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Gerstmann Meets Geschwind: A Crossing (or Kissing) Variant of a Subcortical Disconnection Syndrome?

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Abstract

That disconnection causes clinical symptoms is a very influential concept in behavioral neurology. Criteria for subcortical disconnection usually are symptoms that are distinct from those following cortical lesions and damage to a single, long-range fiber tract. Yet, a recent study combining functional magnetic resonance imaging and fiber tracking concluded that a focal lesion in left parietal white matter provides the only tenable explanation for pure Gerstmann's syndrome, an enigmatic tetrad of acalculia, agraphia, finger agnosia, and left-right disorientation. Such a lesion would affect not only a single fiber tract but crossing or "kissing" of different fiber tracts and hence disconnect separate cortical networks. As fiber crossing is prominent in the cerebral white matter, the authors propose an extension to the subcortical disconnection framework that opens the door to ascribing a more diversified clinical phenomenology to white matter damage and ensuing disconnection than has been the case so far.

Keywords

functional and clinical neuroanatomy, structure–function relationships, functional neuroimaging, diffusion tensor imaging, tractography, human brain

Of all organ systems, the central nervous system is the one in which damage yields the greatest variability of symptoms. This wide range of possible symptoms reflects that the functional anatomy of brain and spinal cord is far more differentiated than that of any other organ. Medical students groaning under the burden of ingesting this knowledge about the brain are compensated for their efforts once they realize that damage to cortex, basal ganglia, cerebellum, and brain stem produces different and fascinating functional deficits. Moreover, these deficits can usually be demonstrated by fairly simple clinical tests and permit an accuracy of lesion localization that mere physical examination cannot attain for any other internal organ (Duus 1998). Historically, the systematic scientific study of such clinicopathoanatomical correlations started in the 19th century with the work of Broca, Jackson, Wernicke, and others (reviewed with an emphasis on language in Roth 2002). The thrust of this endeavor was toward an anatomically differentiated account of brain function and countered competing holistic views.

The richest repertoire of clinical deficits has been related to cortical damage. The discipline of neuropsychology emerged in this context and seeks to understand disturbed cognitive function. Even to date, neuropsychologists continue to describe novel patterns of fine-grained dissociations where patients fail when facing one very selective functional challenge yet performance in other, even closely related domains remains unimpaired. Historically, lesion studies provided the first line of access for understanding the neural basis of cognitive deficits and reached an early climax in the localizationist work for instance of Kleist (1934, see Fig. 1). Since then, lesion studies have been complemented and considerably refined first by electrostimulation studies during neurosurgery (e.g., Mandonnet

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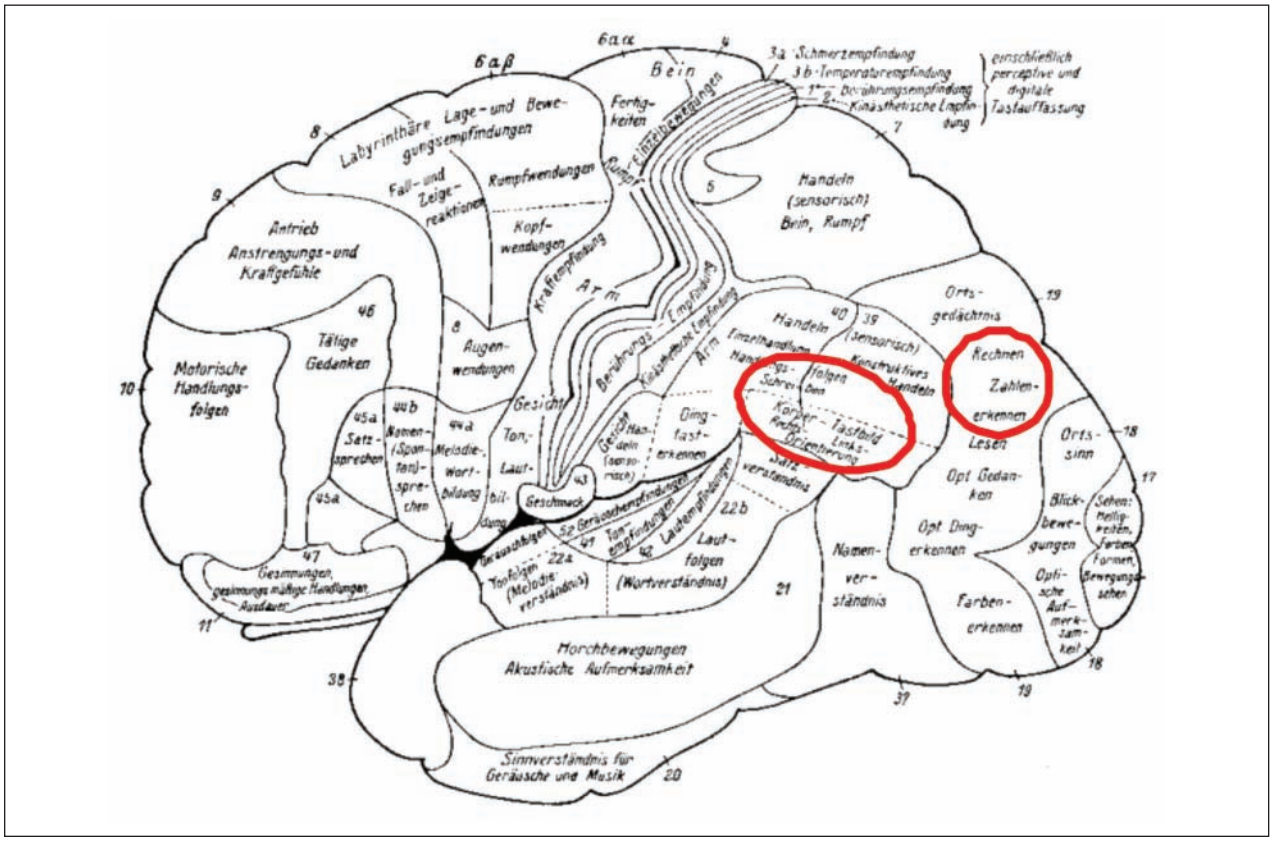

Figure 1. Cortical localization of functions in the left hemisphere according to Karl Kleist. The red circle and oval were inserted to highlight regions that would be implicated by Gerstmann's syndrome and include writing (Schreiben), body scheme (Körper-Tastbild), within which finger agnosia might be situated, right–left discrimination (Rechts-Links Orientierung), and calculation (Rechnen), as well as semantic number recognition (Zahlenerkennen). Adapted from Kleist (1934).

and others 2010 for review) and then by neuroimaging techniques that precisely locate lesions in vivo and permit voxel-based lesion-symptom correlations (Bates and others 2003). And even more recently, noninvasive techniques have permitted mapping task-associated neural activations by neuroimaging (e.g., Bandettini 2009) and creating transient virtual cortical lesion by transcranial stimulation (e.g., Sandrini and others 2011 for a recent review).

Using these tools, a majority of research both in clinical and healthy populations has aimed at demonstrating dissociations at the behavioral level and specialization at the neural level. The bias toward deducing functional segregation from such behavioral or anatomical observations is intimately linked to a bias toward assigning function exclusively to gray matter structures and cortex in particular. In part, this bias may have originated from the fact that many of the older lesion studies, as in Kleist's case, were based on clinical populations with penetrating head injury or because the cortical surface was accessible to study by electrostimulation during open brain surgery. It is probably fair to say that the assignment of function to cortex was also driven by the huge progress that Brodmann and others had made in cortical parcellation whereas differentiation of white matter tracts in the human brain was much less advanced and remains so to date. More recently, the fact that functional neuroimaging records activations at the site of synapses but cannot directly map the routing of neural activity through white matter may have further perpetuated the bias of assigning function to gray matter.

Even at the onset of cortical localization studies, however, neurologists such as Wernicke were aware of the importance of communication between different and distant neuronal populations. Long-distance communication in the brain relies on fibers running through the white matter. The notion of communication is not at odds with functional specialization and not even at odds with segregation of function. However, what is at odds with the notion of segregation (but not functional specialization) is the actual pattern of structural connectivity that fibers form in the brain's white matter and that underpins communication between gray matter structures (Hagmann and others, 2008; see Fig. 2). For a more exhaustive discussion of this pattern and of why it is optimal from a

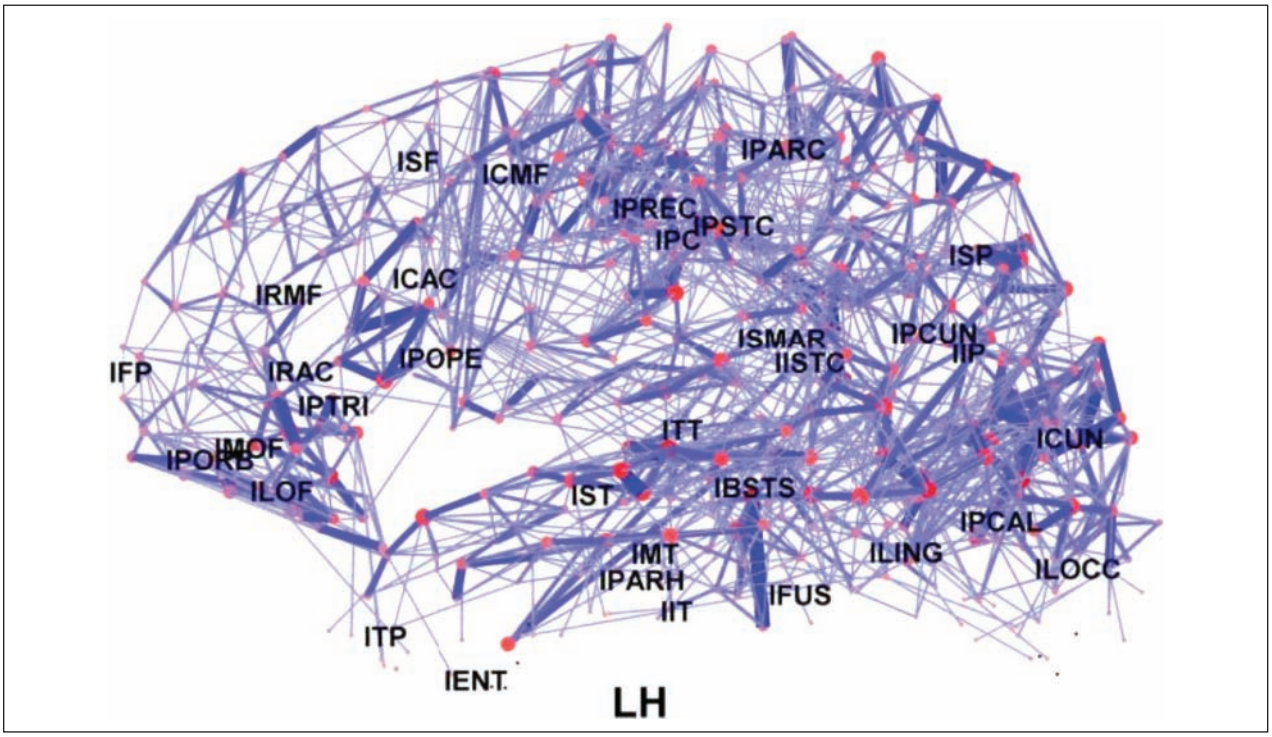

Figure 2. Structural connectivity matrix in the left hemisphere of a single human subject (lateral transparent view). Labels refer to anatomical subregions that are indicated by red dots and their connections as derived from diffusion spectrum imaging (DSI) indicated in blue. Size of dots and width of lines refer to computed indices of degree of connectedness and strength of connection, respectively. For technical details, the reader is referred to the original publication. From Hagmann and others (2008), with permission.

theoretical perspective, we refer to dedicated explorations of this topic (Tononi and others 1994; Bullmore and Sporns 2009). In our present context, it is merely important to point out that structural connectivity involves divergence (of projections from individual brain areas) and convergence (of projections onto individual brain areas). This structural connectivity pattern therefore injects integrative properties into the system that are not compatible with strict functional segregation. Yet, contradicting a common misconception, these integrative properties do not stand in the way of functional specialization where each cortical area and subcortical region serves one or maybe even several unique and different purposes. One indirect indication of functional uniqueness comes from structure in that each cortical area can be characterized by a fingerprint of its local architectonic properties (Zilles and Amunts 2009). Although we stated that fiber tracts provide the substrate of integrative properties, this view does not preclude a similar degree of functional specialization within white matter as within gray matter structures. Just as cortical areas can also be individually labeled by their long-range connectivity fingerprint (Modha and Singh 2010) instead of their local anatomical features, each fiber tract is distinct by virtue of the set of cortical or subcortical regions it connects.

Our current knowledge of the functional neuroanatomy of white matter, however, is still much less refined than our understanding of cortical specialization. Three overall classes of long distance fibers are generally distinguished according to the structures they connect: projection, commissural, and associative fibers (for a more differentiated classification, see Schmähmann and Pandya 2008). From lesion studies we know some more detailed aspects of the functional neuroanatomy of human white matter, but the bulk of this knowledge is confined to projection fibers. For instance, it has been well known that a similar somatotopic pattern as in the primary motor cortex can be demonstrated along the pyramidal tract that descends through the corona radiata and the internal capsule into the brainstem and spinal cord (for more fine-grained recent neuroimaging, see Verstynen and others 2011). To some extent, this greater knowledge about primary tracts parallels our understanding of cortical function, which is also more fine-grained for primary than secondary or associative brain areas.

But when 19th century neurologists as Wernicke and Dejerine started thinking about disturbances of neuronal communication in the brain, they were not referring to communication along primary afferent or efferent systems but rather to disturbances in perception-to-action

transformation. They ascribed such disturbances to a disconnection between the primary systems dealing with afferent information and those producing efferent output. Yet, despite this early "network view" at the functional level, these researchers were not very much preoccupied with differentiating whether the deficits from such disconnection were due to lesions in white matter fiber tracts or heteromodal cortical gray matter. This is understandable, because the experience from primary cortical areas and the associated projection fibers showed that both gray and white matter damage can yield similar clinical deficits as in hemiparesis or hemianopia. Hence, it did not appear immediately compelling to think about a distinction between disconnection due to damage of cortical relay zones and selective disruption of a fiber tract. Even when Geschwind developed his concept of disconnection syndromes almost half a century ago, he did not very explicitly emphasize a distinction between disconnection due to gray or white matter lesions (Geschwind 1965a, 1965b). But Geschwind proposed several now widely accepted disconnection scenarios that complemented the classical disconnection syndromes (for a historical review, see Catani and ffytche 2005).

If the disconnection concept originally was functionally rather than anatomically specified, what then were the criteria to suggest that disconnection played a role in a given clinical syndrome? In general terms, neurologists analyzed whether clinical observations showed associations or dissociations of symptoms. Although systematic association of a set of symptoms across patients indicated shared or at least neighboring neural substrates, dissociations of symptoms across patients were considered evidence of segregated processing of information—or segregated routing. From an anatomical perspective, dissociations hence remained ambiguous and were both the driving force for proposing cortical specialization and also the crucial argument each time a deficit was suggested to be caused by disconnection (Catani and Mesulam 2008). In other words, because the disconnection concept originally did not discriminate between a processing relay station and a specific routing of information through white matter, a selective syndrome defined by way of dissociation (a deficient single function) was compatible both with cortical or white matter damage. Conversely, the systematic association of symptoms into a syndrome has generally been taken as evidence that all symptoms are tied together by failure of a single hidden function (or biological process). Together with the aforementioned bias toward assigning function to cortex, syndromal association has therefore inspired a search for corresponding cortical functional specialization or colocalization but not for disconnection.

There are obvious factual reasons to revisit this overall framework: The first is that because the structural connectivity of cortical areas involves convergence and divergence, the effects of damage to a cortical area should be distinct from those of damage to any one of the incoming or outgoing fiber connections. This difference should become greater the higher the degree of such convergence and divergence, and the postulate therefore remains compatible with our earlier comments on hemiparesis and hemianopia, where lesions of primary cortex or projection tract yield similar effects. The second reason is that the effects of structural disconnection should not be confined to dissociable single clinical symptoms but may readily involve associations of several different symptoms, which in turn alleviates the need to seek a counterpart of cortical functional specialization to account for such associations. The reason for this postulate is that different from cortical architecture, where on a two-dimensional surface contiguous areas are separated by fairly sharp boundaries, different fiber tracts become highly intermingled when traveling through the white matter volume (see Wedeen and others 2008; Fig. 3). It is therefore conceivable that even a small subcortical lesion could damage several different fiber tracts, thereby disconnecting separate cortical networks and hence associating the related clinical consequences.

Over recent years, especially the first postulate has already transpired into reformulations of the disconnection concept by distinguishing between effects from lesions in cortical or subcortical gray matter structures and in white matter (Catani and ffytche 2005). Even contemporary accounts of disconnection, however, highlight similarities between the effects of gray and white matter lesions (Schmähmann and Pandya 2008). In line with this view, it has recently been shown that spatial hemineglect, which has been classically related to cortical function but is found after lesions either in temporoparietal or frontal cortex, may originate from long-distance disconnection between these areas (Thiebaut de Schotten and others 2005). And in recent years, sophisticated imaging methods have related even classical disconnection syndromes as pure alexia (defined by dissociation from preserved graphia) to lesions as diverse as in the corpus callosum (Molko and others 2002) and the ventral visual stream (Gaillard and others 2006). At the same time, these studies have illustrated the neural bases for differences in the precise clinical manifestation of pure alexia as a function of lesion site.

The second theoretical postulate we mentioned above has received less attention so far. Disconnection syndromes that result from focal lesions in white matter have generally been accepted under the following premises: A single, long-distance fiber tract is damaged and this results in the cortical source area turning partially ineffective and the target area becoming partially dysfunctional. It is important that these cortical areas be

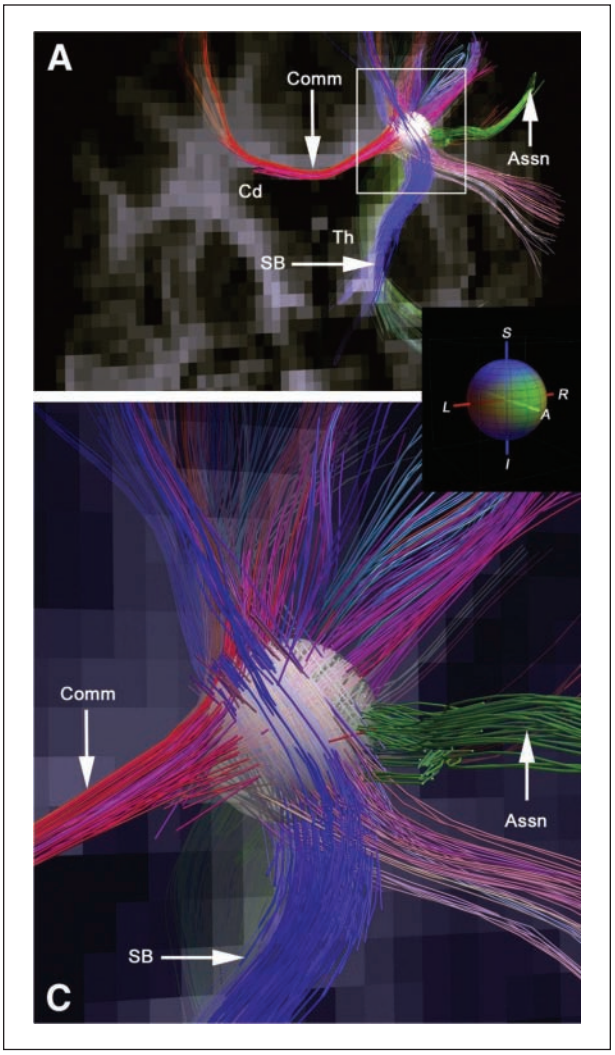

Figure 3. Fibers within the centrum semiovale of in vivo human brain as derived from diffusion spectrum imaging (DSI). The panels show at *(A)* low-power and *(B)* high-power magnification fibers that contact or travel through a sphere region indicated in white. Reconstructed fibers are displayed superimposed onto a coronal structural MRI scan and are color coded according to direction as indicated in the small insert. The single sphere includes very different fiber tracts, callosal fibers (Comm, red, orange), association fibers (Assn, green), and corona radiata fibers (SB, blue). Cd = caudate nucleus; Th = thalamus. Modified from Wedeen and others (2008), with permission from Elsevier.

implicated as essential for a given function and that their other functions remain intact (Catani and Mesulam 2008). For instance, a perceptual area should still be able to project its information to other action-related areas, and, vice versa, an action area should still be able to induce actions relying on other inputs than those of which it has been deprived. A fundamental difficulty in this distinction is that a cortical region may be essential for one function but only involved in others, a problem discussed by Kleinschmidt and Cohen (2006) when comparing pure alexia and prosopagnosia. If, then, the essential role of an area is confined to information relayed by the damaged fiber tract whereas the other functions are routed via different tracts, a lesion of this area could not easily be unconfounded from one of the specific fiber tract. A classic example for a disconnection syndrome defined in accord with the aforementioned criteria has been conduction aphasia as a result of damage to the arcuate fascicle and hence an interrupted link between perceptual and productive speech areas. Even for this textbook example, however, recent neuroanatomical findings for the arcuate fascicle have complicated the picture by identifying a further putative cortical relay station in premotor cortex (Bernal and Ardila 2009).

We recently experimentally addressed our second aforementioned postulate for redefining disconnection syndromes and used Gerstmann's syndrome as a test case. Gerstmann (1924, 1940) first described a peculiar association of acalculia, agraphia, left–right confusion, and finger agnosia. He considered this conjunction to constitute a meaningful association, a syndrome. He related it to damage of the left angular gyrus, which he suspected to house the neural basis of a single cognitive function that would tie together the four different behavioral accomplishments in which his patients failed. Since its presentation, Gerstmann's syndrome has been the object of much interest and heated discussion in neurology and neuropsychology. An initially enthusiastic reception (e.g., Critchley 1953) was followed by a severe and dismissive rebound (see the landmark review by Critchley 1966), which in turn gave way to a progressive rehabilitation due to several well-documented single cases replicating Gerstmann's initial observations. We refer the reader interested in this history as well as the precise description of the symptoms and the testing for ensuing clinical signs to our recent comprehensive review of these aspects (Rusconi and others 2010).

Today, it is generally accepted that, not often but occasionally, pure cases of co-occurrence of these four symptoms can be observed, the grounds on which Gerstmann proposed that this tetrad makes up a syndrome. It is also generally accepted that this syndrome is related to damage of the inferior parietal lobe in the dominant hemisphere. The third claim Gerstmann made is that this syndrome is attributable to a "Grundstörung," damage to a common denominator function required for all four domains in which patients manifest behavioral deficits. Gerstmann's belief was that finger agnosia was most closely related to this underlying cognitive function. As a contemporary of Kleist, and given the topographic implication from the other deficits as acalculia, Gerstmann made a perfectly plausible proposition that was both in

accord with his own pathoanatomical observations and tenable given the existing knowledge (Fig. 1). At least the assumption that this cognitive function could then be tied to a single neuroanatomical location, however, has proven difficult to confirm.

At a much finer grain than lesion studies, reports from electrical stimulation during open brain surgery have investigated the possible cortical bases of the symptoms displayed by patients with Gerstmann's syndrome. The basic idea is that if (disruptive) electrostimulation from a single cortical location produced all four symptoms in a given patient, then this location would be a good candidate for housing the cognitive function that Gerstmann postulated to fail in his patients. Strictly speaking, such colocalization in producing the four symptoms would not be formal proof of a shared substrate because different neural populations might simply be intermingled or might touch on a single boundary point. But at least such colocalization would be a first requirement to be met, and failure in demonstrating it would lead to rejection of Gerstmann's hypothesis, unless technical factors as insufficient cortical coverage could be held responsible.

Following an earlier case report by Morris and others (1984), Roux and others (2003) conducted an electrostimulation study in the inferior parietal lobe during surgery in a series of 6 patients. The examination focused on posterior parietal functions (body representation, calculation, and writing) that were considered most relevant for their patients' quality of life, rather than on Gerstmann's syndrome per se. Some of the patients already showed symptoms of the tetrad prior to intervention. In these cases, stimulation was only considered disruptive if it caused a clear-cut deterioration compared with a patient's own baseline performance. The study did not include tests for right–left discrimination, but each of the remaining three symptoms (agraphia, finger agnosia, and acalculia) could be elicited, usually by stimulation at one or several distinct locations instead of from a contiguous wider area of the cortical surface (Fig. 4). More specifically, stimulation of adjacent cortical territories in the angular gyrus yielded all three tested Gerstmann symptoms. Yet, actual clinical manifestation related to these three symptoms was quite variable, as was the precise localization across patients. Moreover, stimulation at these sites resulted in further deficits as reading and naming deficits that do not pertain to the Gerstmann tetrad. Given the inconsistencies regarding interindividual localization and intra-individual characterization of deficits, the authors of that study remained skeptical of the likelihood of anything like a pure Gerstmann's syndrome arising from a focal cortical lesion.

A false-positive result in electrical stimulation studies would have been conceivable. Participants were patients with significant brain pathologies and accordingly preexisting symptoms ranging from neurological deficit to epileptic seizures. And on a technical side, the effects from local current spread, remote propagation, and stimulation of fiber bundles traveling underneath stimulated cortex are potential confounds that are difficult to control for individually. But could a negative result be false? If so, given the uncontestable case reports with a pure syndrome, this would mean that unlike electrical cortical stimulation, nature can selectively produce this syndrome. One can indeed imagine reasons why electrostimulation might fail. For instance, the functions might depend on a larger extent of cortex than can be disturbed by electrostimulation from a single site. Or cortical sites related to the four functions might be contiguous rather than overlapping, although this latter scenario would already implicitly contradict Gerstmann's initial assertion of a shared functional substrate.

A suitable method to address these scenarios of potential false negative findings is fMRI. Probing function by electrostimulation proceeds from one stimulation site to the next and for practical reasons hence inevitably undersamples cortical function. Conversely, fMRI permits mapping task-associated neural activity changes simultaneously across the entire brain and at a spatial resolution that is fine-grained compared with clinical lesions. Ignoring residual caveats as propagation or white matter stimulation, electrostimulation unequivocally identifies sites that are essential for a given function. Conversely, fMRI maps sites that are more involved in a given function than during a control condition but cannot determine whether functionality of these sites is essential. To demonstrate overlap of cortical zones that activate in response to the four different functional challenges in which Gerstmann patients fail would hence be a minimal requirement for maintaining the idea of a shared cortical substrate of these four functional domains. However, if such overlap was found somewhere on the cortical surface, this would not yet constitute proof that a lesion at this site would entrain Gerstmann's syndrome.

We have recently explored this avenue in an fMRI experiment that was conducted with several participants at high spatial resolution. Participants performed four different tasks in which Gerstmann patients would typically fail, and activations during these conditions were compared against those during control conditions that were approximately matched in terms of low-level sensory and motor features. An overview of the four experimental conditions and the respective control conditions is provided in Fig. 5. Using the simple logic of "cognitive subtraction," we attempted to map cortical regions that are rather specifically involved in Gerstmann-related cognitive functions. At this level of spatial detail, the commonly used procedure of averaging findings from

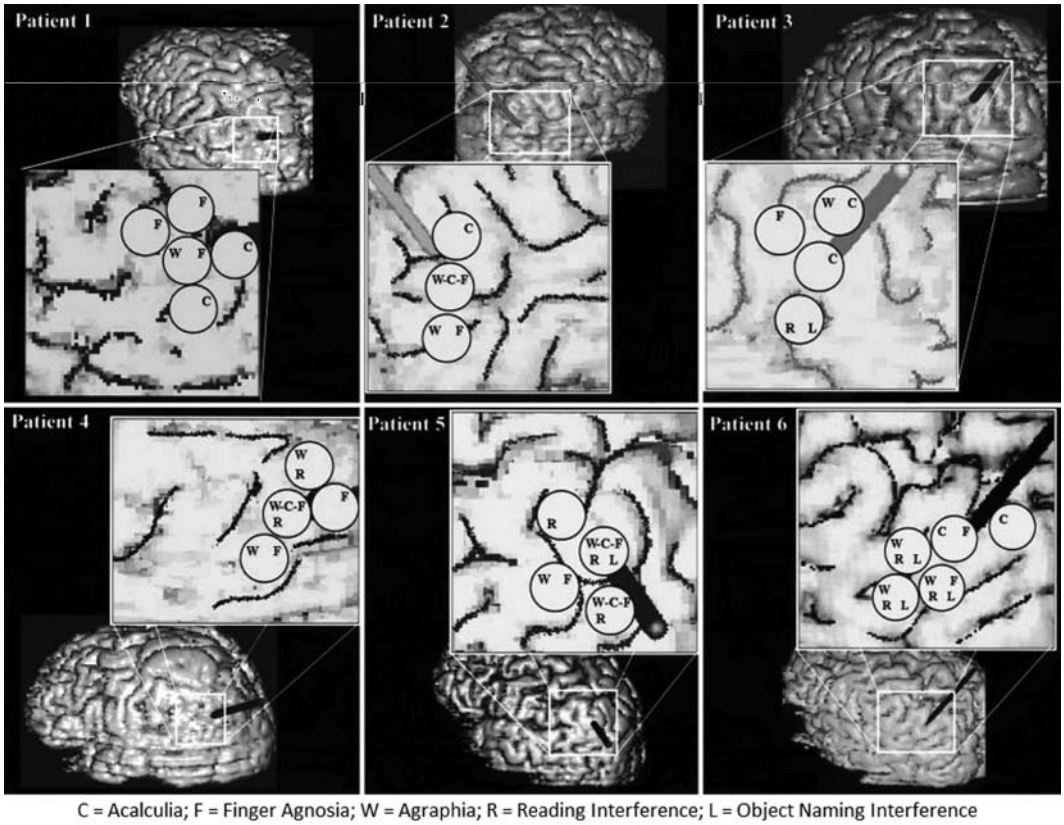

Figure 4. Schematic drawings showing interference sites in the angular gyrus region patients reported by Roux and others (2003). From Roux and others (2003), with permission.

individual participants into a common coordinate system for group analysis might produce spurious overlap from blurring. Instead, we probed in each participant whether we could find any overlap of cortical activation maps related to the four domains that are affected in Gerstmann's syndrome (Fig. 6). Even at lenient statistical thresholds, such overlap was not found in any of the participants, thus suggesting that the four Gerstmann functions do not share a single patch of parietal cortex on which they might all depend.

A negative finding, as the one described above, might always have technical or statistical reasons, but we were not surprised by this result for two reasons. First, we were not aware that any functional analysis would have identified what actual specific cognitive function should selectively tie together the four domains in which Gerstmann patients manifest behavioral deficits. Although several links between different domains of the tetrad have been discussed in the past, no straightforward cognitive model has been presented that would include a bottleneck function for all four domains. Second, the arguably best documented modern-era case report of a patient with pure Gerstmann's syndrome showed a rather focal lesion in the white matter rather than in the cortex of the left parietal lobe (Mayer and others 1999). Given these two considerations, we therefore tested a possibly more intuitive hypothesis, namely that a lesion in the parietal white matter might disconnect rather selectively those cortical regions that are required for the four diverse functions failing in Gerstmann's syndrome.

Our fMRI experiment had identified which cortical regions are involved in the four domains. We considered these regions to comprise the set of suitable candidates with which dysfunction due to disconnection might yield the specific associated symptoms. Following this logic, we used these regions as seeds to trace fiber tracts in diffusion tensor images of the same participants. We hence obtained in every participant four maps of fiber bundles, one related to each functional domain. We then probed whether there was any overlap between these four maps and indeed found in each and every participant such overlap in a fairly small region of the left parietal white matter. Moreover, the location of this overlap zone was very similar to the location of the lesion in the aforementioned patient with a pure Gerstmann syndrome (Mayer and others 1999). We therefore concluded that a lesion at this site

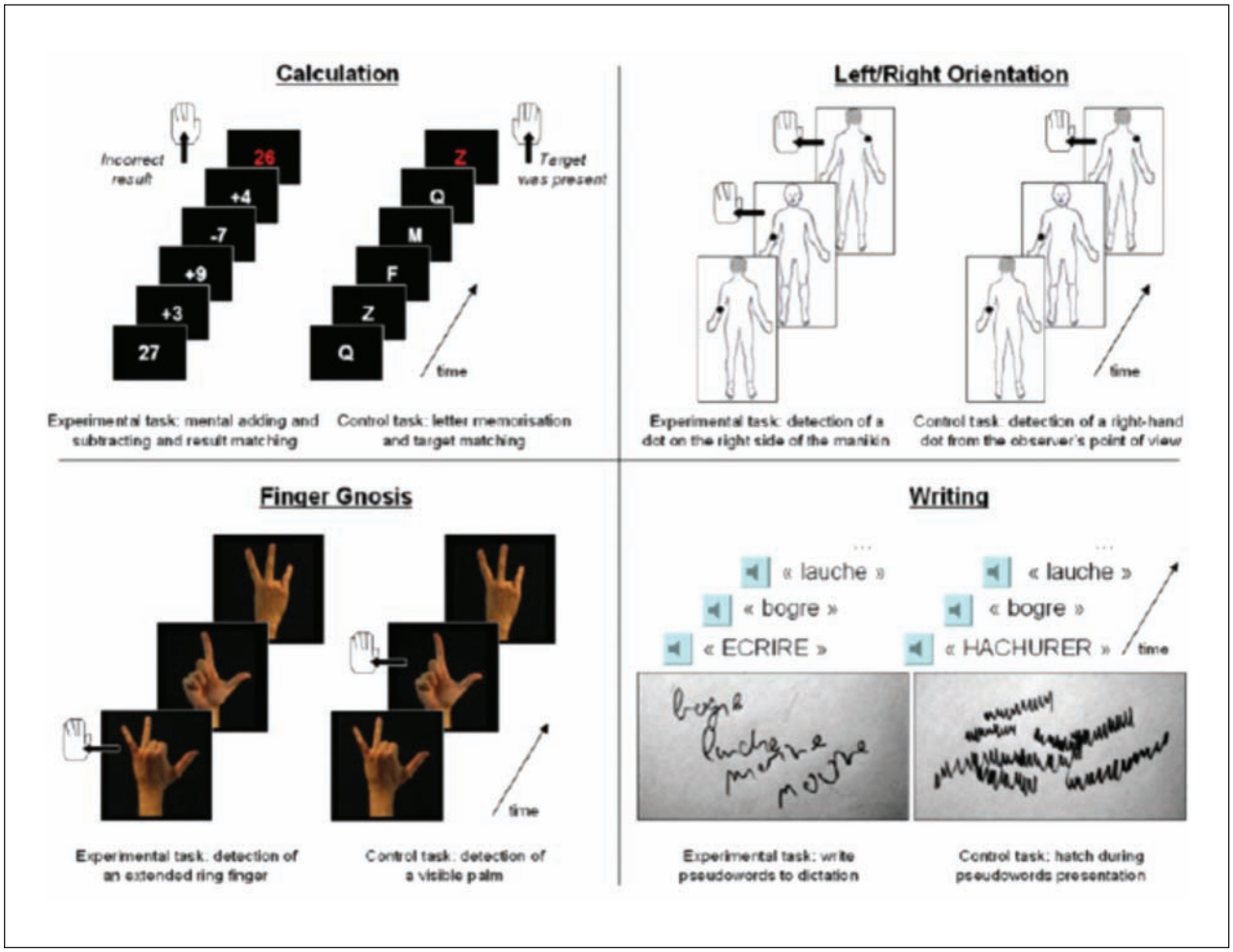

Figure 5. Experimental and control tasks used to localize, in the left parietal lobe, activations related to calculation (upper left panel), finger gnosis (lower left panel), writing (lower right panel), and left–right discrimination (upper right panel). From Rusconi and others (2009), with permission from Wiley and Sons.

might generate a pure Gerstmann syndrome (Rusconi and others 2009). Conversely, previous findings and our own results concur in making it unlikely that cortical damage could have the same result. The reason is that although a lesion might easily be big enough to encompass the non-overlapping cortical zones involved in the four functions, such a lesion would then in all likelihood generate further symptoms than just the Gerstmann tetrad. The latter observation has been frequent in several lesion studies and has in the past furnished one of the major critiques brought forward against the syndrome status claimed by Gerstmann (reviewed in Rusconi and others 2010). Similar conclusions have been derived from a more recent investigation in Alzheimer's disease that could not detect any preferential association of the four symptoms in a degenerative cortical pathology involving the parietal lobe (Wingard and others 2002).

From a more theoretical perspective, we have used our findings to argue that Gerstmann's syndrome can be considered a disconnection syndrome. Yet, there are some interesting differences compared with the way disconnection syndromes have been defined so far, and these differences relate to the two postulates we formulated above. First, unlike generally accepted disconnection syndromes with a single clinical facet, Gerstmann's syndrome involves an association of several different and not overtly related individual symptoms. Second, it is highly unlikely that Gerstmann's syndrome should be tied to damage of a single fiber tract, as is the case in other disconnection syndromes and usually a prerequisite for such a label. If a single fiber tract was involved across all four functional domains, our analysis should have found overlap along that entire tract and not just in a focal region of white matter. Moreover, there should have been a cortical starting or end point to this fiber tract that our analysis identified as overlap of the fMRI findings across the four domains.

We addressed the question of which fiber tracts might be concerned by a "virtual lesion" approach where this

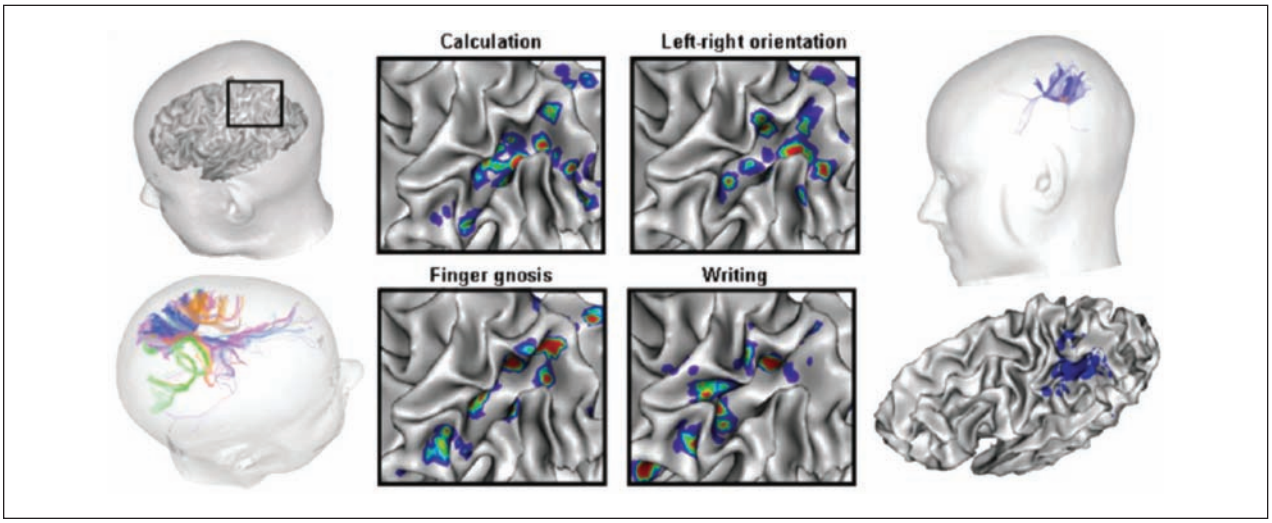

Figure 6. Functional and structural imaging results of left parietal lobe organization in the human brain (illustrated in a single healthy subject). The four middle panels show functional activation results superimposed on a left parietal zoom (see upper left-hand brain). Taking these activation foci as seeding points permits tracking fibers connected with these cortical zones (see lower left-hand head, with different colors for the different domains). The upper right-hand head shows the result of tracking fibers from a bottleneck in the parietal white matter and the lower right-hand hemisphere shows the disconnection effect from such a "virtual lesion" on the cortical surface. From Rusconi and others (2009), with permission from Wiley and Sons.

time we took the previously identified white matter region and not cortical regions as a seed for tracking. Instead of finding a single fiber tract, we found a rich arborescent pattern of fibers connecting from this region of white matter to different areas of parietal cortex and elsewhere (Fig. 6). Displacing the virtual lesion location even slightly resulted in grossly different patterns (Rusconi and others 2009). This approach allowed us to identify which cortical regions would be partially disconnected and could hence potentially turn dysfunctional after a lesion at a given site (Fig. 6).

But how can these patterns be reconciled with the classical notion of a disconnection syndrome? Recently, Catani and ffytche (2005) proposed a framework for lesion-induced deficits in which cortical and subcortical disconnection effects are illustrated. An aspect that this framework did not touch on is the intermingling of fibers traveling through white matter that we have discussed above (and that is illustrated in Fig. 3). In fact, the crossing or "kissing" of different fiber tracts still imposes serious limitations on precisely deriving white matter anatomy from MRI images that are sensitive to diffusion direction, especially when "winner-take-all" methods are used to define fiber direction within a given voxel. However, given the undebatable existence of such unique points of contact between different fiber tracts, it is also clear that the clinical deficit from a lesion at a site traversed by separate fiber tracts could associate the functional consequences from disconnections in separate cortical networks into a syndrome. Moreover, a lesion elsewhere along any one of these fiber tracts would not produce this association but only a subset of symptoms or a different association with other symptoms. The specific disconnection syndrome involving association of damage to separate fiber tracts would hence only be observed for lesions at a very circumscribed site, which is nicely compatible with our previously described empirical observations targeting the Gerstmann tetrad. We therefore propose an extension to the classical mono-tract disconnection syndrome that we have illustrated in the bottom panel of Fig. 7.

Notwithstanding the intellectual appeal of offering a viable solution to the "enigma of Gerstmann's syndrome" (Critchley 1966), pure cases of this syndrome remain a clinical oddity. One may hence rightfully wonder whether a pathomechanism involving disconnection of crossing or kissing fiber tracts might be of any more general importance. One of the major criticisms of Gerstmann's "syndrome" in the past was that in patients with parietal lobe damage, individual Gerstmann symptoms are also found in association with other symptoms (see Heimburger and others 1964; Poeck and Orgass 1966). These findings are, however, perfectly compatible with our proposal: If a lesion of a fiber tract related to a single Gerstmann symptom occurred at a different spot than the one putatively yielding Gerstmann's syndrome, this lesion might affect other crossing fibers and hence yield an overlapping but nonetheless distinct association of symptoms. Yet, just as we discussed above for dissociations, associations of symptoms also remain ambiguous, with cortical

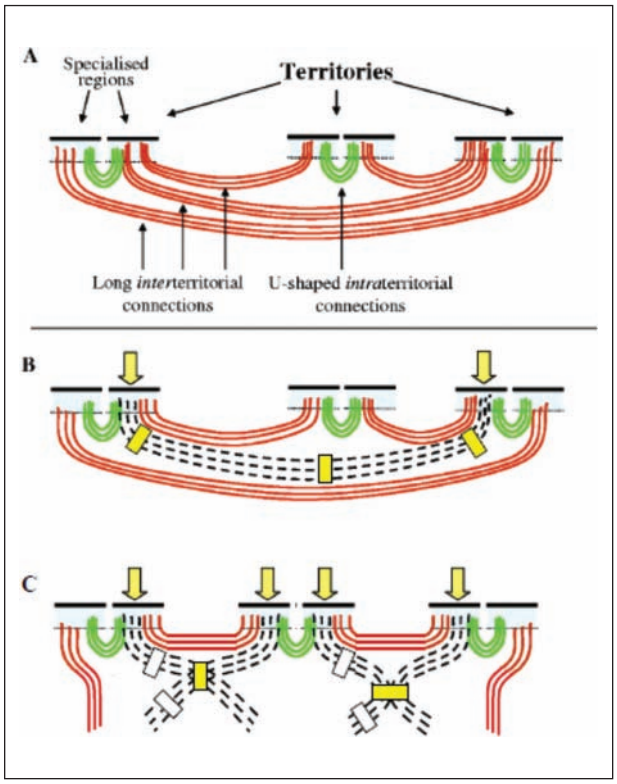

Figure 7. Heuristic framework for illustrating functional consequences from subcortical lesions of fiber tracts. *(A)* Regions are connected by short-range connections (green, "U-fibers") to neighboring regions in the same territories and by long-range connections (red) to remote regions in other territories. *(B)* A classical subcortical disconnection syndrome involves a lesion (yellow square) somewhere along the trajectory of a defined long-distance fiber tract. Such a lesion interrupts communication between regions indicated by yellow arrows and thereby renders them partially dysfunctional despite persisting intact other connections. *(C)* The newly proposed type of disconnection syndrome involves a lesion (yellow squares) at white matter locations where fiber tracts cross (left) or "kiss" (right). In this instance the regions that turn dysfunctional (yellow arrows) are not required to be connected. Moreover, lesions at other positions of one of the affected fiber tracts (white squares) do not associate damage with that of the other fiber tracts and should therefore yield different functional consequences. Based on modification and extension of a schematic introduced by Catani and ffytche (2005), by permission of Oxford University Press.

specialization providing an alternative account. In other words, the clinical deficit per se does not readily indicate its precise neural basis. And clinical lesions very often encompass gray and underlying white matter, rendering it difficult to disentangle the functional consequences in a fine-grained way.

One indirect clue that disconnection of crossing fibers might provide a substantial contribution to clinical phenomenology comes from the following consideration: The direction of water diffusion in a given region of white matter is determined by the orientation of fibers traveling through this region. A single fiber tract occupying an entire such region creates maximal anisotropy of diffusion as it can be measured by MRI techniques. Such maximal anisotropy is observed, for instance, in the corpus callosum. Conversely, an equal number of fibers for all possible directions would show up as perfect isotropy of water diffusion in that region. Anything less than maximal anisotropy can therefore be taken to indicate the presence of more than one direction of fibers. The considerable spatial extent of white matter regions with such submaximal anisotropy hence provides an indication of the degree to which lesions at these sites will not be confined to a single fiber tract.

This line of argument deviates from the more established view that higher fractional anisotropy inevitably signals a greater degree of white matter integrity or functionality. The latter view only holds if a single fiber tract normally dominates in a given volume of white matter, but where this is not the case, increased fractional anisotropy might just as well indicate loss of usually crossing fiber populations of different orientation (Douaud and others 2010; Pierpaoli and others 2001). This consideration may be particularly relevant in white matter under brain regions such as the supramarginal and angular gyrus, where myelination occurs fairly late in development and involves multiple fiber populations (Geschwind 1965a; 1965b). Another caveat that also includes our results is that even detailed fiber tracking faces the same problem as the interpretation of fMRI findings, namely the uncertainty to which degree function depends on their integrity. In a similar way as for cortical areas, not all fiber tracts are inevitably "eloquent," and there may be sufficient redundancy and parallel routing to keep some lesions "silent." A full validation of structural disconnection accounts of neurological symptoms will therefore always need to rely on patient findings. Findings from structural and functional neuroanatomy in the healthy human brain, however, can provide a groundwork that permits conducting such patient studies with plausible and precise prior hypotheses.

Conclusions

In this review, we have discussed lesion-symptom relations in neurological disease with an emphasis on functional consequences of white matter damage. The test case that motivated our considerations was Gerstmann's syndrome, and we describe a putative mechanism for this syndrome based on a detailed study with joint structural and functional neuroimaging in the healthy human brain. We illustrate how this approach can contribute normative findings and build a basis for a functional

neuroanatomy of neurological symptoms. Specifically, it can go beyond previous methods in assigning function to white matter locations even where no single fiber tract dominates. One interest in combining fMRI and diffusion tensor imaging (DTI) is that it permits probing of alternative functional hypotheses in a single experiment and within the same participants: shared cortical substrates versus subcortical disconnection. In this context, we propose an extension to the concept of disconnection syndromes that goes beyond the current use of this label and readily accounts for as enigmatic syndromal associations of different deficits as the one first described by Gerstmann. We suggest that the full impact of disconnecting lesions can only be appreciated by considering the complexity of fiber anatomy in the brain and that this accounts for the ensuing variability of clinical phenomenology from white matter lesions.

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