

ACALCULIA AND NUMBER PROCESSING DISORDERS

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The foundation for the amazing successes of our species in science and technology lies in our ability to do mathematics. Although little is known about the cerebral substrates of mathematics in general, one of its subareas, elementary arithmetic, has received considerable attention from cognitive neuroscientists. The present chapter reviews the organization of the number system from the point of view of cognitive neuropsychology. Brain lesions can selectively affect several components of the number processing system, revealing a highly organized brain architecture for arithmetic that is now being confirmed and refined by brain imaging methods. Current results indicate that (1) the number system is segregated from other symbolic processing systems at multiple levels; (2) parietal lobe lesions can interfere with the semantic component of number processing; (3) dissociations between operations are frequently observed, suggesting that multiple parietal circuits contribute to arithmetic; and (4) developmental disorders of calculation, possibly of genetic origin, can be traced to pre- or perinatal pathology often affecting the parietal lobe.

THE ISOLATION OF THE NUMBER PROCESSING SYSTEM

The specialization of the number processing system can be inferred from the observation that, at virtually all levels of processing, dissociations have been observed between numbers and the rest of language. For instance, high-level calculation abilities may be spared in patients with severe global aphasia (Rossor et al., 1995) or impaired short-term memory (Butterworth et al., 1996). At the visual identification level, pure alexic patients who fail to read words often show a largely preserved ability to read and process digits (Cohen and Dehaene, 1995; Déjerine, 1891; Déjerine, 1892). Con-

versely, a case of impaired number reading with preserved word reading is on record (Cipolotti et al., 1995). In the writing domain, severe agraphia and alexia may be accompanied by a fully preserved ability to write and read arabic numbers (Anderson et al., 1990). Even within the speech production system, patients who suffer from random phoneme substitutions, thus resulting in the production of an incomprehensible jargon, may produce jargon-free number words (Cohen et al., 1997).

Most importantly, numbers may doubly dissociate from other categories of words at the semantic level, suggesting the existence of a category-specific semantic system for numerical quantities. Spared calculation and number comprehension abilities have been described in patients with grossly deteriorated semantic processing (Thioux et al., 1998) or semantic dementia (Butterworth et al., 2001; Cappelletti et al., 2001). The converse dissociation is also on record. Cipolotti and coworkers (1991) first reported a striking case of a patient with a small left parietal lesion and an almost complete deficit in all spheres of number processing, sparing only the numbers 1 through 4, in the context of otherwise largely preserved language and semantic functions. Although such a severe degradation of the number system has never been replicated, other cases, discussed further below, confirm that the understanding of numbers and their relations can be specifically impaired in the context of preserved language and semantics (e.g., Dehaene and Cohen, 1997; Delazer and Benke, 1997).

THE CENTRAL ROLE OF THE PARIETAL LOBE AND ACALCULIA

The parietal lobe appears to play a central role in number processing. It has been known since the beginning of this century that parietal lesions, usually in the

dominant hemisphere, can cause calculation deficits. Gerstmann (1940) reported the frequent co-occurrence of agraphia, acalculia, finger agnosia, and left-right confusion in parietal cases, a tetrad of deficits referred to as Gerstmann's syndrome (although the elements of the syndrome are now known to be dissociable; see Benton, 1992). The lesions that cause acalculia of the Gerstmann's type are typically centered on the portion of the left intraparietal sulcus that sits immediately behind the angular gyrus (Brodmann's area 39) (Mayer et al., 1999; Takayama et al., 1994). In many cases, the deficit can be extremely incapacitating. Patients may fail to compute operations as simple as $2 + 2$, $3 - 1$, or 3×9 . Several characteristics indicate that the deficit arises at a rather abstract level of processing. First, patients may remain fully able to comprehend and to produce numbers in all formats. Second, they show the same calculation difficulties whether the problem is presented to them visually or auditorily and whether they have to respond verbally or in writing, or even merely have to decide whether a proposed operation is true or false. Thus, the calculation deficit is not due to an inability to identify the numbers or to produce the operation result. Rather, patients with inferior parietal lesions and acalculia of the Gerstmann type suffer from a category-specific impairment of the semantic representation and manipulation of numerical quantities (Dehaene and Cohen, 1995, 1997).

One patient, Mr. Mar (Dehaene and Cohen, 1997), experienced severe difficulties in calculation, especially with single-digit subtraction (75 percent errors). He failed on problems as simple as $3 - 1$, with the comment that he no longer knew what the operation meant. His failure was not tied to a specific modality of input or output, because the problems were simultaneously presented visually and read out loud and because he failed in both overt production and covert multiple-choice tests. Moreover, he also erred on tasks outside of calculation per se, such as deciding which of two numbers is the larger (16 percent errors) or what number falls in the middle of two others (bisection task: 77 percent errors). He easily performed analogous comparison and bisection tasks in nonnumerical domains such as days of the week, months, or the alphabet (What is between Tuesday and Thursday? February and April? B and D?), indicating that he suffered from a category-specific deficit for numbers. This and similar

patients (Delazer and Benke, 1997; Takayama et al., 1994) suggest that parietal lesions can cause a selective disturbance to the central representation of numerical quantity.

BRAIN-IMAGING STUDIES OF NUMBER PROCESSING

The involvement of parietal cortex in number processing is confirmed by brain imaging studies in normal subjects. Roland and Friberg (1985) were the first to monitor blood-flow changes during calculation as opposed to rest. When subjects repeatedly subtracted 3 from a given number, activation increased bilaterally in inferior parietal and prefrontal cortex. These localizations were later confirmed using functional magnetic resonance imaging (fMRI) (Burbaud et al., 1995; Rueckert et al., 1996). A positron emission tomography (PET) study of multiplication and comparison of digit pairs revealed bilateral parietal activation confined to the intraparietal region (Dehaene et al., 1996), in agreement with lesion data. Several recent brain-imaging studies all confirm the involvement of bilateral parietal cortices in calculation (Burbaud et al., 1999; Chochon et al., 1999; Dehaene et al., 1999; Pesenti et al., 2000; Rueckert et al., 1996; Zago et al., 2001).

Several features of the inferior parietal contribution to number processing have been clarified by imaging methods. First, the parietal region is active whenever an arithmetic operation or the mere comprehension of the size of a number is called for (Chochon et al., 1999; Dehaene et al., 1999). Second, its activation is proportional to the number of calculations performed per unit of time (Menon et al., 2000). Third, its activation is independent of the particular input or output modalities used to convey the numbers, such as arabic or spelled-out numerals, suggesting that parietal cortex may be coding the abstract meaning of numbers rather than the numerical symbols themselves (Dehaene, 1996; Kiefer and Dehaene, 1997; Pinel et al., 2001). Fourth, the amount of activation correlates directly with the complexity of an arithmetic operation. Thus, event-related potentials (ERPs) and fMRI recordings in a number comparison task reveal that intraparietal activity is modulated by the numerical distance separating the numbers to be compared

(Dehaene et al., 1996; Pinel et al., 2001). Moreover, inferior parietal activity is larger and lasts longer during operations with large numbers than with small numbers (Kiefer and Dehaene, 1997; Stanescu-Cosson et al., 2000). Fifth, parietal activation during number processing can be found even when the subject is not aware of having been presented with a subliminal number (Dehaene et al., 1998; Naccache and Dehaene, 2001). I suggest that parietal cortices provide us with a "numerical intuition," a permanent and often implicit reference to the meaningful size of a numerical quantity in relation to others on the "mental number line" (Dehaene, 1992; Dehaene, 1997). Patients in whom this unconscious reference is impaired suffer a drastic loss of stable reference in the numerical domain.

DISSOCIATIONS BETWEEN OPERATIONS

Although the inferior parietal region seems to play a crucial role in number sense, it is important to note that it is not the only brain region involved in number processing in adults. The phrenologic notion that a single area can hold all the knowledge about an entire domain such as arithmetic has to give way to a more parallel view of number processing in the brain. Multiple brain areas are involved, whether for identifying arabic numerals, writing them down, understanding spoken number words, retrieving multiplication facts from memory, or organizing a sequence of multidigit calculations (Caramazza and McCloskey, 1987; Dehaene and Cohen, 1995; McCloskey and Caramazza, 1987; McCloskey et al., 1992). Correspondingly, a great variety of brain-lesioned patients with number processing deficits, too broad to be reviewed here, have been described.

One of the most striking dissociations occurs among different arithmetic operations. It is not rare for a patient to be much more severely impaired in multiplication than in subtraction (Cohen and Dehaene, 2000; Dagenbach and McCloskey, 1992; Dehaene and Cohen, 1997; Lampl et al., 1994; Pesenti et al., 1994), while other patients are much more impaired in subtraction than in multiplication (Dehaene and Cohen, 1997; Delazer and Benke, 1997). It may not be necessary, however, to postulate as many brain circuits as there are

arithmetical operations (although see van Harskamp and Cipolotti, 2001). Rather, such dissociations may reflect a basic distinction between overlearned arithmetic facts such as the multiplication table, which are stored in rote verbal memory, and the genuine understanding of number meaning that underlies non-table operations such as subtraction (Dehaene and Cohen, 1997; Delazer and Benke, 1997; Hittmair-Delazer et al., 1995). Indeed, patients with impaired multiplication often have associated aphasia and lesions within the left perisylvian areas (Cohen et al., 2000) or left basal ganglia (Dehaene and Cohen, 1997), while patients with impaired subtraction tend to have lesions in the left intraparietal region outside of language cortex *per se*.

Brain imaging has confirmed that different operations rely on partially dissociable parietal circuits, with bilateral intraparietal activation during subtraction and more posterior and left-lateralized subangular activation during multiplication (Chochon et al., 1999; Lee, 2000). Brain imaging also indicates that those parietal circuits are differentially called upon during exact calculation and approximation (Dehaene et al., 1999): exact calculation of addition problems is dependent on language and causes relatively greater activation of the left anterior inferior frontal region and the angular gyrus, while approximation of quantities is independent of language and causes greater activation of the bilateral intraparietal sulci. This finding may explain why some patients with severe deficits of exact calculation may remain able to compute approximations of the desired result (Dehaene and Cohen, 1991; Warrington, 1982).

HEMISPHERIC SPECIALIZATION

There is an as yet unresolved discrepancy between brain imaging and neuropsychological findings. On the one hand, the parietal activations during number processing tend to be bilateral, though often with increasingly greater left lateralization as the task requires exact calculation and arithmetic tables (e.g., Chochon et al., 1999). On the other hand, the lesion site for acalculia and Gerstmann's syndrome appears strictly lateralized to the dominant left parietal lobe. Although this is not fully understood yet, the issue may be partially clarified by studies of split-field presentations in callosal

patients (Cohen and Dehaene, 1996; Gazzaniga and Hillyard, 1971; Gazzaniga and Smylie, 1984; Seymour et al., 1994). Those studies confirm that both hemispheres can process digits and quantities at the semantic level. When two digits are presented simultaneously *within* the same hemifield, split-brain patients experience no difficulty deciding whether they are the same or different (while their disconnection renders them completely unable to compare two digits *across* the two hemifields). Hence, both hemispheres can analyze digit shapes. Furthermore, both hemispheres can also point to the larger digit (or to the smaller), and both can classify digits or even two-digit numbers as larger or smaller than some reference. Hence, both hemispheres seem to possess a quantity representation of numbers.

There are, however, at least two striking differences between the numerical abilities of the left and the right hemispheres. First, digits presented to the left hemisphere can be named normally by the patients, but digits presented to the right hemisphere cannot. This is in keeping with the well-known lateralization of speech production abilities to the left hemisphere. Second, split-brain patients can calculate only with digits presented to their left hemisphere. When digits are presented to their right hemisphere, the patients fail with operations as simple as adding 2, multiplying by 3, subtracting from 10, or dividing by 2. This is the case even when they merely have to point to the correct result among several possible results or to indicate nonverbally whether a proposed result is correct or not. The only calculation ability that seems to be available to an isolated right hemisphere, at least occasionally, is approximation. A patient might not be able to decide whether $2 + 2$ makes 4 or 5, but might still easily notice that $2 + 2$ cannot make 9 (Cohen and Dehaene, 1996; Dehaene and Cohen, 1991). It has been suggested that the right hemisphere may have a special role in the "abstraction of numerical relations" (Langdon and Warrington, 1997).

DEVELOPMENTAL DYSCALCULIA

Deficits of number processing can be observed in adults with acquired brain lesions, but also in young children. Developmental dyscalculia, coarsely defined as a

failure on standardized tests of arithmetic independently of IQ or social factors, is not rare. Kosc (1974) reported an incidence of 6.4 percent in a sample of 375 children between the age of 10 and 12. Badian (1983) studied 1476 children between 7 and 14 years of age and observed that 2.7 percent had both reading and mathematical deficits, another 3.6 percent only had difficulties in mathematics, and yet another 2.5 percent only in reading. In another study in Great Britain, those figures were 2.3, 1.3, and 3.9 percent (Lewis et al., 1994). Other family members are frequently affected, suggesting that genetic factors may contribute to the disorder (Shalev et al., 2001).

A variety of systems of classification of developmental dyscalculia have been proposed. Badian (1983) used a terminology initially proposed for adult acalculia cases (Hécaen et al., 1961) to distinguish dyscalculia due to a reading or writing deficit, spatial dyscalculia due to an inability to organize the figures on a page, dyscalculia due to attentional disorders, and an arithmetic proper. Kosc (1974) adopted a similar though more complex classification. Simpler categories were achieved by Temple (1991, 1994) on the basis of Caramazza and McCloskey's model of number processing (Caramazza and McCloskey, 1987; McCloskey and Caramazza, 1987; McCloskey et al., 1992). She distinguished dyscalculia due to a failure to process the number notations (e.g., difficulties in reading or in writing arabic numerals); arithmetic fact dyscalculia, or a failure to store and retrieve arithmetic tables; and procedural dyscalculia, or an inability to execute a multi-digit calculation in the correct sequence. A particularly striking double dissociation between arithmetic fact and procedural dyscalculia was reported, strengthening the hypothesis that cases of developmental dyscalculia can be as selective as adult neuropsychological cases (Temple, 1991). A similar approach has been adopted to analyze a single case of number-notation dyscalculia (Sullivan et al., 1996) and two series of cases with various subtypes of developmental dyscalculia (Ashcraft et al., 1992; Sokol et al., 1994).

In a series of publications, Geary and colleagues have focused on developmental calculation deficits and have attempted to characterize their origins (Geary, 1990, 1993, 1994; Geary et al., 1992; Geary and Brown, 1991; Geary et al., 1991; Geary et al., 1986; Geary et al., 1987). In comparison to normal children, they

report that dyscalculic children use immature calculation strategies, largely based on counting; make an improper choice of strategy; and show a slower evolution in their strategies with time. Dyscalculic children also have a poorer short-term memory span for digits (Geary et al., 1991; Hitch and McAuley, 1991). Most interestingly, some dyscalculic children may suffer from a lack of understanding of the counting principles proposed by Gelman and Gallistel (1978), suggesting that some of them at least may have a fundamental deficit in understanding the conceptual bases of arithmetic (Geary et al., 1992).

The notion that at least some children with developmental dyscalculia may suffer from a core conceptual deficit is supported by the existence of a "developmental Gerstmann syndrome" in children (Benson and Geschwind, 1970; Kinsbourne and Warrington, 1963; Spellacy and Peter, 1978; Temple, 1989; Temple, 1991). Like in adults, the calculation deficit is accompanied by most or all of the following symptoms: dysgraphia, left-right disorientation, and finger agnosia, which suggest a neurologic involvement of the parietal lobe. Interestingly, even in a sample of 200 normal children, a test of finger knowledge appears to be a better predictor of later arithmetic abilities than is a test of general intelligence (Payol et al., 1998), again supporting a tight correlation between number knowledge and finger knowledge in the parietal lobe.

Very few imaging studies to date have been dedicated to developmental dyscalculia. Levy et al. (1999) report the case of an adult with lifelong isolated dyscalculia together with superior intelligence and reading ability, in whom the standard anatomic MRI appeared normal, yet MR spectroscopy techniques revealed a metabolic abnormality in the left inferior parietal area, exactly where a lesion would be expected in an adult Gerstmann syndrome case. Similarly, Isaacs and coworkers used voxel-based morphometry to compare gray matter density in adolescents born at equally severe grades of prematurity, half of whom suffered from dyscalculia (Isaacs et al., 2001). They found a single region of reduced gray matter in the left intraparietal sulcus, coinciding precisely with the site of fMRI activations during calculation in normal subjects. Those studies strengthen the hypothesis that early parietal dysfunction may underlie isolated developmental dyscalculia.

TURNER'S SYNDROME: DYSCALCULIA OF GENETIC ORIGIN?

If the parietal lobe involvement for arithmetic results at least in part from a genetic predisposition, then one would expect to find genetic diseases targeting the parietal region and causing dyscalculia. Although the search for such dyscalculias of genetic origin has only very recently begun, the possibility that Turner syndrome may conform to this typology has recently attracted attention. Turner syndrome is a genetic disorder characterized by partial or complete absence of one X chromosome in a female individual. The disorder occurs in approximately 1 girl in 2000 and is associated with well-documented physical disorders and abnormal estrogen production and pubertal development. The cognitive profile includes deficits in visual memory, visuospatial and attentional tasks, and social relations, in the context of a normal verbal IQ (Rovet, 1993). Most interestingly in the present context is the documentation of a mild to severe deficit in mathematics, particularly clear in arithmetic (Mazzocco, 1998; Rovet et al., 1994; Temple and Marriott, 1998). Anatomically, the data suggest possible bilateral parietooccipital dysfunction. A positron emission tomography study of five adult women demonstrated a glucose hypometabolism in bilateral parietal and occipital regions (Clark et al., 1990). Two anatomic MRI studies, one with 18 and the other with 30 affected women, demonstrated bilateral reductions in parietooccipital brain volume, together with other subcortical regions (Murphy et al., 1993; see also Reiss et al., 1993, 1995). Interestingly, the phenotype of Turner syndrome can differ depending on whether the remaining X chromosome is of paternal or maternal origin (Xm or Xp subtypes) (Bishop et al., 2000; Skuse, 2000; Skuse et al., 1997). Such a genomic imprinting effect was first demonstrated on tests of social competence (Skuse et al., 1997). It will be interesting to see if a similar effect exists in the arithmetic domain.

CONCLUSION

In this review, we have focused on the large empirical database of patients with number processing deficits. Detailed theoretical models of those deficits have

been published (see, e.g., Caramazza and McCloskey, 1987; Dehaene and Cohen, 1995; McCloskey and Caramazza, 1987; McCloskey et al., 1992) and have been related to cognitive psychological, developmental, and animal research (Dehaene, 1997). As our knowledge of the normal and pathological organization of the number processing system increases, it may eventually become possible to design cognitive rehabilitation programs based on a more accurate anatomic and functional characterization of the impairment (for early attempts, see Girelli et al., 1996; Sullivan et al., 1996).

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