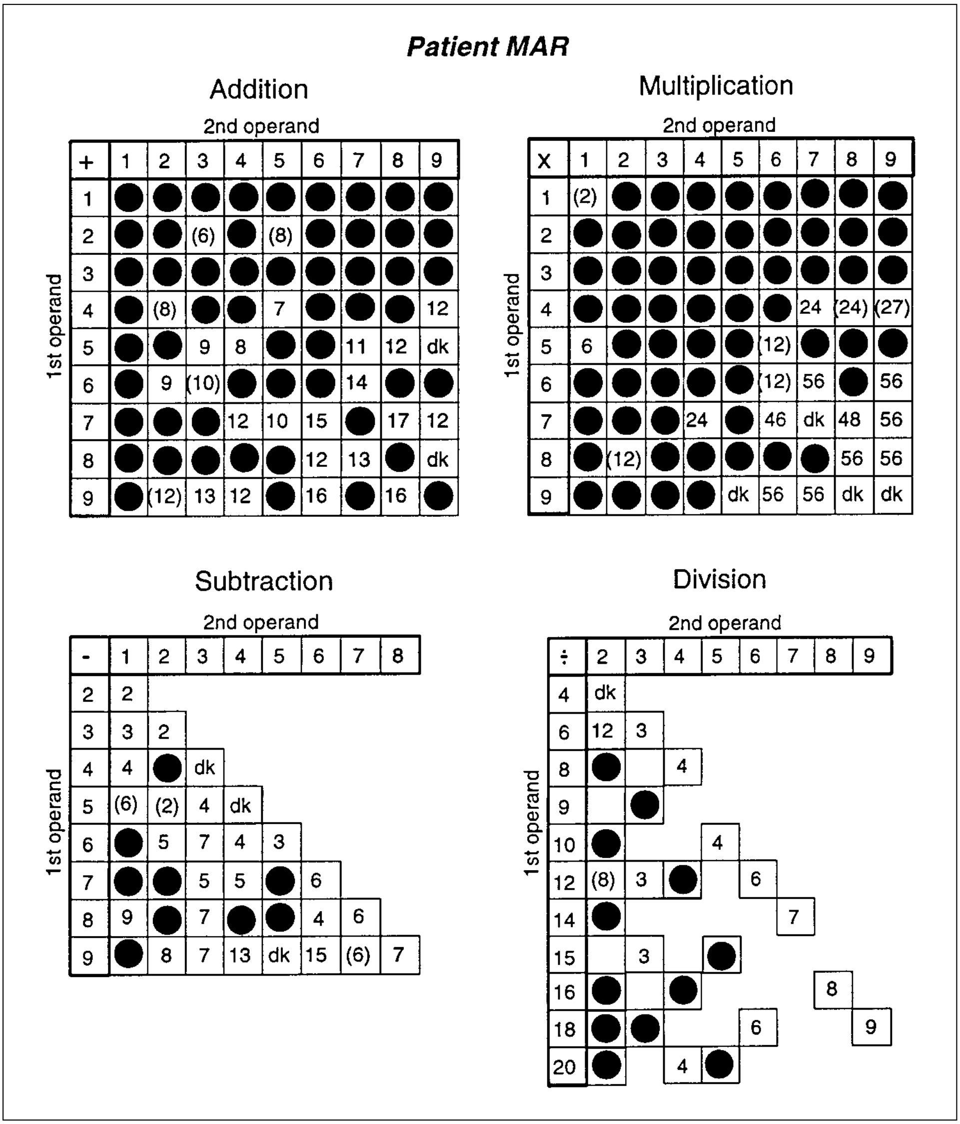

Fig. 4 – *Schematic representation of patient MAR's calculation performance. Each cell represents an arithmetic problem (e.g. 6 × 3, 5 – 2). Filled circles indicate correct performance. Numbers indicate an erroneous response (dk = don't know). Numbers in parentheses indicate self-corrected errors. In patient MAR, addition and multiplication tables are much less impaired than subtraction and division problems.*

Patient BOO

A noticeable clinical characteristic of patient BOO was an occasional slowness in calculation: even when she reached the correct result, she often took a long time to respond (see also Warrington, 1982). To quantify this, we decided to measure calculation times in patient BOO. Over several sessions, the patient was presented which short blocks of addition, multiplication, subtraction or division problem. Each problem – two arabic digits separated by the appropriate operation sign – was presented on a computer screen for an unlimited amount of time. A microphone, connected to a software-controlled sound card and a software timer, recorded response onset time and digitized the patient speech for later offline scoring. An arbitrary cut-off of 3 seconds was used to classify responses as unusually slow.

Overall, patient BOO made 28.0% errors in multiplication, 6.3% in addition, 8.6% in division and 5.7% in subtraction problems. Multiplication was significantly more impaired than either addition or subtraction ($p < 0.0005$). This remained significant even when the comparison was performed on problems with matched operands (e.g. 5×3 vs $5 + 3$ vs $5 - 3$; respectively 35.0%, 2.5% and 5.0% errors, $p < 0.0005$). Error rate in subtraction and addition was uniformly low, and no significant difference was found whether or not the problems were matched. Finally, the raw error rate for division, could not be directly compared with the others because it was based only on a small number of very simple problems (4/2, 6/2, 6/3, 8/2, 8/4 and 9/3). Error rate on multiplication problems matched to the division problems (e.g. 2×3 or 3×2 vs 6/2 or 6/3) was only 16.7%, which was not significantly worse than the 8.6% error rate observed in division. In summary, the main finding in patient BOO was a selective impairment of multiplication relative to addition or subtraction, the data on division being inconclusive due to the small number of problems tested. We then turned to a detailed analysis of errors and response times for each operation.

Multiplication: The problem set comprised 143 multiplications of digits 1-9, some of which were presented once and others twice (2 additional problems were rejected because of technical problems). Out of the 40 errors, 11 were "don't know" responses. The remaining 29 errors comprised 3 operation errors ($2 \times 3 = 5$, $1 \times 1 = 2$, $4 \times 4 = 8$). In 27/29 errors, the response was the correct answer to another multiplication problem, and in 24 cases it was within the correct row or column of the multiplication table. Although errors affected mostly large multiplication problems (Figure 5), simple problems were not spared (7/40 = 17.5% errors on ties; 7/48 = 14.6% errors on problems with operands between 2 and 5; 50% errors on 2×3 or 3×2). Only multiplications by 1, which can be solved by the rule $1 \times N = N$, seemed to be spared except for a single operation error on 1×1.

The mean correct RT was 2556 ms, and 24.0% (23/96[1]) of correct responses were slower than 3 seconds. Tie problems were processed significantly faster than non-ties ($F = 7.13$; d.f. = 1, 94; $p = .009$). On non-tie problems, the product of the two operands was a significant predictor of RT ($r^2(76) = 21.7\%$, $p < 0.0001$). The regression equation was $RT(ms) = 1717 + 43.9 \times$ product. Although RT also increases with the size of the operands in normals, patient MAR's slope and intercept appeared abnormally elevated, indicating that even simple problems were affected. On tie problems, no effect of problem size was found ($p < 0.33$), but the mean RT was 1532 ms, again an abnormally elevated value.

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[1] RT was not recorded on a small fraction of correct trials because of a microphone failure.

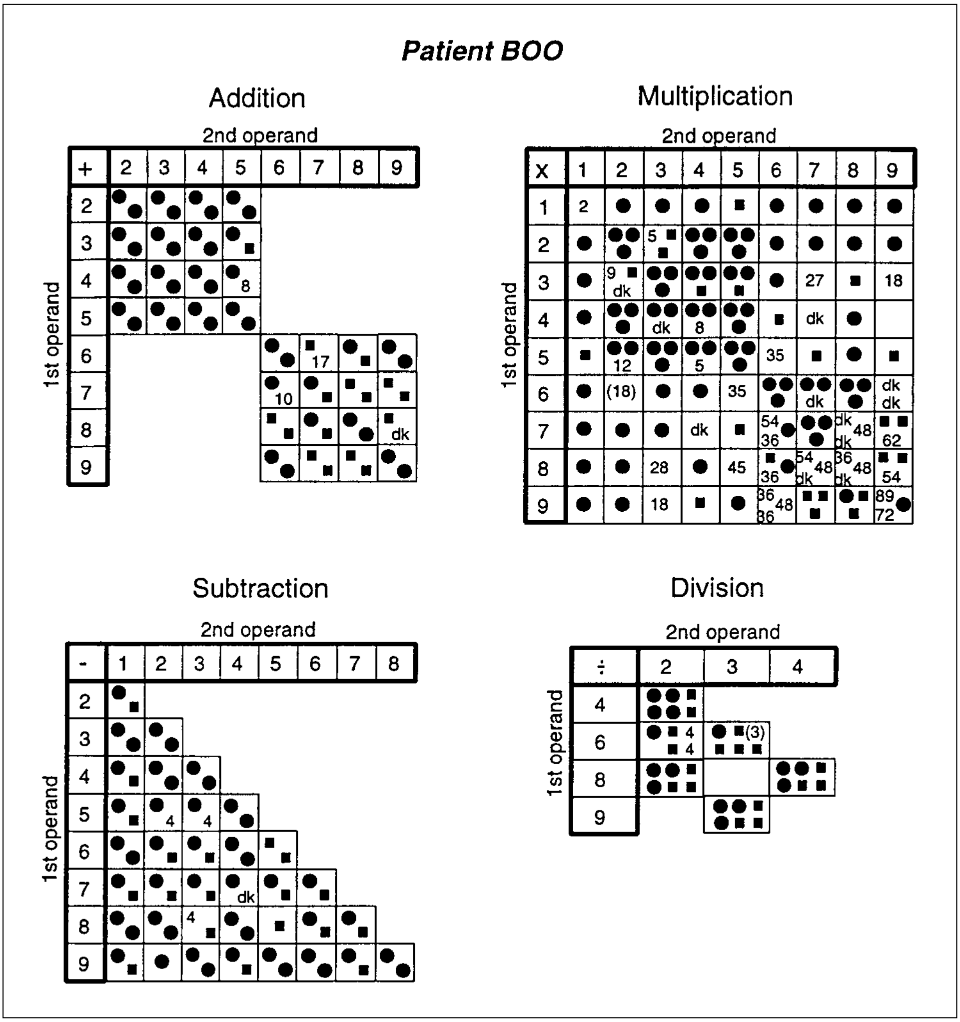

Fig. 5 – *Schematic representation of patient BOO's calculation performance (same legend as Figure 4). Filled squares indicate slow but correct performance (RT > 3 seconds). The multiplication table is more impaired than simple addition, subtraction, and division problems (note that only elementary division problems were used).*

Addition: The problem set comprised 32 additions of digits 2-5 and 32 additions of digits 6-9 (Figure 5). The four errors were 4 + 5 = 8, 6 + 7 = 17, 7 + 6 = 10, and one "don't know" response to 8 + 9. The mean correct RT was 2792 ms, and 30% (18/60) of correct responses were slower than 3 seconds. Tie problems were processed significantly faster than non-ties ($F = 10.8$; d.f. = 1, 58; $p = .0017$). On non-tie problems, the best predictor of RTs was the smaller of the two operands (variable *min*; $r^2(42) = 46.3\%$, $p < 0.0001$), and the corresponding equation was $RT(ms) = 992 + 475 \times min$. However, the product of the operands was also an excellent predictor ($RT = 1745 + 42.4 \times product$;

$r^2(42) = 42.8\%$, $p < 0.0001$). On tie problems, no significant effect of problem size was found; the mean RT was 1807 ms.

Division: The problem set comprised all division problems with single digit operands and an integer result (excluding N/N and N/1 problems), each presented 6 times. Patient BOO made only 3 errors which could all be interpreted as operation errors (subtraction: 6/2 = 4, 6/3 = 3). Interestingly, all errors occurred on problems 6/2 and 6/3; it may not be a coincidence that the corresponding multiplication problems 2×3 and 3×2 were especially slow and error-prone (Figure 5). The mean correct division RT was 4037 ms, and 56.7% (17/30) of correct responses were slower than 3 seconds. No significant predictor of RT was found.

Subtraction: The problem set comprised all 36 subtraction problems with digits 1-9 whose result also fell in the range 1-9, each being presented twice. Patient BOO made only 4 errors: 5 – 2 = 4, 5 – 3 = 4, 8 – 3 = 4 and a "don't know" response to 7 – 4. The mean correct RT was 2854 ms, and 30.2% (19/63) of responses were slower than 3 seconds. No significant predictor of RT was found.

Discussion of Single-digit Calculation

On close examination, acalculia was strikingly different in the two patients. In patient MAR, subtraction and division were significantly more impaired than addition and multiplication; very simple addition and multiplication problems were almost fully preserved, while very simple subtraction and division problems were nearly impossible. In patient BOO, multiplication, and to a lesser extent division, were significantly more impaired than addition and subtraction; even very simple multiplications such as 2×3 were affected.

These dissociations are understandable and even predictable within the triplecode model given the different lesion sites in the two patients. Patient MAR suffered from a localized inferior parietal lesion of the dominant hemisphere. According to the model, such a lesion should affect the ability to guide verbal naming and arithmetical fact retrieval by a semantic representation of numerical quantities. Retrieval of rote verbal knowledge, however, should be spared. Indeed, MAR was better in addition and multiplication, which are learned by rote, than in subtraction and division. His profound impairment with numerical quantities was exemplified by his failure with 2-1 or 4/2. In division, he was however able to use rote verbal knowledge as a backup, mechanically responding "four times four, sixteen" to the division problem 16/4. The preservation of rote arithmetic tables accounts for MAR's good performance with simple addition and multiplication facts. His errors occurred almost exclusively with large addition and multiplication problems, which are least securely remembered in normal subjects and often elicit a recourse to semantic strategies (Lefevre, Sadesky and Bisanz, 1996).

Patient BOO, by contrast, suffered from a localized lesion in the left basal ganglia, a circuit which has been postulated to be partially involved in memory for rote verbal material such as arithmetic facts (Dehaene and Cohen, 1995). According to the triple-code model, retrieval of rote arithmetic tables should be impaired while quantity-based strategies should remain available. In good agreement with this prediction, multiplication and division were most difficult for patient BOO. In normal adults, multiplication is solved largely by memory retrieval (Ashcraft, 1992), and division almost certainly requires a search through multiplication tables. For addition, however, although memory retrieval is the preferred strategy in adults, a variety of other strategies are available (e.g. Siegler and Shrager, 1984). Use of such strategies may explain why BOO was very slow but usually accurate with addition problems. Her reaction times, which increased considerably with the smaller of the operands, were compatible with a counting or decomposition strategy. Subtraction was also very slow and was also probably solved using quantity- or counting-based strategies.

Given that BOO seemed able to apply such strategies, even if slowly, why did she fail on multiplication problems as simple as 2×3 or 5×4? We have very little information on the strategies that she used during multiplication, because the recording of her vocal response times implied that she remained silent until she had reached a result. The patient's introspection, however, was that she knew that she should have been able to retrieve multiplication results by rote, and that she was attempting to do so rather than trying to find alternative strategies for reaching the result. This is consistent with the fact that she often declined to answer and that the vast majority of her errors fell within the multiplication table, suggesting that she was retrieving a result from the wrong cell of the table. It should also be noted that in the few cases where the patient gave a truly bizarre answer ($2 \times 3 = 5$, $5 \times 4 = 5$), she immediately noted that she was not satisfied with that result but that it was the one that first came to her mind. Still, one cannot exclude that she was suffering from a very mild additional deficit of quantitative processing, since she did make a few unusual errors in addition and subtraction (e.g. $6 + 7 = 10$, $5 - 2 = 4$).

Although patients BOO and MAR realized a double dissociation at the anatomical level, it would be simplistic to expect their performance to be fully dissociated on all arithmetic tests. With very simple addition problems with a sum of 10 or smaller, both patients performed well, presumably because these problems could be solved using either rote memory or quantitative knowledge. The model predicts that it would take a large left hemispheric lesion, affecting both rote memory and semantic elaboration, for a patient to be impaired in additions as simple as $2 + 2$ (see e.g. patient NAU, Dehaene and Cohen, 1991). Conversely, both patients had severe difficulties with large multiplication problems with operands between 6 and 9. Presumably, both rote memory and semantic elaboration are required to solve such problems. For instance in applying the strategy $6 \times 7 = (7 \times 7) - 7$, one makes use both of the quantitative knowledge that 6 is one unit below 7, and of the memorized fact that 7×7 is 49. Hence, any deficit affecting either process should bear its toll on large multiplication problems. This may explain why such problems are so frequently impaired in acalculia (Sokol, McCloskey, Cohen et al., 1991).

What, then, are the diagnostic features that best distinguish between the two types of patients? According to the triple-code model, the clearest evidence for a deficit of rote memory should be the occurrence of errors on very simple multiplication problems, because these are almost always retrieved from rote memory in normal subjects. Indeed, patient BOO made 14.6% errors (7/48) on multiplication problems with operands between 2 and 5, including errors such as $2 \times 3 = 5$ or $3 \times 2 = 9$ that are highly unexpected from a school teacher, while patient MAR, who had much less training with arithmetic facts, always answered these problems correctly and rapidly (0/16 errors). Conversely, the clearest evidence for a deficit in the processing of quantities should be an impairment in subtraction problems and in non-tie addition problems with a sum larger than 10. Such problems are not learned by rote in French schools and should therefore necessarily involve quantitative processing. Indeed, patient MAR was severely impaired (75.0% errors in single-digit subtraction, 75.0% errors on additions problems with a sum beyond 10) while patient BOO made fewer errors by far on the very same problems (respectively 11.1% and 12.5% errors). Thus, on this subset of problems selected because the triple-code model predicted that they should show the clearest dissociation, patients MAR and BOO showed a cross-over pattern of errors symptomatic of a double dissociation (Shallice, 1988): MAR performed better than BOO on one task (retrieving rote multiplication facts), and worse than BOO on another (solving simple subtraction and non-rote addition problems).

We now turn to number processing abilities outside of calculation. If the only difference between patients MAR and BOO was a differential error rate in various arithmetic operations, it could be argued that this simply reflects the existence of distinct number processing modules for each operation (e.g. Dagenbach and McCloskey, 1992), and need not imply that different numerical codes (verbal versus quantitative) are used for different operations. In addition to predicting a dissociation of operations, however, the triple-code model also predicts that acalculia should be associated with quite different deficits in the two patients. Patient MAR, on the one hand, should show a category-specific impairment in tests probing quantitative knowledge of number. Patient BOO, on the other hand, should experience no difficulty in representing the meaning of numbers, but should be impaired on non-numerical tests of rote verbal memory. The predicted dissociations were first examined in tasks tapping number series and rote verbal knowledge, and second in tasks tapping semantic number knowledge.

Number Series and Rote Verbal Knowledge

Patient MAR

With series that are normally learned by rote, patient MAR performed well. He readily recited the number sequence from 1 to 20 and could also recite the series 2, 4, 6, 8... up to 20. When reciting 1, 3, 5, 7..., he correctly reached 13 but then jumped to 18 and could not continue, presumably because 13 marked the end of his rote knowledge of this series. Conversely, with series that are not normally known by rote and require subtraction and higher control processes, patient MARS’s performance was poor. When counting backward from 20 to 1, he was blocked twice after 12 and after 10. Counting backward every third number starting with 50 was completely impossible. MAR also experienced some difficulties in a task of saying aloud the number immediately preceding a given number. He was slow and made 3 errors out of 14 trials, all of which were later self-corrected.

Outside the number domain, patient MAR's recitation of the alphabet, musical notes, days of the week and months was perfect.

Patient BOO

Patient BOO correctly recited the number sequence from 1 to 20 with only one long pause at 15. Counting by two's, either from 1 or from 2, was also correct but with long pauses in the teens. When counting backward from 20 to 1, the patient paused also for a long time at 17, 16, 15, 12, 9 and 8. Counting backward every third number starting with 50 was impossible.

Outside the number domain, severe impairments of rote verbal knowledge were found. Patient BOO fluently recited the series of days and paused only once when reciting month names. Reciting the musical scale, however, was impossible beyond "do re mi fa". Likewise, reciting the alphabet was impossible beyond "A B C D". The patient also spontaneously complained of forgetting the words of nursery rhymes, poems, and prayers which she knew by heart before her stroke. Formal testing showed that recitation of overlearned prayers was marred with pauses and errors. When blocked, the patient often repeated the last word several times in an attempt to restart. Errors consisted mostly in misordering of entire phrases. Occasionally, sequence errors also occurred within a phrase (e.g. "et ne nous pardonne mais que ton règne vienne, amen" [and do not forgive but may thy kingdom come, amen]). The patient correctly sang the nursery rhyme "Frère Jacques" [brother John], but she failed on "Au clair de la lune". She failed to retrieve the last four phrases of the first verse, although she correctly hummed the tune.

Discussion of Number Series and Rote Verbal Knowledge

As predicted, patient BOO suffered from a severe deficit of memory for rote verbal material. She performed very poorly in reciting the alphabet or in singing nursery rhymes although she had practiced these activities daily as a school teacher. Her slowness and sequence order errors in verbal recitation paralleled her slowness and fact retrieval errors in arithmetic fact retrieval.

Patient MAR, conversely, experienced no difficulty in non-numerical verbal recitation tasks. In number series, when the task involved automatic associations between words, he performed well. However when the task required to make unusual moves back or forth on the number line in steps of 1, 2 or 3 units, a task comparable to subtraction, patient MAR was again severely impaired.

Quantitative and Non-quantitative Semantic Knowledge

In this final section, we examine our patients' semantic number knowledge. The prediction was that patient MAR would show a category-specific impairment only for the quantitative aspects of number knowledge, but not for other domains such as knowledge of dates or hours. Inasmuch as the tests do no involve rote verbal knowledge, patient BOO should show no impairment.

Patient MAR

Number comparison. Patient MAR was moderately impaired in a paper-and-pencil number comparison task where he had to point to the larger of two horizontally aligned single or multi-digit arabic numerals of the same length (11/68 = 16.2% errors). His errors occurred on both single digits (e.g. 5 vs 6, 9 vs 8, 8 vs l) and on more complex muiltidigit pairs (e.g. 20 vs 30, 75 vs 74, 508 vs 580). All but two of them were later self-corrected. An attempt was made to teach the patient a computerized version of the number comparison test, but this was abandoned because MAR experienced prolonged difficulties in learning the left-right assignment of responses.

Proximity judgement. MAR was presented with a paper-and-pencil proximity judgement task in which he had to circle which of two l-digit or 2-digit arabic numerals was closest in magnitude to a third one (e.g. 4: 5 or 9?). He made 6 errors out of 30 trials (20% errors), 2 of which were later self-corrected. For instance he judged 10 more similar to 5 than to 9, 8 more similar to 4 than to 9, and 28 more similar to 21 than to 27. Hence, like the number comparison task, this task indicated a moderate impairment of knowledge of number magnitudes.

Calculation approximation. MAR was also presented with approximation tasks in which an arithmetic problem was presented, written in arabic numerals, and patient MAR had to select, among two alternative numerals, the one that fell closest to the correct result (e.g. 3 + 5: 4 or 9?). Patient MAR was warned that he did not necessarily have to perform the exact calculation, and that he simply had to select the most plausible quantity and to reject answers that seemed improbable. He made 30% errors in addition (6/20), 30% errors in multiplication (6/20), and 45% errors in subtraction approximation (9/20). These errors were apparently the direct reflection of patient MAR’s poor performance in exact calculation and proximity judgement tasks.

Number bissection. Over the course of several sessions, MAR was presented visually with pairs of arabic numerals ordered from left to right. All but two pairs comprised only single digits. The patient was asked to produce orally the number that fell in the middle of this interval (e.g. for 2 4 he should say 3). MAR found this task extremely difficult. He made 77.4% errors (41/53), only 9 of which were later self-corrected. On a subset of trials in which the stimuli were separated by only two units, he still made 81.8% errors (18/22). Performance was also very slow. Reaction times, collected on a subset of 16 trials, averaged 13.7 seconds.

An analysis of the 41 errors showed that on 8 trials patient MAR repeated one of the two stimuli (e.g. stimulus pair 1 3, answer 3), on 18 trials he gave a number that fell outside of the interval determined by the stimuli (e.g. stimulus pair 4 8, answer 3), and on only 15 trials he answered with a number within the appropriate interval. Four errors could be interpreted as an incorrect recourse to an automatic series (e.g. stimulus pair 10 20, answer 30; stimulus pair 5 7, answer 3). Recitation also accounted for some of patient MAR's correct answers, e.g. for the pair 5 9 patient MAR recited overtly "5 7 9" and then answered 7. Finally, thirteen erroneous answers coincided with the difference of the two numbers (e.g. stimulus pair 2 4, answer 2), as did 5 of the 12 correct answers.

Might patient MAR have misconstrued the task and attempted to compute the difference of the two numbers? This seems unlikely for several reasons. Great pains were taken to explain him the task. Following one of his early failures, which occurred with the pair 30 40 (he answered 20), we asked him to write down the series of numbers from 30 and 40 on a single line. He was then able to point to the middle number, 35. In subsequent test sessions, we introduced the task by presenting him with an array of digits 1 through 9, in correct left-to-right order, and explaining how, when given a pair of digits, he simply had to look for the number that fell right in the middle. He performed quite well when the array was present before his eyes, but returned to his peculiar errors as soon as the array was removed.

Bissection in non-numerical contexts. Further evidence that the number bissection errors did not come from a misunderstanding of the task, and that the deficit was remarkably specific for the number domain, came from studies of bissection in non-numerical domains. Early on during clinical testing, in between two erroneous number bissection trials, MAR was asked what was between the roots and the leaves of a tree, or between the head and the legs of a human body. He instantly came up with correct answers (trunk; trunk and neck).

We then designed formal bissection tasks with days of the week and with letters. As with numbers, patient MAR was presented with a pair of written stimuli, in appropriate left-to-right order, and had to produce verbally the item that fell right in the middle (e.g. stimulus pair "monday friday", answer wednesday; stimulus pair "A E", answer C). Patient MAR was excellent in these tasks, answering both fast and accurately (0/23 errors in letter bissection; 4/21 = 19% errors, all of which were immediately self corrected, in week days bissection). χ^2 tests confirmed that performance was significantly better in either of those tests than in number bissection ($p < 0.011$). Informal testing suggested that patient MAR could also bissect with the series of months (3/3 correct) and with the musical scale (do, re, mi, etc...; 2/3 correct; 1 self-corrected error). With ordinal numerals, however, (first, second, third, etc.), bissection was as poor as with cardinal numerals (7/12 = 58.3% errors).

Thermometer tasks. Patient MAR was shown a vertical line with a mark at the bottom labelled "1" and another at the top labelled "100". This was described to him as a thermometer. In a first test, numbers were read to him and he was asked to point to the appropriate location on the line. He performed satisfactorily and with considerable accuracy. His behavior was much worse, however, in a converse test in which he had to write down the arabic numeral appropriate to a given location on the line. He often wrote down (and simultaneously pronounced) completely inappropriate numerals. For instance he said 90, later self-corrected as 30, for a location that actually corresponded to about 5. Overall, about 50% of his responses (7/14) were inappropriate. Hence, the results from the thermometer tasks suggested that transcoding of spoken numerals into linear magnitudes was preserved, but that the converse operation of providing a number appropriate to a given linear magnitude was impaired.

Cardinal meanings of number in familiar contexts. Patient MAR performed well in a modified version of the cognitive estimation test (Shallice and Evans, 1978), in which he had to verbally provide a numerical estimate for an unknown but concrete quantity such as the number of days it took Columbus to cross the Atlantic. He always gave plausible answers (0/10 errors). He was however moderately impaired in answering questions tapping declarative number knowledge such as the number of days in a year (4/17 = 23.5% errors, 3 of which were self-corrected).

Non-cardinal meanings of numerals. Numbers are not only used to refer to a certain quantity or magnitude. Some numbers also have conventional meanings such as a brand of car (504 = a Peugeot), a famous historical period (1798 = the French revolution), a certain time of the day (12 o'clock), etc. (Cohen, Dehaene and Verstichel, 1994). Such non-cardinal or nominal meanings of numerals seemed to be spared in patient MAR. When familiar numerals were read aloud to him, he was able to provide an adequate description of their meaning in 80% of cases (12/15). His knowledge of time was well preserved. He was able to describe his daily routine using appropriate numerals (e.g. "I get up very early – about 4, 5 in the morning"). Conversely, when probed with specific times, he was able to describe the corresponding events (e.g. "what do you do between 9 and 11 in the morning? I start to work... I get two good hours of work").

Remarkably, he seemed able to perform computations with hours that he was completely unable to perform in the abstract. For instance he could tell how much time elapsed between two hours (0/7 errors), in sharp contrast to his radical impairment in subtraction. Likewise, he was able to convert hours from the 24-hour format to the 12-hour format (both are commonly used in France). For instance he correctly stated that five in the afternoon is "17 hours" or that "20 hours" is eight in the evening (2/12 errors, instantly self-corrected). When presented with very similar addition or subtraction problems with a second operand close to 12 (e.g. 5 + 12, 3 + 11 or 22 – 12), he failed completely (9/9 errors). Hence, he was able to compensate for his arithmetical impairment when the numbers had a concrete referent in the time domain, but not otherwise.

Parity judgement. Yet another domain of non-quantitative knowledge about numbers is their odd or even status. Patient MAR was rather good at parity judgements, making only one error out of 11 trials (9.1%; 1 was judged to be even).

Patient BOO

Number comparison. In the paper-and-pencil task where she had to select the larger of two single or multidigit arabic numerals, patient BOO responded quickly and made only one self-corrected error (1/26 = 3.8%). She also took a computerized test in which she had to press one of two bimanual response keys to indicate the larger of two horizontally aligned digits presented on a computer screen for an unlimited amount of time. She made few errors (3/72 = 4.2%). Her median RT was fast (1046 ms) and affected by a normal distance effect (regression of RT on Log Distance, $p = 0.01$). Contrary to calculation tasks, none of her response times ever exceeded 3 seconds. In a similar computerized test where a single two-digit numeral had to be classified as larger or smaller than 55, again using bimanual response keys, she made only one error (1/176 = 0.6%) and her median RT was fast (1043 ms). RT decreased systematically as a logarithmic function of distance from the standard 55 ($p < 0.00001$), as described with normal subjects (Dehaene, Dupoux and Mehler, 1990). Aside from two trials clustered within the first three trials of the task, none of her response times exceeded 3 seconds. In brief, patient BOO's number comparison performance seemed fully preserved.

Proximity judgement (same task as patient MAR). Patient BOO's performance was fast and accurate (0/15 errors).

Calculation approximation. Patient BOO took only the addition and multiplication subtests of the above-described multiple-choice test of calculation approximation taken by patient MAR. She responded fast and with perfect accuracy (0/20 errors in either addition or multiplication).

Number bissection. Patient BOO initially experienced difficulties understanding the number bissection task. She tended to respond with the difference of the two numbers. After 12 training trials, however, she performed with perfect accuracy (0/8 errors. Bissection of weekdays was also preserved (0/5 errors).

Thermometer tasks. Patient BOO was highly accurate both in finding the location corresponding to a given numeral on a vertical line labelled from 1 to 100 (0/10 errors), and in writing down the numeral corresponding to a given location (0/15 errors).

Cardinal meanings of number in familiar contexts. Patient BOO made no errors in a cognitive estimation task (0/10 errors) and only one error in a task tapping declarative number knowledge (1/12 = 8.3% errors).

Non-cardinal meanings of numbers. Patient BOO recognized famous dates (l/7 error) but otherwise failed to retrieve the meaning of numbers such as brand of cars, game, the age of retirement, etc. (5/6 failures to answer).

Parity judgement. Patient BOO could judge the odd-even status of numbers (0/11 errors).

Discussion of Quantitative and Non-quantitative Number Knowledge

On tasks tapping quantitative number knowledge, the two patients again performed quite differently. Patient BOO behaved essentially normally. As predicted by the triple-code model, her difficulties in retrieving arithmetic facts from memory, stemming for her left lenticular lesion, had no impact on her ability to judge the quantitative relations between numbers.

Patient MAR, however, experienced moderate to severe difficulties in quantitative numerical tasks. In number comparison and numerical proximity judgements, he erred once in every 5 or 6 trials. The clearest deficit appeared in the number dissection tasks. MAR seemed completely unable to decide which number fell between two other numbers, often coming up with quite absurd answers such as that 3 is between 5 and 7. Combined with MAR's inability to compute even extremely simple subtractions such as $3 - 1$, this deficit suggests a critical role for the inferior parietal region in performing semantically meaningful operations on numerical quantities.

Patient MAR also provided remarkable evidence concerning the category specificity of the deficit for numerical quantities. In spite of his total confusion in the number domain, MAR excelled in bissection tasks involving the alphabet and the days of the week, stimuli whose sequential structure is similar to the number sequence but that do not refer to quantities. Even within the number domain, whenever numbers referred to a concrete domain with which he was familiar, MAR performed remarkably well. For instance cognitive estimation of concrete quantities such as the number of children in a typical classroom was preserved. So was the ability to perform simple computations with times of the day. Finally non-cardinal uses of numbers were largely spared, as was the knowledge of the odd/even status of numbers. Only when the task called for numerical manipulations *in the abstract,* without any concrete support, did the patient fail. In brief, MAR's inferior parietal lesion very selectively affected an abstract quantitative representation of numbers.

General Discussion

In this discussion, we first consider how the present cases bear on the functional organization of the human number processing system. We then turn to more speculative remarks on the possible anatomical substrates of calculation processes. Finally, we conclude by examining how the present findings, combined with other recent case reports, suggest a fragmented representation of arithmetical knowledge in the human brain.

Functional Organization of the Human Number Processing System

At the core of our proposal regarding the functional organization of elementary calculation is the opposition between, on the one hand, rote verbal memory for arithmetic facts and, on the other hand, semantic manipulations of numbers and their associated magnitudes. Patients MAR and BOO were tested using three sets of tasks depending to various degrees on these two processing components. First, quantitative tasks such as number bissection and comparison, proximity judgement, etc. were used to assess the internal manipulation of quantities. Second, recitation of automatic series, nursery rhymes, etc. were used to probe rote verbal memory. The third group of tasks, namely solving elementary arithmetic problems, stood in an intermediate position relative to the two hypothesized mechanisms. On the one hand, multiplication and addition facts with small operands are learned by rote, and are generally solved by resorting to verbal automatisms. On the other hand, most subtraction and complex addition problems require semantic manipulations of numerical quantities.

The two patients showed remarkably contrasted performance on these three sets of tasks, in agreement with the hypothesis of a double dissociation between rote verbal and semantic knowledge of numbers. Patient MAR showed difficulties in most quantitative tasks: larger-smaller judgements, number proximity judgements, writing down numbers from a thermometer and, above all, bissection of numerical intervals. In contrast, he was perfect in non-numerical tests of rote verbal memory. Finally, he was differentially impaired in solving various types of calculation problems. Even the simplest subtraction problems were severely affected, while multiplication was much better preserved. Patient BOO showed just the opposite pattern of deficits. She had an excellent understanding of numerical quantities. ln contrast, her knowledge of rote verbal material was compromised, even for routines as familiar and simple as reciting the alphabet. Finally, the multiplication table was most impaired, while addition and subtraction were better preserved.

Thus, the observed double dissociations support our initial hypothesis that there may be multiple routes for mental arithmetic, one specialized for quantitative number processing that was selectively impaired in patient MAR, and another specialized in storing and retrieving rote verbal knowledge of arithmetic tables that was selectively impaired in patient BOO. Of the many tasks that were tested, only a few yielded results that were not in complete agreement with this hypothesis and therefore require further discussion. In patient MAR a few tasks that supposedly require quantitative number processing were partially or totally preserved. In number comparison and proximity judgement, MAR was impaired but still performed way above chance. And in pointing to the location corresponding to a number on a number line described as a "thermometer", he was excellent.

Why should these tasks be partially or totally preserved, in a patient whose semantic number processing deficit is so severe that he cannot compute 3 – 1? The preserved tasks have one thing in common: they require a comprehension of the quantity conveyed by a number, but not the verbal production of a numerical label corresponding to a given quantity. In tasks involving number production guided by quantitative knowledge (subtraction with spoken responses, bissection of two numbers again with spoken responses, and writing down numbers from a thermometer), patient MAR was strikingly more impaired. This suggests that MAR might have suffered only a partial loss of quantitative numerical knowledge, but that the quantitative knowledge he was left with could not be communicated to the verbal system. In brief, MAR's deficit might be best described as a complete disconnection between a partially impaired quantitative system and a fully intact verbal system.

Such an hypothesis fits nicely with the postulates of the triple code model, which supposes that digit identification and quantitative representations are available to both hemispheres. Dehaene and Cohen (1995) and Cohen and Dehaene (1996) reviewed brain imaging and split-brain studies of number processing and concluded that both hemispheres are able to process number magnitudes, and that both left and right inferior parietal areas contribute to quantitative number processing. Hence, the model predicts that a unilateral inferior parietal lesion in the dominant hemisphere should leave the non-dominant parietal magnitude representation intact, so that the patient should still be able to perform simple quantitative tasks such as number comparison. Since the model postulates that the non-dominant inferior parietal area is not connected to left-hemispheric language areas directly, but only through the inferior parietal area in the dominant hemisphere (see Figure 1), a lesion of the dominant hemisphere should effectively disconnect that intact quantity representation from the left perisylvian language areas. Hence, even if some magnitude knowledge remains available to the non-dominant hemisphere, it should no longer be available to guide verbal number production or arithmetical fact retrieval.

This description goes a long way towards describing the details of patient MAR's behavior. The only remaining difficulty comes from MAR's surprisingly good performance in verbally estimating quantities such the time to drive from Marseilles to Paris (cognitive estimation). Note that MAR was somewhat more impaired in retrieving exact number knowledge such as the number of days in January. Further research will be needed to understand why cognitive estimation can be preserved in patients with severe calculation and quantitative number processing deficits (see e.g. patient NAU; Dehaene and Cohen, 1991). Perhaps this is related to a superior ability of the non-dominant hemisphere for the processing of concrete, approximate quantities, as opposed to exact and abstract number knowledge.

The results of patients MAR and BOO also shed some light on several issues in the cognitive psychology of number processing. A first issue concerns the format in which arithmetic facts are stored in memory. McCloskey (1992) proposed that all such facts are represented in a single abstract, amodal form. The present data suggest that, if one is to account for the conjunction of deficits found in patient BOO, the hypothesis that some multiplication facts are coded in rote verbal form seems inescapable. It may never be fully excluded that her multiplication impairment and her deficits of rote verbal knowledge were due to two independent lesions. However this would be a very uneconomical postulate given that the patient suffered from no other numerical deficits aside from her fact retrieval problems. We rather suggest that patient BOO had learnt multiplication facts by verbal recitation, as is frequent in French schools. As a result, her multiplication knowledge was stored in the form of short sequences of words alongside other rote verbal knowledge. This hypothesis fits with experimental studies that indicates a strong interference between multiplication and naming in normal subjects (Campbell, 1994). It also provides a natural explanation for the frequent anecdotal observation that when bilingual subjects have to calculate, they claim that they have to utter numerals in the language in which they first learned arithmetic at school (e.g. Shannon, 1984). If memory for arithmetic facts is tied to a language-specific representation of words such as the phonological or lemma level (Dehaene, 1992; Dehaene and Cohen, 1995), this explains why even a fluent bilingual is obliged to revert to this language in order to do simple arithmetic.

A second issue concerns the existence of asemantic routes for transcoding numerals. Both patient MAR and patient BOO were able to read aloud arabic numerals and to write them down to dictation. The preservation of these abilities is compatible with the existence of distinct transcoding routes, independent from the processes involved in other arithmetic tasks, as postulated by several number processing models (e.g. Cipolotti and Butterworth, 1995; Dehaene, 1992; Dehaene and Cohen, 1995; Deloche and Seron, 1987). It is however more difficult to explain in McCloskey's model of number processing (McCloskey, Caramazza and Basilii, 1985; McCloskey, 1992), which postulates a central abstract representation of quantities involved in all transcoding and arithmetic tasks. In this model, patient MAR's severe deficit in quantitative tasks can only be explained by appealing to a functional lesion of the semantic representation. However, a lesion at this stage should affect all aspects of number processing, including reading aloud arabic numerals and writing them down to dictation. This conflicts with the preservation of number transcoding and the relative sparing of multiplication facts that were observed in patient MAR. Multiple recent single-case studies of brain-lesioned patients (e.g. Cohen and Dehaene, 1991, 1995; Cipolotti and Butterworth, 1995) strongly suggest that McCloskey's model must be supplemented with direct asemantic transcoding routes parallel to the route for quantitative processing.

A third issue, finally, concerns the mental representation of the various arithmetic operations such as addition, multiplication, subtraction and division. One view is that the four arithmetic operations are supported by distinct, functionally segregated processes (Dagenbach and McCloskey, 1992). This hypothesis was initially proposed because there seemed to be no obvious pattern in the observed dissociations between preserved and impaired operations in brain-lesioned patients. In fact, however, there is often a selective sparing or impairment of subtraction as opposed to multiplication and addition, as observed in the present cases as well as in previous publications (Dagenbach and McCloskey, 1992; Lampl, Eshel, Gilad et al., 1994; McNeil and Warrington, 1994). Our model suggests that this segregation reflects the differential contributions of quantitative versus rote verbal processing to these operations. Hence, we suggest that dissociation between operations are not arbitrary and reflect the underlying structure of the two main cerebral pathways for calculation.

Neuroanatomy of Number Processing

Aside from their relevance to the cognitive neuropsychology of number processing, our observations also provide tentative information about the cerebral substrates of number processing and calculation. Clearly, caution is needed in trying to infer cerebral localizations from neuropsychological data. In the present cases, the lesions were only evidenced with CT-scan, which is not an ideal tool for understanding the functional integrity of brain areas. Diaschisis – an influence of a focal lesion on the function of a distant brain area or network – cannot be excluded. This is particularly true for patient BOO, who suffered left subcortical damage that could have impacted on cortical functions. Images of cerebral blood flow or metabolism, which might have disclosed such diaschisis effects, were unfortunately not available in our patients. Another reason for caution is the suspected unusual lateralization pattern of patient MAR. In spite of these shortcomings, however, our study converges rather nicely with previous publications in suggesting different anatomical pathways for rote verbal and quantitative knowledge of arithmetic (Dehaene and Cohen, 1995).

The nature of parietal acalculia. It has been known since Henschen (1919, 1920) that the inferior parietal region is critical for numerical calculation. Modern brain-imaging has also revealed bilateral inferior parietal activations in normal volunteers during numbers processing tasks (e.g. Dehaene, 1996; Dehaene et al., 1996; Roland and Friberg, 1985; Rueckert, Lange, Partiot et al., 1996). Hence converging data point to the importance of this area for number-related tasks. None of these data, however, elucidate the precise nature of its contribution to number processing.

The data obtained with patient MAR may clarify this issue. As others (e.g. Hécaen et al., 1961; Takayama et al., 1994; see also Warrington, 1982), we find that an inferior parietal lesion can leave the transcoding of numbers (reading, writing) totally unaffected, while the ability to calculate is seriously deteriorated. According to classical typology, parietal acalculia would thus fall in the category of "pure inability to calculate" or "pure anarithmetia" (Hécaen et al., 1961). Our proposal, however, is that the core of parietal acalculia should rather be characterized as a category-specific disruption of the quantitative meaning of numbers. This impairment would entail, among other deficits, an inability to solve arithmetic problems not represented in rote verbal memory.

In clinical neurology, acalculia is an important clinical feature which, in conjunction with agraphia, finger agnosia, and left-right confusion, forms a tetrad called "Gerstmann's syndrome" (Gerstmann, 1940) with good localizing value for left posterior lesions (for discussion, see Benton, 1961, 1987, 1992). It is now well established that the four elements of Gerstmann's syndrome can be dissociated from one another. There is therefore no reason to expect that all patients with a parietal acalculia similar to that of patient MAR should display the other components of Gerstmann's syndrome. Conversely, however, if our hypothesis is correct, the acalculia observed in the context of a full-fledged Gerstmann's syndrome should correspond to the parietal acalculia as defined here.

Before this tentative generalization may be accepted, one should return to the unusual fact that patient MAR suffered from a unilateral right-sided inferior parietal lesion, while the vast majority of patients with Gerstmann's syndrome have a left-sided lesion in this area. We note, however, that MAR was strongly left-handed (all his artistic work, including minute engravings, was done with the left hand). In conjunction with the unusual observation of Gerstmann's syndrome following a right-sided lesion, this suggests that language and calculation may have been cross-lateralized in MAR.

It will therefore be important to examine whether our findings extend to more classical cases of Gerstmann's acalculia. In the appendix we report briefly on a case of typical Gerstmann's syndrome following a *left* inferior parietal lesion. Although this patient could not be tested as thoroughly as patient MAR, he showed essentially identical deficits, particularly evident in subtraction and number bissection tasks. In the literature, the numerical deficits of Gerstmann-type patients are generally not analyzed thoroughly enough to warrant comparison with the present case. An exception is Warrington's (1982) detailed analysis of patient DRC, a case of left parieto-occipital haematoma with persistent acalculia (it is not specified whether the other elements of Gerstmann's syndrome were present). DRC was perfect in number reading and writing. He made few errors in calculation, but had exceptionally long response latencies. Examination of Warrington's (1982) Table II and IV shows that like patient

MAR, DRC was much worse in subtraction and addition that in multiplication. Simple rote verbal facts such as ties and addition facts below ten were also largely preserved. Further work should tell whether the less of quantitative knowledge and the preservation of rote arithmetic provide an adequate characterization of most or all patients with parietal acalculia.

The nature of subcortical acalculia. The second case reported in the present paper, patient BOO, confirms that contrary to the classical textbook picture, "calculation" is not a homogeneous function with a single dedicated area in the left inferior parietal cortex. Several patients similar to patient BOO, with acalculia stemming from a left subcortical lesion affecting the basal ganglia, have now been reported (Corbett et al., 1988; Hittmair-Delazer et al., 1994; Whitaker et al., 1985). The present work may shed some light on the nature of this deficit. We suggest that at least these patients were suffering from an inability to execute sequential behavior, and that in some of them at least, this deficit impacted on the retrieval of the sequences of words that we claim are used to encode multiplication facts such as "three times three is nine".

From a neuro-anatomical viewpoint, our hypothesis fits with the idea that cortico-striato-thalamo-cortical loops are involved in the control of sequential behavior (e.g. Houk and Wise, 1995; Dominey, Arbib and Joseph, 1995). Multiple parallel corticostriatal loops may be involved in sequential processing at different levels (Alexander, DeLong and Strick, 1986). In the number processing litterature, one patient with a left subcortical lesion, like patient BOO, suffered from a rather selective deficit of the multiplication table (Hittmair-Delazer et al., 1994). Another had mixed difficulties with both multiplication and addition tables and with multi-digit calculation procedures (Whitaker et al., 1985). In a third patient, memory for single-digit facts seemed intact while procedural knowledge of multi-digit operations was compromised (Corbett et al., 1988). This tentatively suggests that dissociable parallel corticostriatal circuits may contribute to the sequences of number words coding for arithmetic facts and to the sequences of operations involved in complex calculations (see Caramazza and McCloskey, 1987).

Dehaene et al. (1996) recently reported a brain-imaging study of arithmetic in normal subjects, using positron emission tomography. They reported greater activation of the left lenticular nucleus during mental multiplication than during a number comparison task with identical stimuli. This provides converging evidence that a left subcortical circuit may be specifically called upon during the multiplication task.

The hypothesis that a cortico-striato-thalamo-cortical loop is involved in the storage and retrieval of rote arithmetic facts predicts that deficits similar to patient BOO's might be observed following a lesion of the thalamus or of the cortical perisylvian language areas. The first prediction is partially borne out by Ojemann's (1974) finding that thalamic stimulation affected the speed of mental arithmetic. The second prediction is supported by patients such as DAS (Cohen and Dehaene, 1994) who, following poorly localized left parieto-temporal damage, developed slight aphasia, a reading impairment, and a severe deficit in retrieving rote arithmetic facts, particularly multiplication facts. Note that although patient DAS suffered from a left posterior lesion, her deficit was quite different from that of patient MAR, who had an inferior parietal lesion. In particular DAS did not show Gerstmann's syndrome and had no difficulty in tasks tapping quantitative number knowledge. Patient DAS was actually more similar to that of patient BOO, with a left subcortical lesion, and one may suggest that her deficit stemmed from a lesion in the cortical component of the postulated corticostriatal loop. DAS's case should thus serve as a word of caution for anatomical-functional correlations. Because the left posterior lesion sites that subserve the verbal and magnitude representations of numbers are rather close together, many patients with an extended lesion may show a mixture of the patterns of acalculia that were clearly dissociated in patients MAR and BOO.

Representation of Arithmetic Knowledge in the Brain

The double dissociation observed between the patients MAR and BOO suggests that multiple anatomical networks contribute to calculation processes. Two major number processing routes were dissociated in the present paper: a route for quantitative number processing, possibly involving the inferior parietal areas, and a route for rote verbal arithmetic memory, possibly subserved by a left-lateralized corticostriatal loop. There is now a growing list of single-case studies reporting dissociations between yet other aspects of number knowledge. Candidates for dissociation include quantity versus parity knowledge (e.g. knowing that 2 is even and 3 is odd; Dehaene and Cohen, 1991); specific arithmetic facts versus generic arithmetic concepts (e.g. knowing that 2 + 3 = 5 versus knowing the commutativity of addition; Hittmair-Delazer et al., 1994; Hittmair-Delazer, Sailer and Benke, 1995); and quantity versus encyclopaedic knowledge (e.g. knowing that 1789 epitomizes the French revolution; Cohen et al., 1994). Hence, the available data point to a fractionation of number knowledge in multiple segregated circuits, the anatomical substrates of which still remain largely unknown.

The fact that these circuits are dissociable does not, of course, imply that they function in strict independence in normal subjects. In most calculations, they are likely to be activated simultaneously. For instance the magnitude representation of numbers can serve to evaluate the plausibility of the results retrieved from verbal memory (Dehaene and Cohen, 1991, 1995). Functional imaging in normal subjects (Dehaene et al., 1996) has revealed a greater activation of the left lenticular nucleus during multiplication than during comparison, as expected from the present study, but also a bilateral parietal activation during multiplication relative to rest. Chronometric studies also indicate that a magnitude representation of numbers is active even in tasks in which no quantitative computation is needed (e.g. Dehaene and Akhavein, 1995). Thus, although each anatomical area may handle only a restricted or "modular" process, the normal operation of the number processing network most likely involves fast multi-directional interactions across large-scale anatomical circuits.

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Appendix

Patient DUV

Patient DUV was a 78-year-old right-handed retired chemical engineer and manager. He was admitted for an acute confusional state. CT-scan revealed a cerebral haemorrage affecting the left inferior parietal lobule (Figure 6). Confusion cleared within a day. During testing, the patient was alert and cooperative. There was no tactile or motor deficit, and no aphasia. Initially, there was a right homonymous scotoma, as well as some visuo-spatial disorientation with mild right-sided neglect, which made reading and the description of complex pictures difficult.

Patient DUV showed typical Gerstmann's syndrome. He made very few side errors in pointing to parts of his own body on verbal command. However, he systematically chose the wrong side when pointing to parts of the body of the examiner facing him. When asked to point to specific fingers on verbal command, the patient was generally correct when pointing to his own fingers, but made about 35% errors when pointing to the examiner's fingers. Writing was clumsy and sometimes difficult to decipher, but did not include significant spelling errors.

Acalculia was severe, but spared the most familiar arithmetic facts (e.g. 3×9, 4×5, $2 + 2$, $5 + 3$). Subtraction problems were particularly difficult for patient DUV. He could solve correctly, albeit very slowly, most elementary subtraction problems (e.g. $3 – 1$, $10 – 2$, $6 – 5$), although with occasional errors (e.g. for $5 – 2$ he initial responded 2). He was unable to solve subtraction problems spanning a decade boundary. For instance for $31 – 5$ he said "oh my God... 6, I believe... I take away the 5, therefore... I make a complicated move... 31 – 5... I start from 31, I take away 5, and there remains 6... no... 6 plus 30... 33... 30... 31 – 5...". He abandoned after several minutes.

Number bissection was especially difficult. For instance, when asked which number falls between 3 and 5, DUV answered "2... 2 $^1/_2$... no, it's 3". On another occasion, he responded to the same problem "3... between 3 and 5... 3 $^1/_2$... just in the midle... 3 $^1/_2$". When asked to bissect 6 and 10, he responded, after considerable delay, "You ask questions both quantitative and of localization... strange numbers appear to me... there is 4... I have 10 here, and I have taken the 6... it's not... between 6 and 10... I'll think of a clock face, it will help me... 6 and 10... 8 $^1/_2$".

He could easily recite the number series 1, 2, 3... However, when asked to count down from 20 to 1, he jumped directly from 20 to 9, and then correctly decremented to 1. He observed that some numbers were missing, but his second attempt was identical to the first. Similarly, he could easily recite the series 0, 2, 4... up to 20. However, when asked to count by two's starting with 1, he responded "1, 2, 4". On a further attempt, he produced the correct series by reciting the complete number series and uttering the even numbers in a low voice. When asked to refrain from using this strategy, he was again very slow and made errors (13... 14... 15... 17... 19). DUV was completely unable to count down from 50 by 3 on a first attempt (after a long delay, he only produced 42). On a second attempt, he produced the correct sequence 50, 47, 44, 41, although slowly. He himself commented: "I am cheating: I do not jump by 3, I am counting in my head". In contrast, he could flawlessly recite the table of multiplications by 2 and by 7 up to 49.

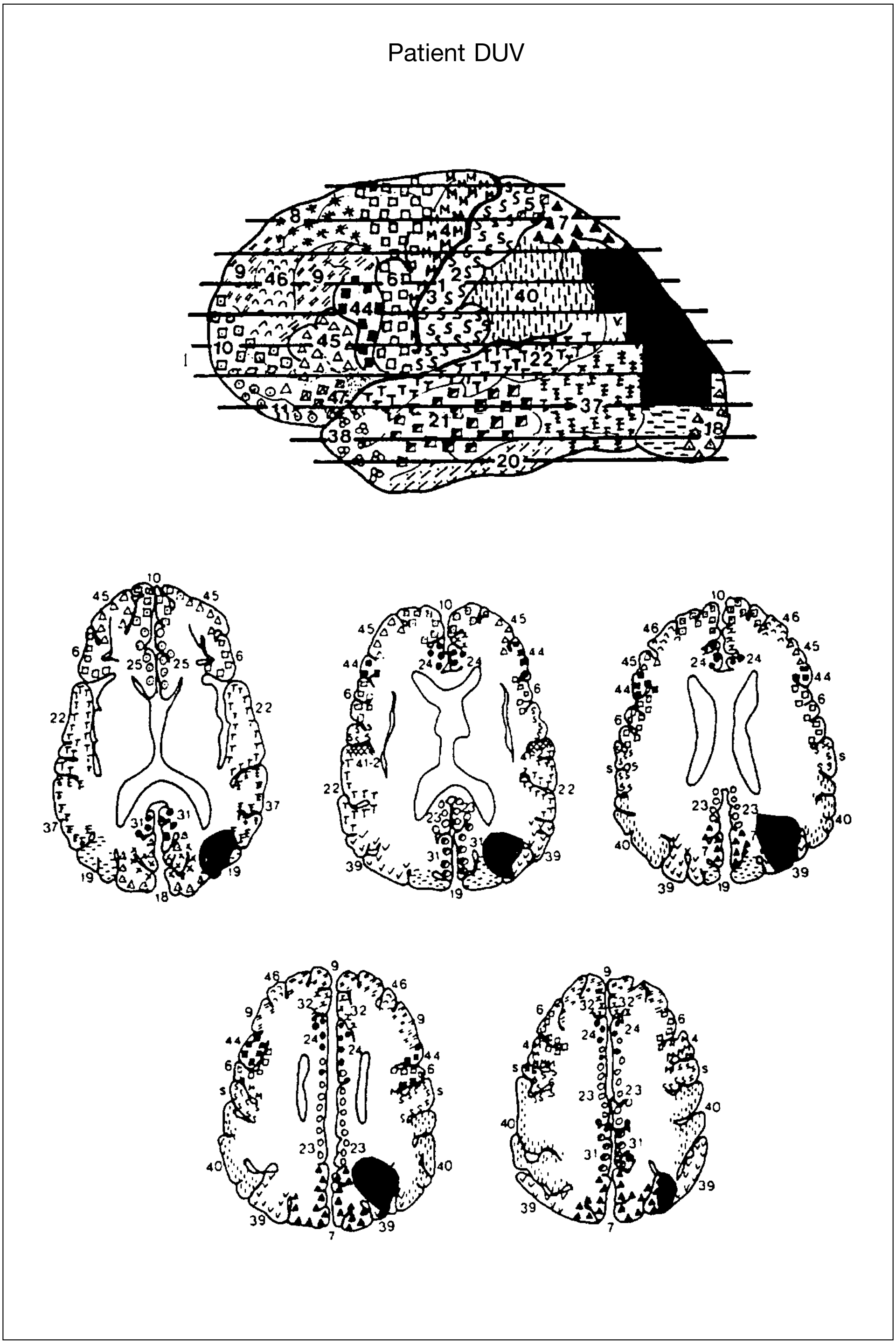

Fig. 6 – *Outline of patient DUV's lesion (same legend as Figure 2).*