

REVIEW ARTICLE

The enigma of Gerstmann's syndrome revisited: a telling tale of the vicissitudes of neuropsychology

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Eighty years ago, the Austrian neurologist Josef Gerstmann observed in a few patients a concomitant impairment in discriminating their own fingers, writing by hand, distinguishing left from right and performing calculations. He claimed that this tetrad of symptoms constituted a syndromal entity, assigned it to a lesion of the dominant parietal lobe and suggested that it was due to damage of a common functional denominator. Ever since, these claims have been debated and an astute synopsis and sceptical discussion was presented 40 years ago by MacDonald Critchley in this journal. Nonetheless, Gerstmann's syndrome has continued to intrigue both clinical neurologists and researchers in neuropsychology, and more frequently than not is described in textbooks as an example of parietal lobe damage. In this review, we revisit the chequered history of this syndrome, which can be seen as a case study of the dialectic evolution of concepts in neuropsychology. In light of several modern era findings of pure cases we conclude that it is legitimate to label the conjunction of symptoms first described by Gerstmann as a 'syndrome', but that it is very unlikely that damage to the same population of cortical neurons should account for all of the four symptoms. Instead, we propose that a pure form of Gerstmann's syndrome might arise from disconnection, via a lesion, to separate but co-localized fibre tracts in the subcortical parietal white matter, a hypothesis for which we have recently provided evidence using combined imaging of functional and structural organization in the healthy brain.

Keywords: Gerstmann syndrome; acalculia; agraphia; left–right confusion; finger agnosia

Introduction

In 1965, MacDonald Critchley was invited to deliver the William Gowers Lecture at the Queen Square National Hospital in London,

a lecture that was intended to celebrate one of the most eminent British neurologists of the 19th century. Critchley admired Gowers because of the methodological reasoning that he applied to neurological studies of higher functions (Critchley, 1949) and

chose for the occasion to discuss a very intriguing and debated issue of the time, Gerstmann's syndrome. The text of his lecture was printed in 'Brain' the following year under the title of 'The enigma of Gerstmann's syndrome'. For its clear reasoning and completeness at the time, Critchley's paper can serve as a major reference when reviewing the first half of the dialectic history of Gerstmann's syndrome. Yet, it is worthwhile to cast a glimpse at the context in which Gerstmann's syndrome was debated at the time of Critchley's lecture.

The 1950s and 1960s saw a renewed interest in topics such as hemispheric specialization, localization of cognitive functions and, in general, the link between brain function and mental activity. This interest emerged in reaction to the behaviourist 'dark age' when any attempt to relate mind states to neurology was deemed useless. Localizationist views first came to the fore during the second half of the 19th century, but the rather crude approaches of that era had provided ample material for critics at the beginning of the 20th. By the middle of the 20th century, however, resurging localizationist concepts regarding the relation between brain and mind had become more sophisticated, embedding concepts of functional systems and temporal dynamics of function rather than simplistic one-to-one spatial mapping between cognitive faculties and brain areas. Sadly, two world wars had resulted in huge numbers of patients with circumscribed, acute brain lesions and neurologists were busy testing new pathoanatomical and pathophysiological hypotheses to explain neuropsychological deficits.

Particular effort was directed at understanding the function of regions that were previously (and in part still are) considered 'silent areas' of 'ineloquent' cortex. So-called 'associative' cortical areas are particularly interesting for the study of higher functions, since they have expanded most during recent stages of phylogeny, e.g. in the inferior parietal lobule of human relative to monkey posterior parietal lobe (Flechsig, 1895, 1900; Hyvärinen, 1982; Smith, 1904a, b). Associative cortex, hence, constitutes most of the cortex in humans (Penfield and Rasmussen, 1950), more than half in monkeys, but only a small portion in cats, rabbits and rats. However, the functional consequences of lesions to associative cortex proved more difficult to test than those from lesions to primary sensory and motor areas.

Critchley was a protagonist of this new movement and in 1953, he published a monograph entitled 'The Parietal Lobes', which exerted an immediate and lasting impact on clinical and experimental neurology (e.g. see Mountcastle, 2003). Critchley's book covered the clinical syndromes produced in humans by localized lesions and whenever possible tried to integrate them with evidence from other relevant disciplines such as monkey neurophysiology. In the 1950s, knowledge of parietal lobe function was based almost exclusively on studies of brain-damaged patients, since monkey neurophysiology was still in its infancy and human functional neuroimaging not yet heard of. The lack of neuroimaging tools also meant that the correlation of clinical phenomenology with brain topography had to rely on either post-mortem analyses or direct evidence from surgical operations.

In reviewing impairments caused by damage to the dominant parietal lobe, Critchley devoted much space in his monograph to Gerstmann's syndrome. He reported to have witnessed the same

tetrad of symptoms in a few neurological patients, and had words of great appreciation for Gerstmann's observations. By 1965, however, Critchley's ideas had radically changed, and he became one of Gerstmann's harsher critics. What happened in between those years? Before examining what changed Critchley's mind, however, we will proceed in chronological order and describe the first 40 years history of Gerstmann's syndrome.

The origins of Gerstmann's Syndrome

Gerstmann's 'shrewd and original communication virtually started a new chapter in parietal symptomatology'

M. Critchley (1953)

Josef Gerstmann (1887–1969) worked in Vienna until Nazi Germany annexed Austria in 1938, when he moved to New York (Lebrun, 2005). The paper that made him known world-wide was written in English (Gerstmann, 1940) but had been preceded by four communications written in German (Gerstmann, 1924, 1927, 1930, 1931–1932). In 1924, Gerstmann reported the case of a 52-year-old female who had suffered a left-sided stroke. She was unable to write, calculate, name or point to her own or the examiner's fingers, or to move fingers named by the examiner. When instructed to point to a lateralized body part with her contralateral hand she in fact pointed to the correct body part but on the same anatomical side as the pointing hand, and when asked to reproduce with the same hand the examiner's movement, she imitated mirror-wise. This cluster of impairments contrasted with her otherwise preserved language abilities. She could still understand, speak and read normally, although reading of long sentences proved to be laborious at times. Moreover, her knowledge of body part names and locations other than those of the fingers was preserved and she still understood the meaning of right and left (she could point to a specified body part with the ipsilateral hand).

Two new cases with the syndrome were reported 3 years later (Gerstmann, 1927). In the newly described patients, the clinical tableau was less clear-cut than in the original case report, because in addition to the four cardinal symptoms, they manifested mild constructional apraxia (which however, was not as severe as their agraphia), colour anomia and impaired number but not word reading. At that time, Gerstmann considered finger agnosia and agraphia as the prominent symptoms of the syndrome. He thought right-left confusion and acalculia to be of minor functional importance and noted an occasional association with constructional apraxia, right-sided hemianopia and colour anomia. In the two successive papers, Gerstmann argued in favour of the localizing value of finger agnosia, agraphia, left-right disorientation and acalculia, whenever found in association. He further proposed that this association was in fact due to a *Grundstörung*, failure of a single cognitive mechanism that could be considered a common denominator across the different behavioural capacities and which he thought to be related to a

disturbance of the lateralized and differentiated elements of the body scheme, i.e. the fingers. A similar interpretation was forwarded by Conrad, a contemporary German neurologist who proposed that the four symptoms could be the consequence of an inability to analyse a whole in relation to its constituents (Conrad, 1932), a hypothesis later pursued by Kinsbourne and Warrington (1963).

When first presenting his views in English at the annual meeting of the American Psychiatric Association in 1939 and in print the following year (Lebrun, 2005) he argued that (i) Gerstmann's syndrome was caused by a lesion localized in the lower part of the parietal lobe at the transition with the second occipital circumvolution; (ii) finger agnosia represented a very selective case of autotopagnosia; and (iii) right–left disorientation was restricted to personal space whereas it did not extend to extrapersonal space. The immediate popularity of this puzzling but fascinating syndrome was well-reflected in Critchley's (1953) monograph.

Fact or fiction?

The Gerstmann syndrome is a fiction; it is simply an artefact of defective and biased observation.

A. Benton (1959)

The first influential attack on the validity of Gerstmann's observations was made by Benton. In 1956, he questioned the primacy of Gerstmann's discovery (Benton and Meyers, 1956) by drawing attention to the French ophthalmologist Jules Badal who had published a case report with 'Gerstmann's' tetrad of symptoms in 1888. Among other deficits—defective visuomotor coordination, alexia, inaccurate sound localization—Badal's patient was unable to name her fingers or to classify them from 1 to 5, and demonstrated left–right confusion and agraphia. Badal attributed all these deficits to a generalized loss of the sense of space (Badal, 1888). While Critchley (1966) later applauded the 'historical acumen of Benton' Gerstmann (1957) rejected Benton's view because in Badal's patient left–right disorientation extended to extrapersonal space rather than being confined to the body. Gerstmann was indeed convinced that the tetrad of symptoms he had described originated from a very selective disturbance of the body schema that was restricted to the hands, rather than a generalized defect in spatial cognition.

The scientific controversy started when, based on an extensive review of the parietal lesion literature, Benton (1959) claimed that left–right disorientation and finger agnosia were not exclusively accompanied by acalculia and agraphia but occurred very frequently in association with—and were perhaps caused by—more global deficits such as mental deterioration or aphasia. In a subsequent report, rather tellingly entitled 'The fiction of the Gerstmann syndrome', Benton (1961) produced apparently compelling empirical evidence against the theoretical value, clinical prevalence and diagnostic relevance of Gerstmann's syndrome. That study tested 100 brain-damaged patients for the four symptoms of Gerstmann's syndrome as well as constructional praxis,

reading and visual memory. The neuropsychological deficits forming Gerstmann's syndrome did not show a stronger correlation with each other than other combinations of deficits. Furthermore, none of the 12 right-handed patients with left unilateral parietal damage showed the full syndrome and certainly not in a pure form. Benton suggested that impairment of verbal functions could well explain each of the four symptoms.

Successive studies on large samples of patients and statistical analyses on symptom co-occurrence and its predictive value for lesion localization provided further support for Benton's critique and his idea of a link between Gerstmann's syndrome and aphasia (Heimburger *et al.*, 1964; Poeck and Orgass, 1966). Remarkably, neither a single patient out of the 111 with one or more components of Gerstmann's syndrome in Heimburger *et al.*'s study nor out of the 50 patients in Poeck and Orgass's study could be labelled a 'pure' case because Gerstmann's symptoms were always associated with some other 'extraneous' symptoms, the most common being aphasia. Benton's (1959, 1961) and Heimburger *et al.*'s (1964) studies suggested that the probability of aggregating the physical signs of Gerstmann's syndrome became larger with lesion size, as did the association with further symptoms. They hence concluded that these signs did not constitute a separable syndrome but that their co-occurrence merely indicated the extent of brain damage.

Poeck and Orgass (1966) demonstrated that Gerstmann's syndrome did not satisfy their criterion of 'electivity' (essentially because it was never found in a pure form), did not show a strong inner connection between its components (at least not stronger than the association of these symptoms with other symptoms external to the syndrome), and was only predictive of lesion side when at least three of the four Gerstmann's symptoms were present. This latter situation was meaningless for diagnostic purposes because in the presence of three or four Gerstmann symptoms, aphasia was very likely to be present as well. Finger agnosia and dysgraphia *per se* were not informative about lesion side, because they could also present in right hemisphere impairment. Moreover, their findings suggested that apraxia should have been included from the beginning in the cluster of Gerstmann's syndrome.

'The Gerstmann Oligarchy' dismissed

I plead guilty to having been...one of the begetters of this heresy. [...] Gerstmann had perhaps been particularly fortunate in his timing, in that his clinical observations were made at a most opportune moment in neurological history.

M. Critchley (1966)

The impact of the studies described above was such that by 1965 Critchley's former enthusiasm for Gerstmann's syndrome had completely vanished and given way to a very explicit scepticism—along with a contemptuous attitude towards Josef Gerstmann, as if he had benefited for a few years from an ill-deserved fame. In his Gowers lecture, Critchley reviewed the

history of related reports and proposed that Gerstmann's syndrome was popular in the neurologist community because it suggested a clear-cut localization of some complex mental functions.

In reviewing the clinical manifestations, however, Critchley eloquently illustrated that the neurological tests used for diagnosis were not sufficiently specific to tie the symptoms of the tetrad to selective mental functions. As a clinician, Critchley was concerned with the fact that failure in any single but demanding task involving higher order cognition might be due to very different functional deficits across patients. Moreover, Critchley criticized the variety of tests that had been proposed both by Gerstmann himself and others in the wake of the initial observations. As each of these tests draws on different instrumental cognitive faculties, a diagnostic label such as 'finger agnosia' or 'agraphia' might be attached to various disrupted cognitive mechanisms. Critchley considered that attempts to differentiate symptoms further by various tests in fact disintegrated the originally proposed symptom label, leaving little specificity to the clinical observations tested in such a way. In summary, Critchley had highlighted one of the core criticisms which had been and in the following years continued to be brought forward against Gerstmann's syndrome. None of these four symptoms corresponds to a deficit of any precisely defined function; rather, each of the symptoms could originate from a class of disabilities, and clinical tasks are ambiguous since they may detect impairments occurring in any one of the several mental operations they subtend (e.g. see Benton, 1977).

Having thus set the stage with a critical discussion of the constituting symptoms, Critchley moved on to address Gerstmann's more audacious proposal that the aggregation of symptoms was due to a *Grundstörung*, a 'basic unitary defect' as Critchley put it. Gerstmann had postulated a single cognitive process to be the common functional denominator across heterogeneous cognitive operations such as writing, mental calculation, etc. Obviously, this idea had intrigued scientists who sought to relate specific mental functions to cerebral areas and who tried to construe neuro-anatomical models of cognition based on the neuropsychological deficits observed in brain-lesioned patients. Along those lines, it was an intellectually stimulating challenge to reduce four diverse behavioural phenomena to a single common cognitive component.

Critchley reviewed the existing proposals. Gerstmann himself had hypothesized as *Grundstörung* a very specific disturbance of body schema that affected its most differentiated and vulnerable component (i.e. fingers). Others considered finger dyspraxia (i.e. loss of digital dexterity) rather than finger agnosia (i.e. impaired finger discrimination) to be the crucial underlying factor (e.g. Herrmann and Pötzl, 1926). Alternatively, a spatial disorder (e.g. either in distinguishing direction in space or in relating parts to the whole; see Conrad, 1932; Lange, 1933; Mayer-Gross, 1935; Stengel, 1944; Arbuse, 1947) was postulated to underlie the syndrome. Critchley (1966) argued against this latter explanation by pointing out that, for instance, the vertical direction did not seem to be affected in patients of Gerstmann's type. Several of the concepts listed above were grounded in the notion that both body-centred left–right distinction and calculation might bear intimate developmental or cultural relations with finger

gnosis. Although this idea is intuitively appealing, and as we will see continues to be brought forward nowadays (Mayer *et al.*, 1999; Ardila and Rosselli, 2002; Roux *et al.*, 2003), none of the proponents of such accounts ever defined or identified a precise mechanism by which a deficit in finger gnosis could lead to any numerical disturbances in brain-damaged adults (see Butterworth, 1999).

In other proposals, Gerstmann's syndrome was merely the tip of an iceberg of generalized mental impairment. According to Benton (1959), all symptoms could be interpreted to express non-specific damage to a generic process of symbolic thought. A variant of this account was 'the latent aphasia hypothesis', which Critchley found particularly attractive due to the frequent association of Gerstmann symptoms with aphasia and the dependence of clinical tests for Gerstmann's syndrome on the integrity of language.

Finally, Critchley reviewed the aforementioned studies on brain-lesioned patient populations. He noted the lack of statistical association between Gerstmann symptoms over and above that with other signs of dominant parietal lobe damage and in particular, he pointed out (i) the presence of incomplete cases and hence dissociation within the syndrome and (ii) the exclusion from 'the fellowship of the Gerstmann oligarchy' of frequently associated symptoms, such as aphasia and apraxia. In summary, he declared his scepticism with respect to this syndrome and raised all those questions, which have continued to fuel the debate ever since.

Modern neuropsychological approaches and pure cases

Essential to finger agnosia is the manner of testing for it. If a test involving the fingers is complex enough, it may reveal deficit in a variety of brain lesions. But specificity is lost. (Kinsbourne and Warrington, 1962, p. 47)

At about the same time as Benton and others were launching their critique of Gerstmann's syndrome, Kinsbourne and Warrington (1962) published a study in this journal that, at least as far as finger agnosia was concerned, challenged the latent aphasia hypothesis and dealt with the methodological objections raised by Benton, Critchley and others. The way in which Gerstmann (1924) tested the impairment that he interpreted as finger agnosia was to ask for indicated fingers to be named and named fingers to be indicated. Performance on this test could obviously be vitiated by expressive and receptive aphasia. Similarly, other procedures to test finger recognition required intact general visual orienting capabilities (e.g. Badal, 1888).

Kinsbourne and Warrington, therefore, reasoned that patterns of consistent or divergent performance across a set of tasks were more informative than performance in any single task. They argued that it was necessary to employ a variety of tests to ascertain whether a patient had an impairment that could be attributed to some relatively higher function, as for instance a hypothetical 'finger sense'. Generating a neuropsychological

profile from a battery of tests permitted alternative explanations for deficits in a single demanding task to be discarded, e.g. the presence of impairments at lower sensory or motor levels or of generic instrumental cognitive processes and/or the use of idiosyncratic strategies related to task contingencies. In addition, specificity of a given symptom could be established from failure across several different tests that targeted the same cognitive function but relied on different instrumental components.

Kinsbourne and Warrington (1962) employed tests involving either verbal or non-verbal functions in patients with elements of Gerstmann's syndrome as well as in a control group with other forms of cortical cerebral disease. They also assessed general intellectual function for each patient. They could hence test both whether tasks involving verbal functions were more sensitive than non-verbal tasks (as one could predict on the basis of Benton's 1959 proposal) and whether generalized intellectual impairment was necessary for a full Gerstmann's syndrome to occur (as proposed by Heimbürger *et al.*, 1964). Contrary to these predictions, patients with Gerstmann's symptoms had a specific difficulty in relating the fingers to each other in correct spatial sequence. Non-verbal tests proved a more sensitive index of finger agnosia than conventional language-dependent tests and gave no false positives in control patients with other forms of cortical disease, including aphasia and dementia. These observations led Kinsbourne and Warrington to put forward the hypothesis that rather than a covert iceberg of aphasia, the common denominator in Gerstmann's syndrome was a specific deficit affecting sequential ordering and the arrangement of parts in a whole (see also Kinsbourne and Warrington, 1963).

The conceptual progress in Kinsbourne and Warrington's study was that they demonstrated that the notion of a syndrome depended on (i) the comprehensiveness of examination and (ii) the theoretical background. They also illustrated the importance of studying single patients extensively. To test the claim of language impairment accounting for Gerstmann's syndrome, a rare single case with Gerstmann's syndrome but no aphasia was highly informative and theoretically far more relevant than the more frequent instances of Gerstmann's syndrome plus aphasia, which had driven the views of Benton and others. In other words, Kinsbourne and Warrington showed that the low clinical probability of 'Gerstmann's syndrome without aphasia' was insufficient and even irrelevant for answering the theoretical question of a causal link between aphasia and Gerstmann's syndrome.

A decade later, Strub and Geschwind (1974) confirmed Kinsbourne and Warrington's (1962) claims of independence between aphasia and finger agnosia by reporting a single case of Gerstmann's syndrome without aphasia—but with constructional apraxia. They also pointed out a few similar cases in the group studies by Heimbürger *et al.* (1964) and Poeck and Orgass (1966). As a consequence, aphasia could no longer be considered a necessary prerequisite for Gerstmann's syndrome, even though both were frequently associated. Another decade later, Roeltgen *et al.* (1983) published a well-documented pure case of Gerstmann's syndrome. This 62-year-old-man suffered from an ischaemic lesion in the upper part of the left angular gyrus that extended to the supramarginal gyrus and the posterior-inferior

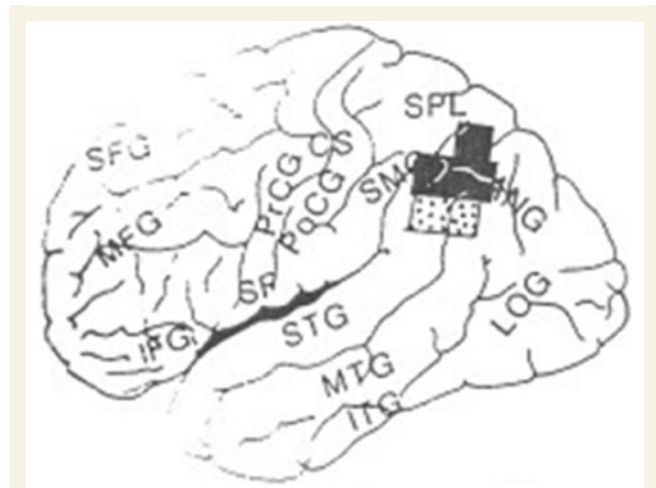


Figure 1 Plot derived from the tomographic scan. Lesions are projected onto a diagram of the left hemisphere.

ANG = angular gyrus; CS = central sulcus; IFG = inferior frontal gyrus; LOG = lateral occipital gyrus; PoCG = post-central gyrus; PrCG = pre-central gyrus; SF = sylvian fissure; SFG = superior frontal gyrus; SMG = supramarginal gyrus; SPL = superior parietal lobule; STG = superior temporal lobule. From Roeltgen *et al.* (1983; Fig. 1).

aspect of the superior parietal lobe (Fig. 1). In the acute phase, he demonstrated all four symptoms of Gerstmann's syndrome but no aphasia, anomia, alexia, constructional or ideomotor apraxia or memory impairment. Roeltgen *et al.* suggested that pure Gerstmann's syndrome might be rare because lesions are seldom restricted to a critical area.

The following year Varney (1984) described a relatively pure case of Gerstmann's syndrome in a right-handed 59-year-old man. In the acute phase after left parietal stroke, he showed marked impairment on tests of all four Gerstmann symptoms despite intact verbal skills and normal intellectual functioning. After a grand mal seizure, his neuropsychological impairment worsened and included severe non-fluent aphasia and visuo-constructional deficits. When tested in the chronic phase, 4 months after a second stroke, left-right confusion and agraphia had abated to near-normal levels, whereas acalculia and finger agnosia did not show any improvement. Varney concluded that such a differential recovery argued against a coherent syndrome that one might have taken the initial examination to suggest. Subsequently, Mazzoni *et al.* (1990) reported the case of a 44-year-old-male right-handed patient who had sustained a penetrating left parietal head wound (Fig. 2). Immediately after surgery he reported several parietal symptoms, including dyslexia, dysgraphia, dyscalculia and anomia. A few days later, dyslexia disappeared and after 1 month only slight visual memory and constructional praxis deficits were associated with Gerstmann's tetrad. Eight months later, only Gerstmann's syndrome persisted.

In more recent years, at least two other cases of pure Gerstmann's syndrome have been reported. Tucha *et al.* (1977) published the case of a 72-year-old right-handed woman with

pure Gerstmann's syndrome caused by a tumour comprising the left angular gyrus, supramarginal gyrus and underlying white matter (Fig. 3). In the absence of aphasia, constructional apraxia or other neuropsychological impairments (e.g. in intelligence, memory and attention), she demonstrated all four Gerstmann symptoms. In addition to finger agnosia, the patient showed pathological results in testing for toe agnosia, prompting the authors to propose the concept of 'digit agnosia'. Finally, Mayer *et al.* (1999) published perhaps the most detailed description of pure Gerstmann's syndrome (including toe agnosia) in a 59-year-old right-handed male with a focal lesion in the subangular white matter (Fig. 4). More extensive testing of numerical abilities in the same patient was carried out and reported in a successive paper by Martory *et al.* (2003).



Figure 2 CT scan mapping of the lesion. Initial lesion area is delimited by the continuous line and oedema by the dashed line. The dotted area shows the lesion on a CT scan taken 8 months later. From Mazzoni *et al.* (1990; Fig. 4).

Rehabilitation of the syndrome but persistence of the enigma

'The contention that Gerstmann's syndrome can occur as a combination unaccompanied by other behavioural deficits, such as anomia, alexia, and constructional apraxia, is fully supported.

A. Benton (1992)

Even before these last two pure cases were reported, the relevance of these new studies for the debate on Gerstmann's syndrome was not ignored by Benton. In 1992, he published a commentary with an updated view on this matter: 'Gerstmann's syndrome, either in 'pure' form or with other deficits that can be attributed to posterior parietal disease, is clinically meaningful in that it points to the probability of the presence of a lesion in this area. It is a tribute to Josef Gerstmann's diagnostic acumen (or his imagination) that he drew this inference based on his own inadequate patient sample' (Benton, 1992, p. 447). Acknowledging defeat did not come easily though and, as in his attack on the primacy of Gerstmann's neuropsychological observation, Benton continued questioning whether Gerstmann really deserved a syndrome to be named after him, as various other symptom combinations can be observed in posterior parietal lobe lesions and would hence deserve the syndrome status at least as much as Gerstmann's. 'It seems evident that the prominence of Gerstmann's syndrome is, as Critchley (1966) suggested, a matter of historical accident. Because it occurs so rarely in pure form, Gerstmann's syndrome may in fact be less useful as a diagnostic indicator of focal parieto-temporo-occipital disease than are some other symptom combinations.' (Benton, 1992, p. 447).

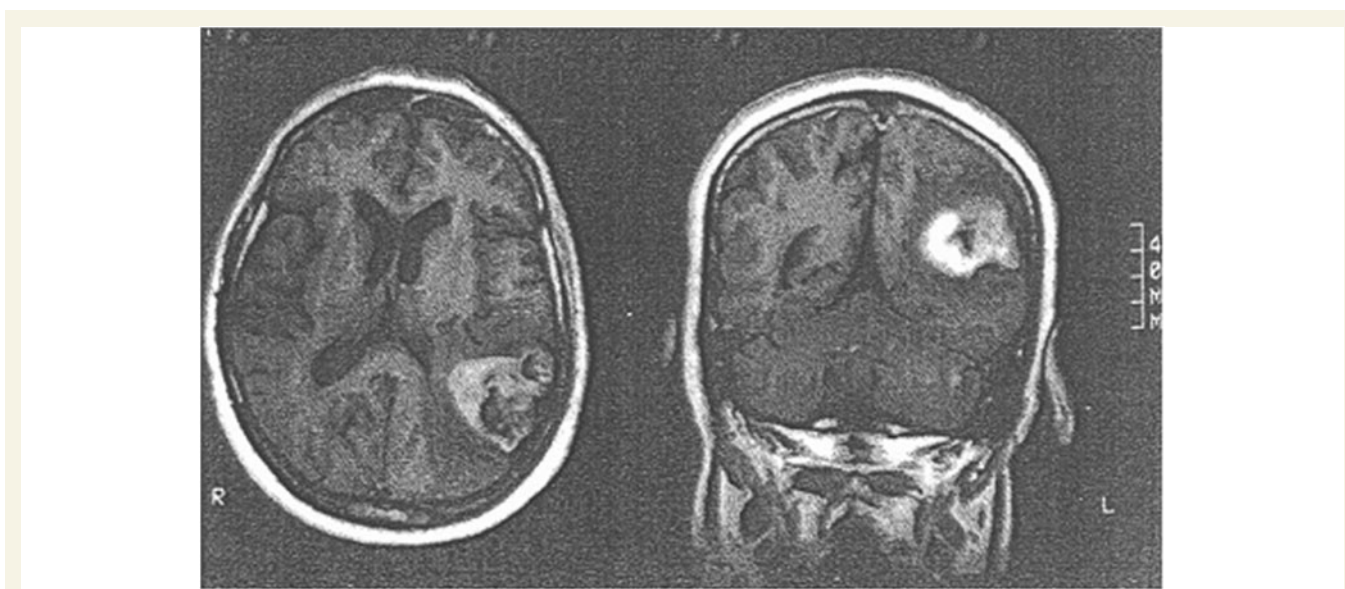


Figure 3 Contrast-enhanced T₁-weighted MRI in transverse and coronal orientation showing a left parietal tumour with perifocal oedema. From Tucha *et al.* (1997).

hypothesis, they retrospectively analysed neuropsychological profiles of 38 patients with probable Alzheimer's disease. Gerstmann symptoms were assessed by scores in finger naming, serial seven subtractions, sentence writing and a test of right–left orientation. A hierarchical cluster analysis on all tests of parietal function did not reveal Gerstmann symptoms to stand out as a distinct syndrome. The unavoidable shortcoming of this interesting approach is that the psychometric tests might have assessed overall functionality of quite different parietal lobe networks whereas damage to a single essential node, if it was shared between these networks, might be sufficient to account for the syndrome.

More conclusive findings with respect to the question of a shared neural substrate have been provided by studies using electrical stimulation in patients who were submitted to neuropsychological testing during awake open-brain surgery. Morris *et al.* (1984) reported the case of a 17-year-old male with intractable partial seizures. Stimulation of different loci in the posterior-perisylvian region resulted in several parietal symptoms. In particular, the four Gerstmann symptoms could be produced by stimulation within a relatively small patch of cortex in the region of the left angular gyrus—but never from a single electrode position. Moreover, stimulation at these sites was not associated with any extraneous symptoms which could be elicited from stimulation of more inferior sites, e.g. alexia, anomia and constructional apraxia (Fig. 5). These findings suggested that a fairly focal lesion in the region of the left angular gyrus might indeed result in a pure Gerstmann's syndrome.

A similar, by and large confirmatory study in a series of patients with brain tumours and with finer spatial sampling was reported more recently. Roux *et al.* (2003) found sites in the left angular gyrus where electrical stimulation produced interference in calculation, finger recognition and writing. Finger agnosia and acalculia sites were also found elsewhere, such as in the supramarginal gyrus or close to the intraparietal sulcus, which provides a

substrate for the observation that Critchley found troubling, namely that following lesions of the left posterior parietal lobe isolated symptoms of the Gerstmann tetrad could occur in dissociation. Moreover, even within a single domain such as calculation, electrostimulation studies have produced a rather fine-grained picture regarding the neural sites required for different types of calculation (Duffau *et al.*, 2002). Such reports provide a basis for clinical dissociations that have been observed within the calculation domain and suggest an even more complicated picture of the underlying functional cortical architecture.

A hypothesis instead of a conclusion

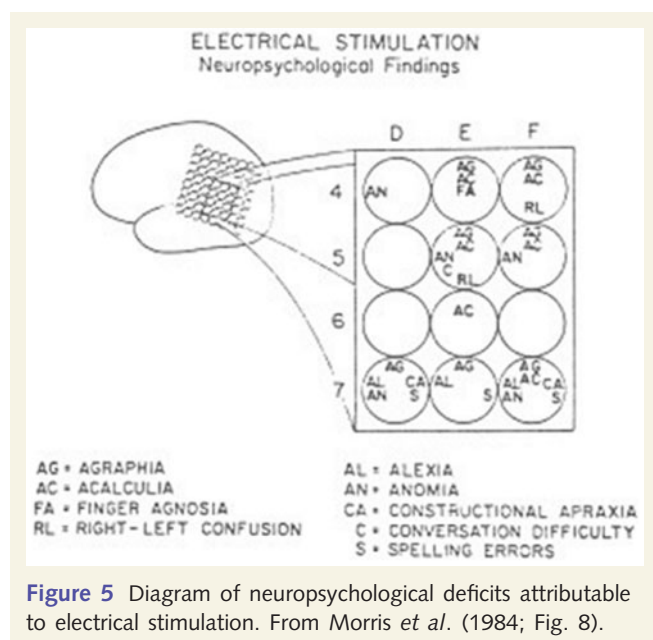
Nothing pays except that which gives some new suggestion.

Gowers (cited from Critchley 1966)

Gerstmann had observed the co-occurrence of four symptoms and had proposed that this association was not random but presented a meaningful syndrome. He argued that this syndrome had a localizing value and that its elements were bound together by a common functional denominator. In summarizing this review we must acknowledge the sceptical but astute discussion of these claims that Critchley provided more than 40 years ago. Quite tellingly, Critchley referred to Gerstmann's syndrome not as an artefact, as others had, but as an enigma and concluded 'Whether the Gerstmann saga has been closed is a matter of opinion' (Critchley, 1966; p.196).

From today's perspective with the abundant use of brain imaging technology it is important to put Critchley's discussion into perspective. At his time, neuropsychological syndromes were not only scientifically interesting but actually clinically important in that, as with other neurological signs, they often provided the only clue for localizing the site of brain damage. In that sense, Gerstmann's syndrome was practically meaningless because it almost never occurred in a pure form and when it was associated with other signs, these latter were in themselves informative enough about the lesion site. Nonetheless, Critchley had personally seen enough patients with parietal lobe damage to realize that there was some specific information hidden in Gerstmann's clinical observations. He sympathized with the interpretation of early critics like Schilder, who had considered these clinical observations to reflect 'a cluster of symptoms brought about by mere propinquity of pathology' (Critchley, 1966; p. 192). In essence, these intuitions have been confirmed since. The more recent evidence from the last 40 years that we discussed here was the result of a conservative selection of theoretically relevant cases in which Gerstmann's syndrome manifested in a relatively 'pure' form; i.e. without aphasia, constructional apraxia and verbal or visual memory disturbances. The few cases of pure Gerstmann's syndrome reported in the literature have confirmed that these clinical signs can manifest together without further neuropsychological deficits.

Regarding the localizing value, these case reports have also confirmed Gerstmann's statement that the syndrome is associated



with damage to the dominant parietal lobe. Although some claims have been made in the literature of Gerstmann's syndrome after lesion to other parts of the brain, in particular the left frontal lobe, we found none of these cases to fulfil the diagnostic criteria for a full but pure syndrome convincingly (for a detailed discussion of these criteria see the clinical appendix). Neuropsychological studies during open brain surgery have also confirmed a relation between the Gerstmann tetrad and left parietal cortex and have, moreover, demonstrated a certain degree of proximity and overlap of those cortical sites where electrical stimulation can elicit these symptoms: empirical evidence in favour of the aforementioned 'propinquity'. Even without a single shared cortical or functional substrate, one might speculate that the association of symptoms in Gerstmann's syndrome is not incidental but meaningful (see discussion in Ardila and Rosselli, 2002). If anatomical neighbours in cortex are functional relatives in cognition, then spatial proximity of different functions could indicate that they have emerged from common precursors and differentiated into separate specializations. Yet, our current knowledge about the neural bases of cognition and specifically about parietal lobe function does not include viable concepts for a functional unit that would explain Gerstmann's syndrome.

Instead of continuing the hunt for a neurocognitive account of Gerstmann's syndrome, however, we would like to conclude with an alternative hypothesis. We believe that the reason Critchley chose to call Gerstmann's syndrome enigmatic was because its symptoms lack a functional logic that would withstand more rigorous examination. We agree with this view and therefore propose that there is no such functional logic but a structural logic instead. In other words, we suggest that Gerstmann's syndrome does not (or if so only indirectly) reflect the functional architecture of cognition but rather the functional architecture of the brain and that it results from disconnection.

At the same time as Critchley was raising critical questions about this clinical syndrome and as Warrington and collaborators were devising methodological approaches to provide answers, another innovative concept was published in this journal as well. Geschwind's proposal of cortical and subcortical disconnection as a pathophysiological mechanism proved very influential and has seen a recent renaissance thanks to modern neuroimaging techniques permitting an at least approximate non-invasive charting of fibre tracts in the human brain *in vivo* (e.g. see Geschwind, 1965a, b; Catani and Ffytche, 2005; Catani and Mesulam, 2008). The classical approach to describing disconnection syndromes has been to relate a clinical phenotype to the functional consequences of damage to a single, usually long-range fibre tract. For such a classical disconnection syndrome the clinical syndrome would stay much the same wherever along that fibre tract the disruption occurs. However, white matter tract anatomy, especially in regions underlying heteromodal cortices as in the parietal lobe, results from a complex interweaving of fibres travelling over various distances and in various directions. Even diffusion tensor tractography studies that have explicitly addressed this 'crossing fibre' problem in their analysis have nonetheless focussed on the extraction of long-range fibre connections (Schmahmann *et al.*, 2007).

Critchley referred to Gerstmann's syndrome in the context of the 'complex symptomatology now associated with lesions of the

parieto-temporo-occipital crossroads' (Critchley, 1966; p. 197). Expanding the classical disconnection concept we, therefore, propose that pure Gerstmann's syndrome is the result of disconnection of such 'crossroads' in the parietal white matter. We postulate that the resulting disconnection affects at least partially separate cortical networks underpinning the four cognitive domains. The innovative aspect of this proposal is that different from classical disconnection syndromes, only a fairly unique lesion site could then yield a given syndrome because the latter results from a conjunction of damage to several distinct but crossing fibre tracts. While this formulation assigns great importance to the precise anatomical lesion locus in determining clinical symptoms, it is not at odds with the view that distributed large-scale networks underpin cognitive operations as those that fail in Gerstmann's syndrome.

The existing functional neuroimaging literature is only moderately helpful with respect to our hypothesis because the majority of relevant activation studies have not targeted the precise counterpart of Gerstmann symptoms but more general sensorimotor or cognitive aspects of writing and body schema or spatial transformations (e.g. Menon and Desmond, 2001; McCrea, 2007; Creem-Regehr *et al.* 2007). Moreover, these studies were conducted as group analyses with spatial smoothing, which in light of the aforementioned electrostimulation findings might readily generate a false positive impression of a shared cortical substrate across different functions. However, along with lesion studies the existing functional neuroimaging literature illustrates that many more domains than just the four affected in Gerstmann's syndrome recruit regions of left parietal cortex (Simon *et al.*, 2002). Accordingly, extensive damage to the dominant parietal lobe readily results in Gerstmann's syndrome but it also results in other cognitive deficits that make it virtually impossible to test for Gerstmann's syndrome in an uncompromised way. The most elaborate body of literature with respect to a single Gerstmann symptom can be found for mental arithmetic (Menon *et al.*, 2000; Gruber *et al.*, 2001; Zago *et al.*, 2001; review in Dehaene *et al.*, 2004). A meta-analysis of functional neuroimaging studies has identified three nodes related to numerical cognition in the parietal lobe, with only one restricted or at least strongly lateralized to the dominant hemisphere, namely in the angular gyrus (Dehaene *et al.*, 2003) where cortical lesions can result in pure acalculia. Yet, the existence of several cortical nodes for numerical cognition even within a single lobe illustrates that complex mental operations cannot be reduced to activity of single brain 'centres' even if different cortical regions probably perform different computations and hence differ in their precise functional response properties. The latter aspect can then explain the variety of clinical phenotypes that have been observed for disturbances of calculation (Ardila and Rosselli, 2002).

Our hypothesis regarding Gerstmann's syndrome posits that an appropriately situated white matter lesion, e.g. disrupting connections between intra-parietal and angular cortex, is likely to impair calculation performance. Similar considerations probably also hold for the other domains that fail in Gerstmann's syndrome. We therefore propose that the most parsimonious explanation for a pure case of Gerstmann's syndrome should be a disconnection of neighbouring but non-identical parietal regions due to a lesion in

the underlying white matter. We note that similar ideas have already been formulated in the past (Hrbek, 1979). We also note that this hypothesis is compatible with the best available lesion imaging of a pure case (see the schematic in Fig. 4).

To explore this possibility further, we hence recently submitted our disconnection hypothesis for Gerstmann's syndrome to empirical testing by functional and structural neuroimaging of parietal lobe organization in the intact human brain (Rusconi *et al.*, 2009b). For each of the four symptoms we designed mirroring cognitive tasks and control conditions that were meant to activate those functions that fail in Gerstmann's syndrome. Although in all four domains probed this way we observed several sites of robust left parietal activations, we could not identify even a single region in any of the subjects that showed a consistent overlap across all four domains. This result is in accord with the aforementioned findings from electrostimulation during open brain surgery (Fig. 6). However, when using the cortical activation patterns in the four domains as seed points for fibre tracking in diffusion tensor images we found that fibre tracts from all four domain-related networks consistently travelled through a locus of white matter that is consistent with the lesion reported in Fig. 4, as well as all other reports of pure Gerstmann's syndrome that included lesion images. We simulated the disconnection effect from lesions at various white matter positions and observed that even slight displacements yielded vastly different cortical disconnection patterns (Fig. 6). Together, these findings outline a structural and functional organization of the left parietal lobe that makes it plausible that Gerstmann's syndrome can occur in isolation, but also why this is such a rare clinical event. As this finding was fairly

robust in terms of stereotactic coordinates after normalization to standard space, future patient-based studies can now specifically interrogate the occurrence of the Gerstmann tetrad in relation to whether a lesion covers this very circumscribed region of parietal white matter. Such a study would then provide the final answer to the long-standing enigma.

Appendix I

Clinical semiology and neuropsychological testing of Gerstmann's syndrome

The operational definition of the symptom to which Gerstmann attributed paramount importance, finger agnosia, has evolved throughout the years. In his first report, Gerstmann (1924) described a deficit related to the use of finger names but by 1957 he had added a confusing variety of related phenomena. The number of testing procedures grew exponentially and became more and more challenging: from finger naming to imitation of the experimenter's gestures, from pointing to any particular finger on request to the use of drawings and mannequins, with or without sight and speech. In accordance with Gerstmann's first observations, recent cases of pure Gerstmann's syndrome were impaired on finger naming, in the absence of autotopagnosia and aphasia. Interestingly, Morris *et al.* (1984) found a double dissociation between the two tasks they used to

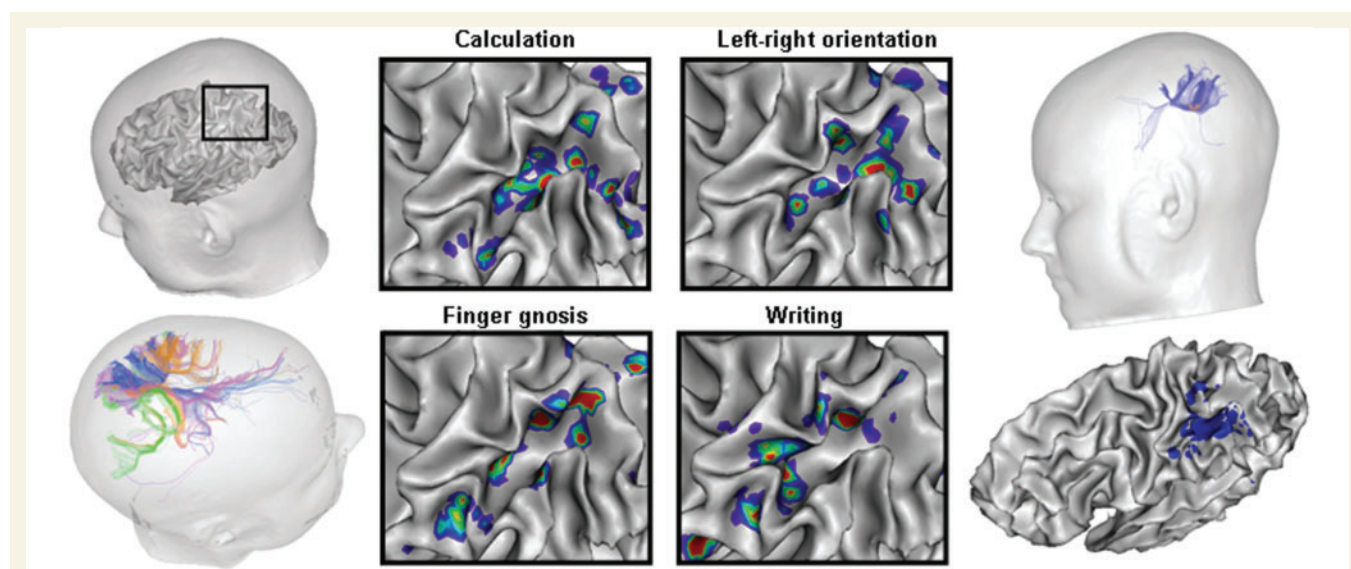


Figure 6 Functional and structural imaging results of left parietal lobe organization in the human brain (illustrated in a single healthy subject and modified from Rusconi *et al.*, 2009b). The upper left-hand picture provides a rendering of the left hemisphere cortical surface for reference. The four middle panels show functional activation results superimposed onto a left parietal zoom of this surface rendering. Activations are from experiments separately probing the four domains as labelled in the figure. These different task-related activation zones do not show significant overlap across all four domains. Taking these activation foci as seeding points permits tracking fibres connected with these cortical zones, as shown in the lower left-hand panel by different colours for the different domains of the tetrad. The upper right-hand panel tracks fibres from a bottleneck in parietal white matter and the lower right-hand panel shows the disconnection effect from such a 'virtual' lesion on the cortical surface. For more details see Rusconi *et al.* (2009b).

test for finger agnosia: stimulation at E4 (within the angular gyrus) interfered with the task requiring the patient to hold up a particular finger on verbal command (e.g. index) when requested but not with the task requiring to name specific fingers, whereas at electrodes D7, E5 and D4 the patient could not name his fingers but could hold up one when asked. Roux *et al.* (2003) interfered both with finger naming and with pointing to the experimenter's fingers on verbal requests, when stimulation was delivered over the angular gyrus. Some of these finger agnosia sites were common with or close to naming—or reading—interference sites (Cases 3–6); nevertheless in two patients (Cases 1 and 2) there were no related language sites close to the angular gyrus.

By itself, impairment of finger naming cannot discriminate between finger anomia and finger agnosia, and must be integrated with some other tests of non-verbal type. One such test is the Two-Point Finger Test proposed by Kinsbourne and Warrington (1962), in which the fingers are touched in two places, and the patient is asked to judge whether the two touches are on the same or two different fingers. The patient's answer, therefore, is still verbal but is a simple 'same' or 'different' judgment and does not require naming any finger. In the In-Between Test (Kinsbourne and Warrington, 1962) two fingers are touched simultaneously and the patient is asked to report how many fingers are in-between the ones that are being touched. This test, therefore, requires a small numeral as a response (0, 1, 2 or 3 are the response alternatives), a characteristic that renders it less than suitable as a unique test for assessing finger gnosis in the context of parietal disease. In the presence of impaired number processing, a deficit in the In-Between Test might simply constitute a false positive (but see Rusconi *et al.*, 2009a, Experiment 3, for the possibility of detecting structural finger processing in a modified version of the In-Between Test).

A persistent finding across different protocols of testing, is that the external fingers (thumb and little finger) appear to be more resistant to impairment than the three medial ones (index, middle and ring; e.g. Kinsbourne and Warrington, 1962). This might suggest that eye-sight could facilitate the correct execution of task for finger gnosis. Critchley (1966) noted that in addition to their relative position on a hand, individual fingers may also be distinguished from each other by some characteristic signs as a stain of nicotine, the impression of a ring, a peculiar deviation from a straight line, and so on. Accordingly, tests allowing the patient to use eye-sight seem to be less sensitive to impairment than tests without sight (see Tucha *et al.*, 1997; Mayer *et al.*, 1999). An interesting alternative is the task described by Tucha *et al.* (1997), who touched a finger of one hand and asked their patient to move the corresponding finger on the other hand. This test permits to discard finger anomia and any other verbal influence; moreover, when a suitable control task is employed (e.g. by asking the patient to move the same finger that has just been touched by the experimenter) it is possible to discard low-level sensori-motor impairments.

Left-right confusion was first described by Gerstmann as a tendency to mix up left and right in one's own body space. Subsequently, tests involving either an experimenter facing the patient or two-stage commands (i.e. point with your left hand to your right knee) were found to be more sensitive. Indeed,

two tasks have been used consistently with each of the pure cases: distinguishing left from right on the patient's own body and distinguishing left from right on the experimenter's body. It appears that not all the patients have problems in distinguishing left from right on their own body (a task for which many ready-made alternative strategies may be available to individuals, such as exploiting body signs and/or motor automatisms typically performed with the dominant hand)—which renders this task essentially useless. Where patients constantly fail, however, is in discriminating left from right on the examiner's body and in carrying out two-stage commands related to their own body. At electrodes E5 and F4, Morris *et al.*'s (1984) patient confused commands such as 'Put your right hand on your left ear'.

Acalculia in Gerstmann's patients was probably the least clear of all the symptoms. Ordering figures according to magnitude, counting backwards, enumerating the odd or the even numerals, acalculias of spatial and dysphasic origin, but also failures in the understanding of arithmetical principles were suggested by Critchley (1966) to be part of the syndrome. Apart from one pure case (Meyer *et al.*, 1999; Martory *et al.*, 2003) with a profound impairment in several numerical tasks, the most consistently reported finding concerns impaired arithmetic processing, which can be more evident in complex calculations. Morris *et al.* (1984) tested their patient's calculation abilities with serial subtractions by 7, whereas Roux *et al.* (2003) employed additions with two digit numbers. Roux *et al.* (2003) found that angular gyrus sites causing 'acalculia' were common to other functions, but they could also be calculation-specific (at least one specific site was found for each patient, which allowed them to discard the hypothesis of a primarily linguistic impairment). Rusconi *et al.* (2005) found that transcranial magnetic stimulation over the left angular gyrus interfered with a magnitude matching task between single Arabic digits but not with parity matching or arithmetic priming (implying spared automatic retrieval of the result of additions and multiplications between single-digit numbers).

Different impairments were also included under the label of *agraphia*, such as typically dyspractic and dysphasic symptoms. Patients could be either able or unable to copy correctly and showed difficulties either in writing single letters or in the spatial arrangement of entire words. Critchley (1966) was very sceptical about claims for the absence of aphasia in these patients and suggested that they might actually show a form of minimal or subclinical aphasia.

More recently, it has been claimed that *agraphia* of Gerstmann's type is due to a relatively peripheral impairment (Mayer *et al.*, 1999), since it is limited to handwriting. But how peripheral is it? Does it affect individual elements such as letters, or rather higher level groupings such as words and sentences? Are these patients still able to copy? In any case, only the output system is impaired since none of the pure cases presented alexia or any difficulties with naming from either written or oral spelling. The most common errors include both peripheral motor and more central letter/word-form deficits. Roeltgen *et al.*'s (1983) patient's *agraphia* was simply described as 'sloppy handwriting, with frequent substitutions, yielding almost unintelligible writing' (p. 47). Interestingly, no right arm motor impairment was noted. Varney's (1984) stroke patient not only had severe *agraphia*,

affecting the copying of words, but sensori-motor deficits of the right arm as well. Left-hand writing was totally unintelligible. With his right hand, he made spelling errors when writing words to dictation, was able to write down single letters in a series (the alphabet) but failed at times when asked to write single letters to dictation.

Mazzoni *et al.*'s (1990) patient was able to copy words but was extremely slow when writing to dictation and made elisions, substitutions of letters, wrote the letters *n* and *m* with too many vertical stems, and at times in the middle of a word used block letters to replace normal handwriting. Tucha *et al.*'s (1997) patient did not show any primary motor impairment, nonetheless she produced omissions, additions and substitutions both when she was asked to write words/sentences to dictation and when she was asked to copy words. According to Mayer *et al.* (1999; see also Zesiger *et al.*, 1997) their patient demonstrated a peripheral agraphia with some disturbance of the allographic level and a strong deficit of the motor graphic pattern. He showed impaired motor representations for some letters and digits, and made letter omissions in the middle or at the end of long words. Crucially, his agraphia was not modulated by syntactical class, orthographic regularity, degree of imagery or frequency of the stimuli. Morris *et al.*'s (1984) agraphia from stimulation over sectors E4 and F4 varied, from an inability to write virtually anything to an occasional misspelt word or substitution. The patient's rapid alternating finger movements were intact during stimulation at those sites. In Roux *et al.*'s (2003) patients, agraphia during stimulation consisted of repeated words, interrupted writing, irregular letter shape or unintelligible handwriting.

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