Disconnecting cognition

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Purpose of review
The aim is to assess whether the recent surge in brain 'connectivity' studies has improved our understanding of neurological deficits and in particular so-called disconnection syndromes.

Recent findings
Across a large variety of brain diseases, functional connectivity measures obtained from 'resting state' studies show alterations in distributed neural networks that may be of explanatory value for disease severity. In parallel, studies of structural connectivity reveal how damage to identified fiber tracts can yield specific clinical symptoms. These methods are not only permitting testing of the disconnection mechanism in the few syndromes where it has classically been suspected, but also starting to propose disconnection accounts for other syndromes that have not been conceptualized this way before. Finally, both structural and functional connectivity studies contribute to improve the mechanistic understanding of cognitive deficits in disseminated white matter disease.

Summary
In many respects, studies of structural and functional connectivity using MRI are providing critical novel empirical evidence for – and also against – disconnection as the relevant pathomechanism in neurological syndromes. At the same time, the observation of altered long-range correlation of activity in a wide variety of brain diseases may also be overinterpreted as disconnection, which dilutes an originally rather specific understanding of this concept.

Keywords
brain connectivity, diffusion tensor imaging, functional magnetic resonance imaging, tractography

INTRODUCTION

Sooner or later any student of neurology inevitably comes across the concept of disconnection syndromes [1]. Part of its current popularity is undoubtedly due to advances in MRI of fiber tracts that permit quantitative and statistical in-vivo analyses of structural connectivity in the human brain and that, despite ongoing technical concerns [2▪], now constitute a crucial building block in mapping the human connectome [3▪]. Another reason might be the recent surge in functional connectivity results from so-called resting state functional neuroimaging studies. These studies generally analyze spatially distributed coherent signal fluctuations that occur in the absence of any explicit activation paradigm [4]. In the present review, we analyze recent empirical contributions to the disconnection concept and to what extent they are shaped by findings from imaging studies of structural and functional brain connectivity.

Although measured by very different imaging approaches, these two connectivity types are not independent. Functional connectivity arises from context-sensitive dynamics that unfold fairly rapidly but are shaped by a backbone of structural connectivity that can change only slowly. Although task-free recordings can comprehensively assess the entire repertoire of functional connectivity [5], task-dependent functional connectivity changes permit study of a more constrained, but also more readily interpretable sub-set of this repertoire [6]. Hence, earlier studies have attempted to link symptoms in diseases such as schizophrenia or Parkinson's disease to disconnection by showing reduced functional connectivity in the context of a specific task paradigm [7,8]. These approaches have been largely superseded by the popularity of resting-state studies. Altered, usually reduced, correlation of resting state fluctuations across distant brain regions is being

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KEY POINTS

- Disconnection is increasingly recognized as a powerful determinant of clinical deficit.
- Functional connectivity is a useful way of probing the integrity of distributed brain networks.
- What disturbed functional connectivity means is not yet fully understood, and it cannot be equated with disconnection.
- Structural connectivity measures can establish relations between specific fiber tracts and selective clinical symptoms, thus indicating disconnection as the causative mechanism.

described for an ever increasing number of neurological and psychiatric diseases, suggesting that functional connectivity can be a proxy or surrogate marker of brain integrity [9].

DISCONNECTION SYNDROMES: A TRIVIAL OR A TRICKY CONCEPT?

The basic idea, namely that a neurological deficit could result from the disruption of a neural connection, seems intuitively accessible and obvious – but probing deeper into this concept and its relation to brain disease quickly turns confusing. Part of this confusion stems from the fact that two quite different logics have been called upon when attributing the disconnection label: a structural logic and a functional logic.

Neurons mostly connect to each other, and to a minor extent also interface with the external and internal environment via receptors and effectors. They are generally thought to integrate signals received by afferent synaptic connections into an output that is transmitted by discharges along their own efferent connections. All nervous functions are hence mediated by connections and neuronal damage inevitably means damage to connections. As many connections are long-range, such damage readily results in effects at a distance, a notion first introduced a century ago by von Monakow [10]. His 'diaschisis' concept went even further in proposing that effects from focal lesions propagate progressively throughout the brain according to its structural connectivity. This at its time audacious prediction has been well matched by computational simulations in more recent years [11▪]. Neural activity alterations in brain disease are not confined to the site of primary structural damage and this effect is mediated, and in fact shaped, by neural connections. This consideration may be useful for understanding the clinical phenomenology, especially for cognitive functions that heavily rely on integrative long-range connections. Furthermore, this notion is not restricted to focal brain lesions. From this background, it does not appear too surprising that recent publications have proposed that even Alzheimer's dementia can be thought of as a disconnection syndrome [12,13], or that the range of cognitive and affective semiology in Parkinson's disease is accounted for by functional disconnection [14,15].

Although it is understandable on which basis such proposals are forwarded, we nonetheless feel, as do others [16], that by applying the disconnection concept too broadly to brain diseases, it will lose any specific explanatory value it might have, and eventually turn trivial. So what could such a specific explanatory value be?

CLASSICAL DISCONNECTION SYNDROMES

For didactic or illustrative purposes, a classical example of a disconnection syndrome is an agraphia and apraxia, and maybe tactile anomia, of the left hand [17]. The functional logic here is that the right hemispheric cortical representation of the left hand becomes deprived of access by linguistic, abstract or symbolic information that is represented in the left hemisphere. The corresponding structural logic is that transfer of such information relies on the integrity of anterior commissural fibers traveling through the corpus callosum. These mechanisms can now be visualized *in vivo* by noninvasive imaging and electrophysiological techniques that track fibers and assess interhemispheric communication [18▪].

Apraxia and agraphia of the left hand falls within a more restrictive definition of a disconnection syndrome. The main point here is that there is no corresponding disorder of the right hand and that the left hand displays no low-level deficit of sensorimotor function. So neither a lesion that produces effector-independent agraphia and/or apraxia nor a lesion that results in a wider loss of left hand functions can account for the clinical syndrome. Translated into a structural perspective, the notion of disconnection is grounded in the fact that neural connections are not one-to-one and exclusive but show great divergence and convergence. For our example, this means that purely on clinical grounds it is possible to distinguish left-hand apraxia from damage to a 'left hand center' and damage to a 'praxia/graphia center'. Among the input converging onto the left hand center, it is only that emanating from the 'praxia/graphia center' that is missing, and among the output diverging from the

'graphia/praxia center' it is only that targeting the 'left hand center' that is compromised. Damage to the connection hence results in a deficit that is distinct both from damage to the target and damage to the source region of that connection. This syndrome is compelling because it is grounded in a functional as well as a structural logic, in other words it combines specific clinical signs and an identified fiber population.

Similar claims have been made for other clinical syndromes. Classical examples are pure alexia (without agraphia) and conduction aphasia. Yet, the structural logic here is more ambiguous. Although alexia can result from damage to a specific fiber tract [19,20], it can as well result from damage to a cortical region that is critical for reading [21,22]. The clinical signs in the latter case are still compatible with a functional logic that emphasizes transfer of information, but what misses here is to show that visual word information, while not available for reading, is still available elsewhere via another route diverging out of the initial perceptual processing of written material. Instead, there is some evidence to suggest that alexia from disconnection may extend beyond the visual letter domain into the kinesthetic letter domain, which is called upon during letter tracing and challenged for rehabilitative purposes [23].

In conduction aphasia, perception of language is preserved and spontaneous production usually only mildly disturbed whereas repetition of heard material is grossly compromised. The functional interpretation of this clinical dissociation of language functions has been that the conduction from brain regions dealing with the heard material to those required for repeating is disturbed. And the proposed structural logic has pointed to damage to the arcuate fascicle, in accord with recent tractography data in patients [24]. Yet, conduction aphasia can arise from cortical lesions as well, and the arcuate fascicle provides a different connectivity than initially assumed [25]. Moreover, damage to this tract might also result in a very different clinical picture as tone deafness [26].

DISCONNECTION IN COGNITIVE SYNDROMES

Pure alexia and conduction aphasia illustrate the difficulties of a functional logic that relies on clinical semiology to ascertain that disconnection is necessarily the underlying structural mechanism. This does not inevitably mean that disconnection is not a powerful factor shaping the clinical deficit. The latter point is suggested by a series of recent studies on hemispatial neglect, one of the most common disorders following right hemisphere damage. Neglect is characterized by an inability to orient attention and behavior toward the contralesional left side [27], but the exact cognitive components and anatomy of this multifaceted syndrome still remain unresolved and debated [28▪,29▪].

Neglect can result from lesions in various cortical and subcortical regions, and this has been taken as evidence that the neural functions impaired in neglect are anatomically implemented in large-scale distributed brain networks. Accordingly, mechanisms controlling spatial attention are associated with two distinct circuits in fronto-parietal areas: a dorsal system responsible for endogenous (voluntary) orienting based on internal task goals, and a ventral system responsible for exogenous (reflexive) orienting driven by external salient information [30,31▪▪]. The dorsal attentional network comprises superior parietal regions (e.g., intraparietal sulcus) and the superior and middle frontal gyrus (e.g., frontal eye field), whereas the ventral attentional network combines the inferior parietal cortex (e.g., angular and supramarginal gyri) and posterior temporal cortex (constituting the temporo-parietal junction) with the inferior frontal cortex and anterior insula.

Converging evidence has established that not only damage to parietal and frontal cortical nodes but also disruption of the white-matter tracts connecting them may cause contralesional spatial neglect [29▪]. Using activation likelihood estimation procedures originally developed for functional brain imaging, two recent lesion mapping meta-analyses both confirmed a higher frequency of deep subcortical white-matter damage in patients with neglect relative to those without neglect [32,33▪]. Damage most consistently overlapped with the superior longitudinal fasciculus (SLF), with lesser effects also in the inferior fronto-occipital fasciculus (IFOF) and thalamic radiations. The SLF is composed of several branches along a dorsoventral gradient that connect different anterior and posterior brain regions. Neglect correlates most strongly with damage to the fronto-parietal segment of the SLF, particularly its branch SLF II [34▪▪]. On the basis of diffusion tensor imaging (DTI) tractography in individual patients, interruption of the anterior or long segment of SLF seems more likely to induce contralesional spatial neglect than interruption of other tracts such as the temporo-parietal segment of SLF, IFOF, inferior longitudinal fasciculus, or optic radiations [34▪▪,35]. A critical role for SLF in neglect symptoms has also been suggested by direct electrical stimulation during brain surgery [29▪,36▪▪]. It remains unclear whether neglect after

white-matter disconnection constitutes a specific form of this syndrome or stays similar to other cases with more focal cortical damage.

Other recent reports also related white-matter pathways in posterior corpus callosum to overall neglect severity [37], neglect in mental imagery [29▪], or spatial biases in temporal order judgments for bilateral visual stimuli [38▪]. And there is some indication that interhemispheric interactions could be critical in recovery from neglect [39▪]. In addition, recent tractography has charted specific white-matter pathways between early visual cortex and cortical and subcortical structures that mediate spatial attentional selection [40,41▪▪], although their implication in neglect remains to be determined.

Together, these studies complement our increasing knowledge of brain circuits serving higher cognitive functions such as perception and attention. The findings are plausible in that tract parcellations generally dovetail nicely with cortical functional segregation and provide a precise structural basis for the delineation of various distributed brain networks, for example those mediating attention [42▪▪], face recognition [43▪▪], or voice perception [44].

However, the example of neglect also points out some of the problems in deriving an underlying structural disconnection mechanism from a clinical deficit. Similar considerations apply to left-hemispheric fiber tracts and language [45▪▪]. Commissural connections could represent a special case due to hemispheric lateralization and dominance; but the role of associative intrahemispheric connections may be more difficult to distinguish from that of the cortical source or target regions. A single tract could potentially constitute the dominant source of input to or output from a given cortical region, in which case one would indeed predict that clinical signs following damage to such a tract are fairly similar to those generated by lesions to the regions it connects. Alternatively, associative intrahemispheric tracts may gather fibers to or from several distinct regions that are juxtaposed or even distant but projecting via a shared tract. An interesting result in neglect is that some white-matter structures may constitute bottlenecks where function is especially vulnerable. Accordingly, the impact of white-matter damage to SLF in neglect was found across different tests, including both line bisection and cancellation, even though the severity of neglect on these tests has previously been associated with different cortical sites in parietal and frontal lobe, respectively [32,33▪,46]. In addition, intrahemispheric disconnection can also modify functional neural activity in structurally intact cortical regions within an extended network in a task-dependent manner [31▪▪,47], although few data exist to determine whether similar effects also occur after commissural disconnection or not.

These considerations lead us to a somewhat different scenario wherein disconnection seems to provide a virtually exclusive explanatory account. If not one but several different fiber tracts travel through a given location in white matter, then a lesion at this site will selectively disrupt several separate functional networks. Such an account has been recently proposed for Gerstmann syndrome, a notoriously controversial tetrad of symptoms [48]. Using fiber tracking informed by functional neuroimaging, several cortically segregated functions were structurally associated with a single spot in white matter [49]. Lesions at this 'crossroad' could selectively produce this multicomponent syndrome, whereas obtaining identical clinical consequences from a cortical lesion is hard to imagine because it would have to be extensive and discontinuous at the same time so as not to encroach on interspersed cortical functions. As crossing and 'kissing' of fiber tracts are frequent in white matter, this mechanism might account for other symptom associations in the neuropsychological literature that so far have been taken to indicate highly specialized cortical modules [50▪▪].

COGNITION IN WHITE MATTER DISEASE

In this last scenario involving Gerstmann's syndrome, a focal lesion in hemispheric white matter yields a highly selective association of clinical symptoms due to disconnection of distributed cortical circuits. In many brain pathologies, however, white matter damage is extensive and diffuse. There is good reason to assume that ensuing clinical deficits in these diseases can be ascribed to disconnection. This is the case in cerebral small vessel disease [51] but perhaps even more selectively in multiple sclerosis (MS). Several recent studies have established correlations between cognitive impairment and white matter alterations in MS [52▪,53]. Functional neuroimaging has highlighted the consequences of white-matter damage for coordinated neural function across large-scale networks, but also shown how this can relate to clinical deficits [54,55▪] and be used to detect and quantify pathology in individual patients [56▪].

An interesting finding in the latter studies was that greater clinical impairment was associated with increased functional connectivity in particular networks. In contrast, the usual observation in brain disease is a reduced functional connectivity, which may have straightforward explanations related to tissue loss with lower functional signal-to-noise

ratio. Yet, connectivity is not as readily interpretable as activity or 'activation' because it is driven by variability over time. Higher functional connectivity might indicate 'healthy' neural dynamics in many instances. Yet, in situations where sustained efforts can no longer be maintained and activity levels turn volatile, impaired network recruitment would also transpire in functional connectivity increases. Or if fine-grained differentiated neural processing is compromised and patterns return to less complex macroscopic mass interactions, this could also be picked up as increased functional connectivity at the scale of imaging measures. Future work is, therefore, needed to better understand the determinants of functional connectivity and disambiguate such different scenarios.

CONCLUSION

Sophisticated and sensitive measures of structural and functional connectivity in brain disease have encouraged the tendency to explain clinical neurological deficits by disconnection within cortico-subcortical networks. Accumulating evidence has pointed to disconnection as a key factor in neuropsychological disorders such as neglect or Gerstmann syndrome, but also in diffuse brain disease such as MS, hence extending the notion of disconnection beyond the traditionally considered specific syndromes. However, a careful distinction of the structural and functional logics implied by these different accounts is warranted to precisely characterize the specific impact of disconnection, and thus ensure that it remains a heuristically useful concept.

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Conflicts of interest

There are no conflicts of interest.

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This study reported that white matter damage in MS patients is associated with disturbances in large-sale brain network organization as assessed with resting state fMRI, and correlates with a paradoxical increases in functional connectivity between several regions associated with default mode. Although these changes were related to a measure of reduced cognitive efficiency, gains in connectivity were attributed to plasticity or dedifferentiation secondary to multifocal white matter disconnections.
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This study measured functional connectivity between brain areas at rest in patients with mild MS and identified distinctive patterns of alterations at different frequencies of temporal fluctuations, relative to age-matched controls. Anomalies in MS patients predominantly affected intrahemispheric connectivity of anterior temporal areas, thalamus, and basal ganglia, as well as interhemispheric connectivity. These anomalies could be used to discriminate patients from healthy controls using data-driven pattern classification approaches with high sensitivity and specificity.