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How to cite

CARRERA, Emmanuel, TONONI, Giulio. Diaschisis: past, present, future. In: Brain, 2014, vol. 137, n° 9, p. 2408–2422. doi: 10.1093/brain/awu101

This publication URL: https://archive-ouverte.unige.ch/unige:155171
Publication DOI: 10.1093/brain/awu101

doi:10.1093/brain/awu101 Brain 2014: 137; 2408–2422 | 2408

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Diaschisis: past, present, future

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After a century of false hopes, recent studies have placed the concept of diaschisis at the centre of the understanding of brain function. Originally, the term 'diaschisis' was coined by von Monakow in 1914 to describe the neurophysiological changes that occur distant to a focal brain lesion. In the following decades, this concept triggered widespread clinical interest in an attempt to describe symptoms and signs that the lesion could not fully explain. However, the first imaging studies, in the late 1970s, only partially confirmed the clinical significance of diaschisis. Focal cortical areas of diaschisis (i.e. focal diaschisis) contributed to the clinical deficits after subcortical but only rarely after cortical lesions. For this reason, the concept of diaschisis progressively disappeared from the mainstream of research in clinical neurosciences. Recent evidence has unexpectedly revitalized the notion. The development of new imaging techniques allows a better understanding of the complexity of brain organization. It is now possible to reliably investigate a new type of diaschisis defined as the changes of structural and functional connectivity between brain areas distant to the lesion (i.e. connectional diaschisis). As opposed to focal diaschisis, connectional diaschisis, focusing on determined networks, seems to relate more consistently to the clinical findings. This is particularly true after stroke in the motor and attentional networks. Furthermore, normalization of remote connectivity changes in these networks relates to a better recovery. In the future, to investigate the clinical role of diaschisis, a systematic approach has to be considered. First, emerging imaging and electrophysiological techniques should be used to precisely map and selectively model brain lesions in human and animals studies. Second, the concept of diaschisis must be applied to determine the impact of a focal lesion on new representations of the complexity of brain organization. As an example, the evaluation of remote changes in the structure of the connectome has so far mainly been tested by modelization of focal brain lesions. These changes could now be assessed in patients suffering from focal brain lesions (i.e. connectomal diaschisis). Finally, and of major significance, focal and non-focal neurophysiological changes distant to the lesion should be the target of therapeutic strategies. Neuromodulation using transcranial magnetic stimulation is one of the most promising techniques. It is when this last step will be successful that the concept of diaschisis will gain all the clinical respectability that could not be obtained in decades of research.

Keywords: diaschisis; stroke; brain organization; brain function

Abbreviations: DCS = direct current stimulation; TMS = transcranial magnetic stimulation

Introduction

What are the remote effects of a focal lesion on the function of the brain? More than 125 years ago, the question was the subject of an emotional debate at the French Society of Biology between Charcot, defender of the concept of localizationism, and Brown-Séquard, who suggested that part of the functional deficit following a brain lesion may be due to its distant effects

Received November 7, 2013. Revised February 13, 2014. Accepted March 7, 2014. Advance Access publication May 28, 2014

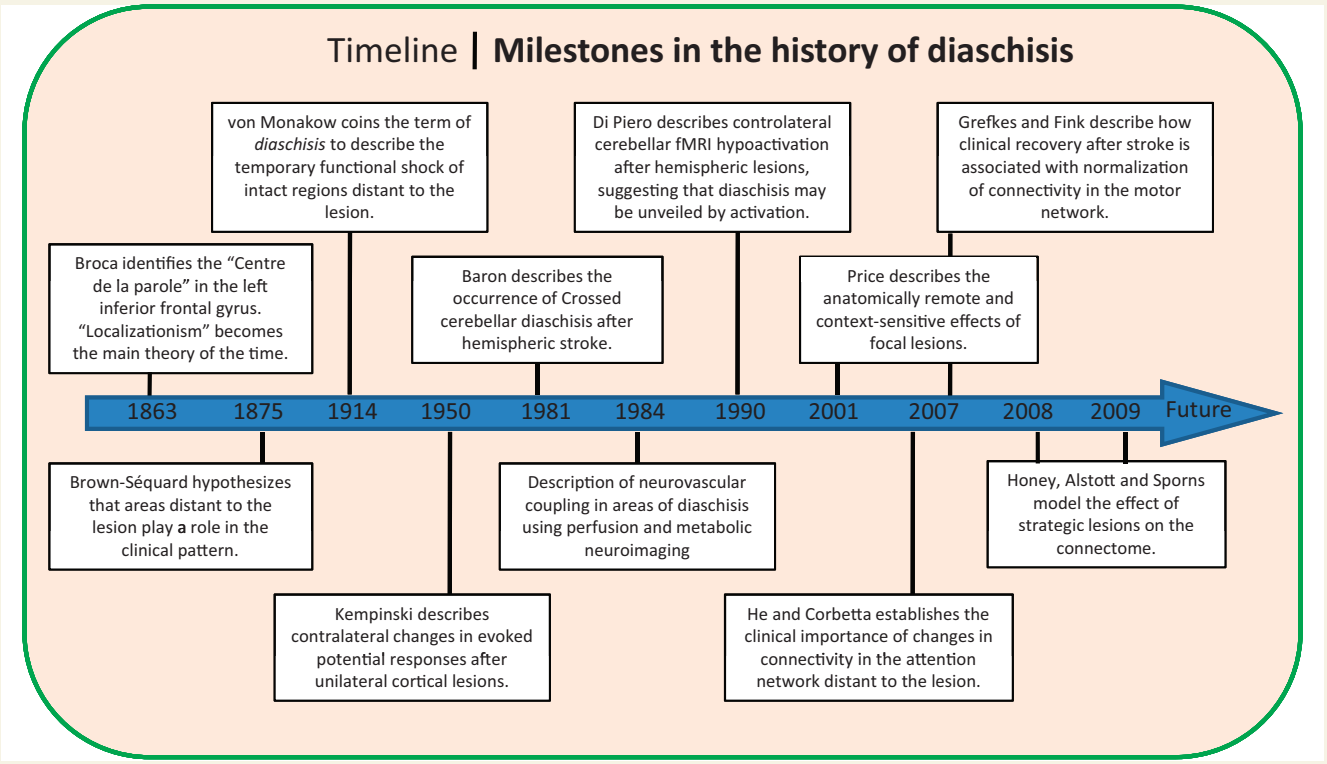

Figure 1 Selected milestones in the history of diaschisis.

(Brown-Séquard, 1875). If the reactions to Brown-Séquard's hypothesis included condescendence or at most polite indifference, far more respect was shown to von Monakow's masterpiece in which he introduced the term 'diaschisis' (from the Greek *dia* 'in half' or 'across' and *schizien* 'to split') (Fig. 1). In 1914, his most complete definition was published, which included four key aspects: (i) the presence of a focal brain lesion; (ii) a remote loss of excitability or 'functional stillstand'; (iii) the interruption of the connections between the lesion and remote areas; and (iv) a clinical and dynamic nature of the progress that decreases over time (von Monakow, 1914; Kempinsky, 1966; Feeney and Baron, 1986). In the following 50 years, diaschisis remained a clinically ill-defined concept. In fact, the clinical pattern not directly explained by the lesion was overly attributed to diaschisis, excluding in turn other physiological mechanisms such as the ischaemic penumbra, unknown at the time, or brain oedema. This may explain why the first studies failed to demonstrate a clinical impact of diaschisis. In the late 1970s, the development of metabolic and perfusion imaging techniques gave a new impulse to the topic. For the first time, spatially refined measures of cerebral glucose metabolism could be obtained for the entire brain using *in vivo* autoradiography techniques (Raichle *et al.*, 1975; Phelps *et al.*, 1979). Areas of diaschisis remote to the lesion were defined by reduced metabolism and/or cerebral blood flow (attributed to reduced neuronal and synaptic activity). This operational definition was based on the hypothesis that the neurovascular coupling is preserved in the areas of diaschisis (Baron *et al.*, 1984). Clinically, the role of diaschisis remained debated because cortical diaschisis only partially correlated with behavioural changes, mainly after subcortical and only rarely after cortical lesions. Additionally, no relation was documented between the resolution of remote neurophysiological changes and the course of the clinical recovery, again questioning the importance of diaschisis in clinical practice (Feeney and Baron, 1986; Andrews, 1991).

Several years after this intriguing concept has largely disappeared from the mainstream interest of the neurological and neuroscientific communities, new developments in experimental methods to investigate brain function are revitalizing the topic. In animal research, new techniques are now available to model brain lesion and to investigate the distant physiological changes. The need to expand the definition of diaschisis is also necessary in light of new advancements in the understanding of brain organization: experimental and human connectivity studies of functional networks have recently revealed the impact of a focal lesion on distant connections and its behavioural consequences (Grefkes and Fink, 2011). Furthermore, as a consequence of a better knowledge of complex networks, we can begin to study how a lesion impacts on network dynamics, depending on its location in the architecture of the network (Honey and Sporns, 2008; Alstott *et al.*, 2009; Joyce *et al.*, 2013). Although the changes in brain networks due to the direct effect of the lesion (diaschisis) may be difficult to distinguish from other mechanisms of recovery such as plasticity and vicariation (process by which intact brain areas assume the functions of lesioned areas), we propose that the study of the functional consequences of diaschisis should not be limited to focal neurophysiological changes distant to the lesion.

Table 1 Original and proposed definitions of the different types of diaschisis

		Original definition	Proposed definition
Focal diaschisis	Diaschisis 'at rest'	Remote loss of excitability or 'functional stillstand' distant to the lesion (von Monakow, 1914; Feeney and Baron, 1986).	Focal decrease in energy metabolism at rest without stimulation or activation, in anatomically intact brain regions distant from the lesion.
	Functional diaschisis	Alteration of functional responsiveness of a neural system remote from a lesion when challenged by physiological activation (Ginsberg *et al*., 1989; Di Piero *et al*., 1990).	Focal abnormalities in metabolism or neuronal activity following activations or stimulations, in anatomically intact brain regions distant from the lesion.
	Dynamic diaschisis	Anatomically remote and context-sensitive effects of focal brain lesion (Price *et al*., 2001).	Context-sensitive effects of focal brain lesion on anatomically intact brain regions distant from the lesion (subtype of functional diaschisis).
Non-focal diaschisis	Connectional diaschisis	Selective changes in coupling due to lost afferents from a lesioned node of a defined network (context-sensitive) (Campo *et al*., 2012).	Selective change in coupling between two nodes of a defined network (context-sensitive or not), involving areas distant from the lesion.
	Connectomal diaschisis		Changes in the structural and functional connectome, including disconnections between and reorganization of subgraphs, involving areas distant from the lesion.

Characterization of the multifaceted nature of diaschisis is essential to understand how, as a whole, the brain is functionally affected by a focal lesion.

In this manuscript, we will investigate how after a century of research, new strategies are emerging to investigate the remote impact of a focal brain lesion. More specifically, we will first present a definition of diaschisis and its limitations. Based on this definition and the current literature, we will then identify different types of diaschisis based on their mechanism and neurophysiological correlates. Finally, we will describe new approaches that may help understand the behavioural impact of diaschisis.

Definitions

For the purpose of the review, we define diaschisis as the distant neurophysiological changes directly caused by a focal injury. To fulfil the definition, these changes should additionally correlate with behaviour and tend to normalize with time. We will consider as distant neurophysiological changes any remote alteration directly caused by the lesion, not limiting our definition to focal metabolic or electrophysiological aspects (Table 1 and Fig. 2).

At this point, it is important to reaffirm our intent to distinguish, whenever possible, the neurophysiological changes due to diaschisis as a direct inhibitory or excitatory effect of a brain lesion from other mechanisms of recovery, including neuroplasticity and vicariation. This distinction may be challenging as reorganization of brain function is likely to occur instantly or very soon after any brain lesion. In human studies, diaschisis has mainly been studied after stroke due to the focal nature of the resulting lesion, the high incidence of this pathology and its acute onset. However, diaschisis has also been reported following focal lesions of other origins (traumatic brain injury, haemorrhage). Finally, we will only consider diaschisis resulting from focal pathologies and not in the setting of progressive and diffuse neurodegenerative diseases such as Alzheimer's disease or frontotemporal dementia.

Types of diaschisis

We first distinguish two types of diaschisis. Focal diaschisis refers to the presence of remote circumscribed neurophysiological changes based on the 'classic' understanding of diaschisis and von Monakow's (1914) definition. Non-focal diaschisis relates to non-focal changes such as changes in strength and direction of distant connections of a network. This approach to the concept of diaschisis is now possible with the development of tools to determine the distant changes in connectivity. Although we do not intend to oppose these two types of diaschisis, we will see that they may have distinct clinical relevance.

Focal diaschisis

Focal diaschisis can in turn be subdivided into two types: diaschisis at rest and functional diaschisis. Diaschisis 'at rest' is defined as the focal decrease in energy metabolism at rest without stimulation or activation, in anatomically intact brain regions distant from the lesion. By contrast, functional diaschisis, described in animals (Ginsberg *et al*., 1989) and in humans (Di Piero *et al*., 1990) originally referred to the alteration of functional responsiveness of a neural system remote from a lesion when challenged by physiological activation. In this review, we propose a very similar definition of functional diaschisis, as the focal abnormalities in metabolism or neuronal activity following activations or stimulations, in anatomically intact brain regions distant from the lesion. For instance, after a cortical lesion, an increase in the response

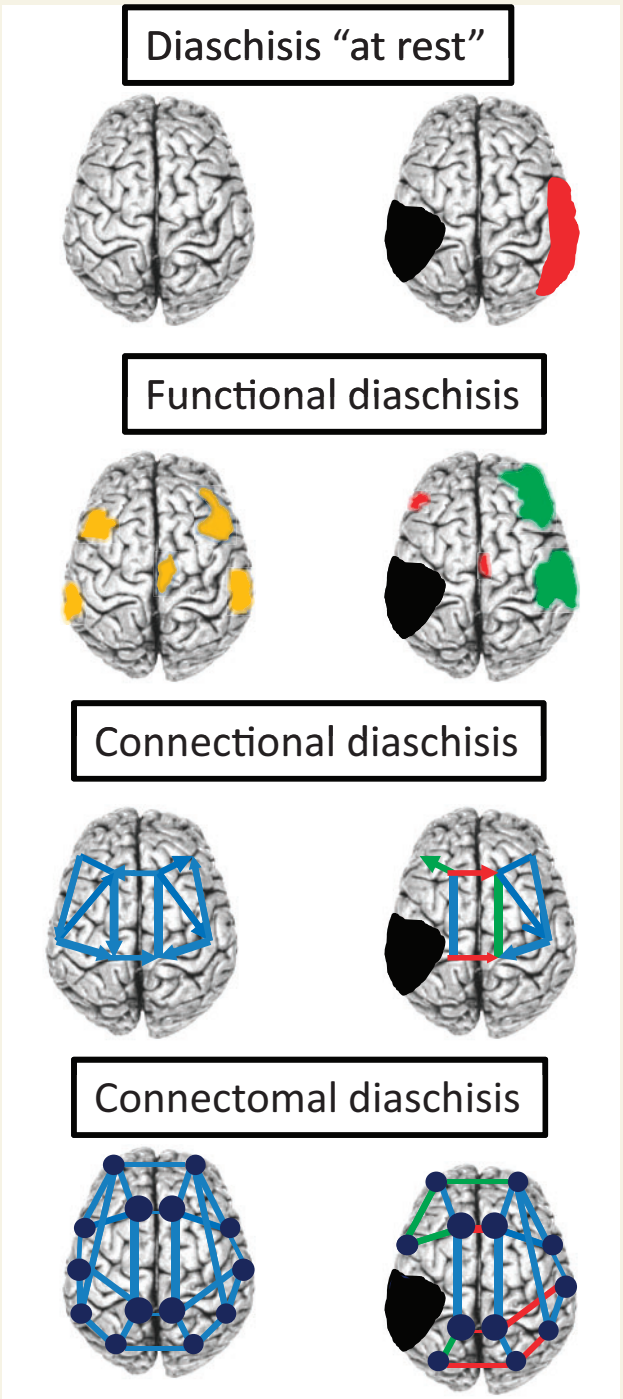

Figure 2 Types of diaschisis. Types of diaschisis before (*left*) and after (*right*) a focal brain lesion (black). Diaschisis at rest: a focal lesion induces a remote reduction of metabolism (red). Functional diaschisis: normal brain activations (yellow) during a selected task may be altered, either increased (green) or decreased (red) after a lesion. Connectional diaschisis: distant strengths and directions of connections in a selected network may be increased (green) or decreased (red). Connectomal diaschisis: a lesion of the connectome induces widespread changes in brain network organization including decrease (red) or increase (green) in connectivity.

to evoked potentials can be observed in the contralesional cortex, without concomitant alterations of metabolism 'at rest' in the same areas (Nakashima *et al.*, 1985; Mohajerani *et al.*, 2011).

Diaschisis 'at rest'

How can we identify areas of diaschisis 'at rest'? What is the neurophysiological nature of focal areas of diaschisis distant to a brain lesion? One key element of the classic definition of diaschisis is the preservation of neurovascular coupling, assuming that a reduction in cerebral blood flow follows a decrease of the metabolic demand, itself the consequence of a suppressed synaptic activity. This was first described in studies comparing the reduction of cerebral blood flow in areas of reduced oxygen and glucose metabolism due to diaschisis (Baron *et al.*, 1984). However, several animal studies have recently revealed that areas of decreased metabolism may not always correspond to regions of decreased cerebral blood flow. More specifically, the area of diaschisis defined by measures of perfusion seems to underestimate the extent of diaschisis identified by the measure of energy metabolism or neuronal activity. In an imaging study using a rat model of cortical stroke, hypometabolism was found in the ipsilateral thalamus and striatum but with only a non-significant reduction in cerebral blood flow in the same areas (Carmichael *et al.*, 2004). Using intracerebral monitoring, the same pattern was observed following a left cortical stroke (Gold and Lauritzen, 2002; Enager *et al.*, 2004), with a reduction in spiking activity that was significantly larger than the decreases in cerebral blood flow in the right contralateral cortex (layers III–V) and cerebellum (Purkinje cells). Taken together, the studies reveal the difficulties in delineating the areas of diaschisis and provide arguments for a partial disruption of the neurovascular coupling in areas of diaschisis. To confirm these findings, however, further studies are needed as cerebral blood flow remains difficult to assess *in vivo* and depends on significant confounding factors such as haemoglobin concentration or temperature. The preservation of perfusion in areas of impaired metabolism may be a sensitivity issue.

As outlined above, the behavioural impact of diaschisis is drastically different whether the lesion is cortical or subcortical (Feeney and Baron, 1986). Patients with a subcortical lesion and an area of cortical diaschisis tend to display clinical deficits that are similar to those seen after isolated cortical lesions in the same area. Although the evidence is mainly restricted to case reports or small case series, the concept of diaschisis is decisive to define the thalamo-cortical projections from the individual thalamic nuclei and to understand in particular, the neurobehavioural changes after focal thalamic stroke (Baron *et al.*, 1986; Carrera and Bogousslavsky, 2006). For example, in a patient with a stroke of the left anterior thalamic nucleus and global amnesia, a decrease in glucose metabolism was found in the posterior cingulate cortex (Clarke *et al.*, 1994). These findings illustrated the role of the posterior cingulate cortex in thalamic amnesia and the clinical relevance of projections from the anterior thalamic nuclei to the cingulate cortex. In patients with bilateral dorsomedian and intralaminar thalamic strokes, a decrease in frontomesial cortical perfusion was clinically related to a loss of psychic self-activation (Bogousslavsky *et al.*, 1991; Levasseur *et al.*, 1992; Engelborghs

et al., 2000). This clinical pattern consisting of apathy, lack of spontaneity, indifference, loss of motor and affectic drive is virtually identical to focal cortical lesions directly involving the medial part of the frontal lobe (Paradiso *et al.*, 1999). Further evidence of the clinical importance of cortical diaschisis after subcortical lesions was provided by longitudinal PET studies of patients who underwent thalamotomy for disabling tremor (Baron *et al.*, 1992) and in studies following vascular lesions of the lenticular nucleus (Giroud *et al.*, 1997).

Following cortical lesions, different patterns of diaschisis have been identified, but their impact on behaviour is more controversial (Feeney and Baron, 1986). The crossed cerebellar diaschisis is a well-described neurophysiological phenomenon that consists of a reduction in energy metabolism and blood flow in the cerebellar hemisphere contralateral to a supratentorial lesion (Baron *et al.*, 1981). This form of diaschisis results from the interruption of cerebrocerebellar pathways (excitatory corticopontine tracts). However, no definite clinical correlates of this cerebellar diaschisis have been identified so far in human, non-human primates or rodents (Feeney and Baron, 1986; Lewis *et al.*, 2012). Similarly, following cortical stroke, hypometabolism and hypoperfusion in the ipsilateral thalamus and striatum is not an uncommon phenomenon, but has no clear behavioural significance (Kuhl *et al.*, 1980; Celesia *et al.*, 1984). The impact of a cortical lesion on distant cortical metabolism is a frequent phenomenon investigated extensively using various neuroimaging and electrophysiological methods (Andrews, 1991; Lewis *et al.*, 2012).

The most frequently investigated form of cortico-cortical diaschisis is transhemispheric diaschisis, which represents a decrease in metabolism in the contralateral cortex by interruption of transhemispheric pathways. Despite a lower spatial resolution than most neuroimaging techniques, EEG and MEG can provide useful and complementary information in the investigation of transcortical diaschisis. Both techniques are of particular interest to monitor changes in neuronal activity over time and simultaneously in both hemispheres. Using standard and high density EEG, an increase in low frequencies after a stroke was reported in the homotopic controlateral hemisphere, with a reduction in alpha peak frequency (Juhasz *et al.*, 1997) and an increase in delta activity (Assenza *et al.*, 2013). A similar pattern is found using magnetoencephalography (MEG), with an increase in contralateral low-frequency rhythms after hemispheric strokes (Tecchio *et al.*, 2005, 2007). Transcallosal diaschisis is a subtype of transhemispheric diaschisis mediated by neural pathways in the corpus callosum. Trans-hemispheric diaschisis may also be mediated through connections via the thalamus or the anterior and posterior commissures, as reported in acallosal mice (Mohajerani *et al.*, 2011). As for other forms of diaschisis following cortical lesions, the clinical impact of transhemispheric diaschisis and ipsilateral cortico-cortical diaschisis has not been convincingly demonstrated (Iglesias *et al.*, 1996, 2000). In these studies, in line with non-human primate data (Pappata *et al.*, 1993; Touzani *et al.*, 1995), a reduction of contralateral cortical metabolism was delayed to days or weeks after the acute lesion, even though the patients clinically improved. In this case, changes in metabolism possibly reflected neural degeneration rather than diaschisis *per se*.

Why cortical diaschisis after cortical lesions has no clinical correlate, whereas cortical diaschisis after subcortical lesion apparently does, is unknown. One reason may be that non-specific thalamic nuclei project diffusely to multiple cortical layers in the same area and in this way interfere with local cortical networks, whereas long range cortico-cortical projections have more restricted projections with limited impact. Additionally, the absence of clinical consequences of crossed cerebellar diaschisis may be related to the recruitment of an archaic tract without behavioural significance. In the future, a more refined behavioural assessment with respect to the areas of diaschisis, performed as soon as possible after lesion onset, would be of value to refine the clinical significance of diaschisis.

Functional diaschisis

Another important and long neglected component of diaschisis is its functional aspect. After the study of diaschisis at rest, we will review the effects of a lesion on a distant response to activation or stimulation (i.e. functional diaschisis) to determine if these changes are more likely to correlate with behaviour. In other words, could activation or stimulation unmask dysfunctional regions distant to the lesion, overlapping or not with the areas of diaschisis at rest? Following initial work of Kempinski (1954, 1956, 1958, 1966), several studies investigated the functional aspect of diaschisis focusing on the response to somatosensory evoked potentials (Obeso *et al.*, 1980; Nakashima *et al.*, 1985). These studies revealed an increase in amplitude of the evoked potentials in the contralesional cortex. In recent years, functional neuroimaging has enabled a reliable measure of changes in brain activations after focal lesions. Functional PET is based on the measure of changes in cerebral blood flow whereas functional MRI is based on the measure of changes in the blood oxygen level-dependent haemodynamic response. Using these neurophysiological and imaging techniques, different patterns of functional diaschisis may be identified. After a focal lesion, a decrease or absent neuronal activations/response to stimulation can be found distant to the lesion. These areas of functional diaschisis may correspond or not to the areas that are involved in diaschisis at rest. In one patient with a left putaminal lesion investigated with functional PET, hypoactivation of the right cerebellum was found during a motor task involving the right hand but no reduced activity at rest (Di Piero *et al.*, 1990). Interestingly, the capacity of activation of remote areas depends on whether the input originates from the damaged area or from another region. In a study of four patients with lesions of Broca's area, decreased functional MRI activations were observed in the undamaged posterior inferior temporal region during a reading task. However, in one of the patients, this region could be activated during a semantic task, together with widespread temporo-parietal activations. This study suggests that the posterior inferior temporal region may not be unresponsive *per se* but rather as a consequence of losing input from the damaged area. The authors coined the term of dynamic diaschisis to describe this phenomenon (Price *et al.*, 2001). In this *princeps* paper, dynamic diaschisis was considered as 'the anatomically remote and context-sensitive effects of focal brain lesions'. The 'dynamic' dimension of diaschisis referred to the fact that brain areas distant to the lesion were activated depending on the task (i.e. context-

sensitive). In this review, we will use the slightly modified definition of 'dynamic diaschisis' as the 'context-sensitive effects of focal brain lesion on anatomically intact brain regions distant from the lesion and consider this form of diaschisis as a subtype of "functional diaschisis" '.

Contrary to von Monakow's definition, it is now established that a remote increase in brain activity in response to stimulation may be considered as part of the concept of diaschisis, as a consequence of a loss of inhibition. However, defining the role of diaschisis in this increase is challenging because mechanisms of recovery, including plasticity and vicariation begin immediately after the lesion. Human and animal studies consistently demonstrated an increase in the amplitude of somatosensory potentials cortex contralateral to the lesion. This phenomenon was attributed to an increase in remote excitability secondary to a loss of inhibition from the lesioned hemisphere (Mohajerani *et al.*, 2010) mediated by the interruption of transcallosal pathways. In experimental models, focal cortical strokes induce a long-lasting impairment in gamma-aminobutyric acid (GABA) transmission (Domann *et al.*, 1993; Buchkremer-Ratzmann *et al.*, 1996; Schiene *et al.*, 1996) in the contralesional cortex and an increase in *N*-methyl-D-aspartate (NMDA) receptor binding in the same area (Que *et al.*, 1999; Redecker *et al.*, 2002). Similarly, in rats, the long-lasting alterations in GABA-receptors after focal cortical infarcts seem to be mediated by NMDA-dependent processes. After stroke, spreading depression and inflammation (Mohajerani *et al.*, 2011) may also play a role in distant increase in excitability in addition to the interruption of transcallosal connections. This increase in contralateral evoked potentials response is consistent with the definition of diaschisis as it occurs remotely to the lesion within minutes after stroke (Mohajerani *et al.*, 2011), and tends to regress over time. Longitudinal studies performed after hemispheric strokes indicate that there is an initial increase in task-evoked functional MRI activation contralesionally. This process has been extensively described in humans and experimental studies during different tasks involving the motor (Calautti and Baron, 2003) and language systems (Saur *et al.*, 2006). For instance, after a right cortical stroke, an increase in brain activation in the left M1 cortex may occur during a motor task involving the left affected hand. With subsequent recovery, these activations tend to shift back ipsilesionally. In this case, two elements suggest that these changes in the pattern of activations may be understood as part of the concept of diaschisis. First, the contralesional over-activation occurs early after stroke. There is no strong evidence that this is a progressive process. Furthermore, the activation balance between hemispheres tends to shift back to a normal pattern as recovery takes place. The decrease in contralesional activation correlates with an improvement in recovery. Neurophysiological studies confirmed the results obtained from neuroimaging studies by demonstrating an initial increase in the beta range activity (16–26 Hz) over the contralateral hemisphere following subcortical strokes (Gerloff *et al.*, 2006). The 'normalization' of neural activation in the unaffected hemisphere was similarly correlated with good clinical recovery in a MEG study of neural activation following median nerve stimulation in patients with middle cerebral artery strokes (Tecchio *et al.*, 2007).

As we will see in the final section of the manuscript, inhibition of the contralesional over-activation using transcranial magnetic stimulation (TMS) is one of the strategies used to promote recovery (Nowak *et al.*, 2008; Sharma and Cohen, 2012). Only one study specifically compared the relationship between areas of diaschisis at rest (cerebral blood flow, assessed using ^{15}O-PET) and functional diaschisis (blood oxygen level-dependent signal during functional MRI block-design activations). In four patients with left frontal strokes, blood oxygen level-dependent signal was unaffected in areas of hypoperfusion suggesting only a partial overlap between areas of diaschisis at rest and of functional diaschisis (Fair *et al.*, 2009).

Further studies should be performed to understand the neurophysiological basis of this subtype diaschisis, but also to determine whether areas of functional diaschisis distant to the lesion may be a better correlate of behaviour than diaschisis at rest.

Connectional diaschisis

Diaschisis has long remained a concept restricted to the study of physiological changes in circumscribed areas distant to the lesion (Feeney and Baron, 1986). The first studies reporting changes in the language network were based on the measure of brain metabolism using ^{18}F-PET and Structural Equation Modelling (Metter *et al.*, 1984, 1988). With the development of novel imaging and neurophysiological techniques, it is now possible to assess the brain's functional coupling in healthy subjects and its alterations in pathological states including changes in directions and strengths. More specifically, after a focal lesion, recent studies have demonstrated widespread remote changes in connectivity in both hemispheres and between them. If it seems trivial that a lesion may cause distant changes in connectivity, it is more challenging to determine whether the cause of the remote changes in connectivity is due to diaschisis or other mechanisms of recovery such as plasticity (positive or maladaptive) and vicariation. Determining the role of diaschisis as a cause of remote changes in connectivity may help understand the direct consequences of a lesion on a brain network and determine the adequate treatment based on the underlying mechanism. The term of connectional diaschisis has recently been coined by Campo *et al.* (2012) as 'a selective change in coupling due to lost afferents from a lesioned node of a defined network'. In our understanding of connectional diaschisis, we consider a broader definition including all types of distant changes in coupling in a network regardless of context sensitivity. As focal diaschisis may be divided into diaschisis at rest and functional diaschisis, we think that connectional diaschisis may take two forms, depending on whether it is context-specific or not. The direct consequences of the interrupted connection on brain connectivity are not considered as part of the concept of connectional diaschisis.

To date, several studies have demonstrated how connectivity in different functional networks is affected by a focal lesion. This has been shown based on the measure of functional connectivity, referring to the temporal correlations between neural or haemodynamic signals arising from distinct brain regions, and on the measure of effective connectivity, which describe the intrinsic or task-dependent influences that a particular area exerts over

another (Friston, 2011; Westlake and Nagarajan, 2011). Changes in the motor network have attracted the most attention. In studies using resting state (Wang *et al.*, 2010; Park *et al.*, 2011) and seed-based functional methods in humans (He *et al.*, 2007; Carter *et al.*, 2010) and rats (van Meer *et al.*, 2011), a decrease in interhemispheric functional connectivity between homotopic cortical areas of the motor network was found after purely subcortical strokes. These changes in interhemispheric connectivity are of particular interest as they fulfil the definition of diaschisis: they are maximal early after the stroke and correlate with functional impairment. Additionally, these changes normalize over time and are related to functional recovery. Effective connectivity studies showed concordant results when interhemispheric connectivity in the motor network was investigated. In patients with subcortical strokes, a reduced influence of the ipsilateral M1 on the contralateral M1 regions (Grefkes *et al.*, 2008; Rehme *et al.*, 2011) was found, which subsequently normalized with recovery. By comparison, other interhemispheric changes in effective connectivity were less likely caused by diaschisis. For instance, there was no acute change in effective connectivity from the contralateral on the ipsilateral M1, but a positive effect in the subacute phase. In this case, other mechanisms of recovery including plasticity seem to be more likely than diaschisis. In the ipsilateral hemisphere, the severity of the motor deficit was consistently correlated with a reduction in effective connectivity between the supplementary motor area and M1 (Grefkes *et al.*, 2008, 2010; Wang *et al.*, 2010; Rehme *et al.*, 2011). Coupling parameters between these areas increased with recovery and predicted a better outcome, consistent with the concept of diaschisis. Interestingly, changes in distant connections seem independent of brain activation in the same areas, suggesting that connectional diaschisis is independent of focal diaschisis (Sharma *et al.*, 2009; Campo *et al.*, 2012). This opens new perspectives in the treatment of stroke patients including measure of connectivity (Grefkes *et al.*, 2010; Grefkes and Fink, 2012; Rehme and Grefkes, 2013). However, definitive conclusions about the functional consequences of diaschisis are limited by the use of different networks for motor representations and various techniques to assess connectivity.

The study of the impact of a lesion on distant connections is not limited to the motor network (Ovadia-Caro *et al.*, 2013). In a seed-based study (event-related functional MRI attention task) of 11 patients with right cortical stroke, the interhemispheric functional connectivity between homotopic areas of the posterior parietal cortices was acutely disrupted in correlation with the impairment of the attentional processing (He *et al.*, 2007). These changes fully resolved. In another study, the disruption of interhemispheric connectivity was significantly correlated with attention deficit in a visual task (Carter *et al.*, 2010). In both studies, a role of diaschisis may be suspected for changes in interhemispheric functional connectivity. Electrophysiological measures of effective connectivity using magnetoencephalography (MEG) dynamic causal modelling (DCM) in aphasic patients showed a correlation between the behavioural presentation and changes in connection strengths. More precisely, a negative correlation between phonemic perception and an interhemispheric connection (left to right superior temporal gyrus), and a positive correlation between semantic performance and a feedback connection (right superior temporal gyrus to right primary auditory cortex) (Teki *et al.*, 2013). Finally, in the study of 11 other patients with left mesiotemporal epilepsy who performed a working memory task, bidirectional strengthening of connectivity between the right inferior frontal cortex and the right medial temporal cortex was found (Campo *et al.*, 2012). Because of the nature of the lesion and the absence of longitudinal measures, it is, however, difficult in the reported cases to distinguish whether these changes result from a pathological state (diaschisis) or from a compensatory mechanism. Nevertheless, based on their findings, the authors used the term of connectional diaschisis to describe the nature of these changes. As discussed above, we propose to apply the term of connectional diaschisis to all changes in coupling in a selected network, irrespective of context-sensitivity, even if results from functional connectivity measures do not provide the mechanistic information effective connectivity measures do. Furthermore, to fulfil our definition, these changes should be maximal immediately after the insult and progressively normalize in parallel with clinical function.

Diaschisis: future directions

Different strategies may be used to better understand the distant impact of a brain lesion. As we will see in the following sections, the emergence of new strategies to model brain lesions and to determine their distant impacts can be used to investigate the different types of diaschisis. Additionally, the impact of lesion on complex network is largely unknown.

New strategies to model brain lesions

In rodent studies, diaschisis is most frequently investigated after ischaemic strokes (Table 2). Different techniques have been used for vessel occlusion including intraluminal filament, photothrombosis, thromboembolization and arterial vasoconstricton (Carmichael, 2005). These techniques have the advantage to be based on a physiopathological model (stroke) but also have limitations in the study of diaschisis. Variability in lesion size is observed depending on the individual variations of collaterals in the ischaemic territory. Furthermore, inflammation and waves of spreading depolarization secondary to ischaemia may affect distant cortical and subcortical structures (Mohajerani *et al.*, 2011). Pharmacological inhibition has been used for focal and controlled deficits and to overcome some of these limitations. A robust but non-selective local inactivation of a discrete brain region can be achieved using stereotactic injection of GABAa or GABAb agonists (muscimol, baclofen) (Poulet *et al.*, 2012) or voltage-gated sodium channel blockers (tetrodotoxin) (Gold and Lauritzen, 2002). Although the area of inhibition is more controlled than after a vascular lesion, determination of the duration of this inhibition is challenging and the inhibition of a selective neuronal population impossible. Similar limitations can be addressed to focal cortical cooling using cryoloops and cooling plates used for selective focal inactivation (Coomber *et al.*, 2011). With the development of genetics tools to manipulate neurons, it is now possible to achieve this goal. Optogenetics is an emerging technique for excitation or inhibition

Table 2 Current models used for brain lesions

		Spatial resolution	Temporal resolution	Reversibility	Physiological model
Animal models					
Ischaemic models	With or without craniotomy	Restricted to a vascular region	Seconds	+/−	+
Focal cooling	cooling plates and loops	Contiguous to cooling device	Seconds/minutes	+	−
Pharmacological inhibition	GABAa inhibitors	Determined by injection site and inhibitory drug	Seconds/minutes	+/−	−
Optogenetics	Inhibitory opsin (ArchT, halorhodopsin)	Highly selective, limited to a selected neuronal population	Milliseconds	+	−
Pharmacogenetics	DREADDs	Highly selective, limited to a selected neuronal population	Minutes	+	−
TMS		Determined by location and type of stimulation	Milliseconds	+	−
Human models					
Stroke		Restricted to a vascular region	Variable (usually hours)	−	+
Trauma		Lesions may be multiple	Variable (usually hours)	−	+
TMS		Determined by location and type of stimulation	Milliseconds	+	−

DREADDs = Designer Receptors Exclusively Activated by Designer Drugs.

of a selective neuronal population in response to illumination with high spatial and temporal resolutions (Fenno *et al.*, 2011). Selective excitation or silencing can be achieved in a specific region using laser stimulation of membrane-bound proteins (opsins). Long-range callosal projections of cortical neurons have been investigated following local excitation using channelrhodopsin ChR2 in slice (Petreanu *et al.*, 2007) and in living animals (Lim *et al.*, 2012; Palmer *et al.*, 2012). However, the remote effects of inhibition have not been investigated so far, but could be considered given the different inhibitory opsins available [most frequently, enhanced halorhodopsins (eNpHR2.0 and eNpHR3.0), archaerhodopsin from *Halobacterium sodomense* (Arch) and from *Halorubrum* sp. (ArchT)]. In the study of diaschisis, optogenetics seems an ideal tool to induce local inhibition because it allows a precise control of the start and duration of the inhibition and seems fully reversible after interruption of illumination (Fig. 3). The use of optogenetics as a lesion model is nevertheless currently limited by the restricted diffusion of the light source in brain tissue and by the spatial extension of the opsin expression. These limitations may be overcome in the near future by the use of transgenetic mice expressing the selected opsin in a predefined neuronal population and by the development of new devices for light delivery including LED (light-emitting diode). To achieve a larger area of inhibition, the DREADDS (Designer Receptors Exclusively Activated by Designer Drugs) technique may represent a valuable alternative to optogenetics (Alexander *et al.*, 2009). For instance, a neuronal population may be silenced with the activation of an extrinsic muscarinic receptor hM4D expressed in the selected neuronal population instead of the inhibitory opsin (Sasaki *et al.*, 2011). With this technique, inhibition is not limited by the light source. However activation of this receptor requires the intraperitoneal injection of clozapine, a synthetic, pharmacoinert ligand, limiting the temporal resolution of the inhibition.

In humans (Table 2), TMS can be used to induce a highly specific, temporally and spatially precise interruption in cognitive processing resulting in a 'virtual brain lesion' of the cortical target (Pascual-Leone *et al.*, 2000). The precise effect of TMS in inducing a virtual lesion has not been fully elucidated, e.g. whether it results from the suppression of neural signals, the disruption of ongoing processes, or the addition of neural noise. The impact on the targeted cortical area depends on the initial state of activity. When applied before a perceptual or cognitive process, the TMS pulse seems to facilitate the investigated process. On the contrary, an inhibitory effect corresponding to 'a virtual brain lesion' can be obtained when TMS is performed during the cognitive process (Silvanto and Muggleton, 2008). A virtual brain lesion can be induced using single or repetitive pulses. However the risk of side effects including seizures seem higher with the use

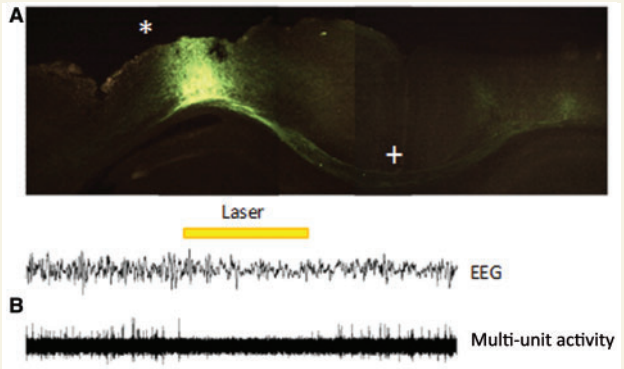

Figure 3 Transient cortical inhibition using optogenetics. (**A**) Coronal section of a mouse expressing ArchT–YFP in the right parietal cortex. ArchT-expressing axons projects to the controlateral homotopic left parietal cortex. Corpus callosum (+); injection site (*). (**B**) A 5-s pulse of yellow light silences an ArchT-expressing neuron in the right parietal cortex. Note that multi-unit activity levels return to normal after the pulse.

of repetitive TMS. In the context of diaschisis, remote changes in connectivity can be assessed after a focal virtual lesion is induced by TMS. For this purpose, it is essential to combine TMS with functional MRI or EEG (Ruff *et al.*, 2009).

New strategies to determine distant effects of the lesion

In experimental studies, neurophysiological techniques are widely available for chronic monitoring of brain activity in freely behaving animals. As previously described, the measure of extracellular fields has been used to investigate areas of diaschisis (Gold and Lauritzen, 2002; Enager *et al.*, 2004) but this technology has long been limited by technical issues. With the development of new microelectrodes using silicon-based polyoptrodes, it is now possible to monitor multi-unit activity and local field potentials with a better spatial coverage and resolution (Buzsaki *et al.*, 2012). Furthermore, by comparison of local field potential and multi-unit activity in different regions, it is possible to determine the strength and directions of connections between them. For instance, Saalmann *et al*. (2012) recently demonstrated the regulation of the connections between V4 and the temporo-occipital area by the pulvinar in monkeys performing a visuospatial attention task. In the near future, a similar approach, applied to the concept of diaschisis, may be used to determine the impact of a lesion or inhibition on distant connections. Two-photon microscopy allows 3D imaging of biological specimens *in vivo* and may be used to investigate diaschisis. Compared to confocal microscopy, two-photon microscopy offers a slightly lower resolution but induces less photodamage of tissue. So far two two-photon microscopy studies investigated the remote dendritic plasticity and functional remapping after stroke. However, in the absence of acute measures, the remote impact of a lesion remains unknown (Takatsuru *et al.*, 2009; Johnston *et al.*, 2013). With two-photon microscopy, the blood flow in individual cortical vessels can now be assessed in addition to the local cellular activity (Shih *et al.*, 2012). This technique will be useful to investigate the nature of focal neurophysiological changes distant to the lesion especially the integrity of neurovascular coupling. In humans, brain imaging has provided key information to the understanding of diaschisis. In the future, new imaging techniques such as spectroscopy MRI (Abe *et al.*, 2000; Chu *et al.*, 2002) or combined high resolution MRI and PET (Catana *et al.*, 2012) will provide additional metabolic and perfusion information. Complementarily, electrophysiological studies using high-density EEG (Dubovik *et al.*, 2012; De Vico Fallani *et al.*, 2013) and MEG (Westlake *et al.*, 2012) can be used to determine changes over time distant to the lesion with a higher temporal resolution and using novel approaches of the concept of diaschisis. Finally, as we will discuss in the following section, the concept of diaschisis may be applied to complex networks.

Diaschisis and the connectome

We have previously described how the concept of diaschisis can be applied to the study of coupling changes in specific networks distant to the lesion. The recent application of graph theory to brain data has provided insight into the complex network organization of the human brain. While it is now possible to determine the impact of a focal lesion on the global brain network architecture, it is more difficult to investigate whether this impact on architecture might have a clinical relevance.

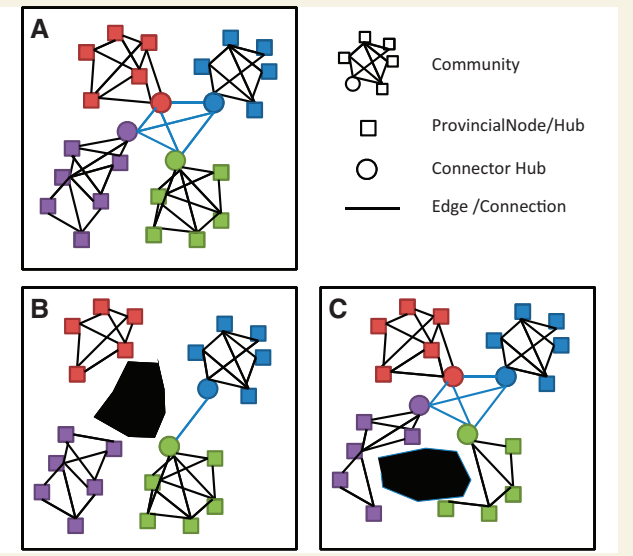

Figure 4 Representation of the impact of the lesion on segregation and integration of the network. Representation of a 'healthy' (**A**) and lesioned networks (**B** and **C**). (**B**) A lesion of connector hubs alters the global functional integration of the different communities. Each disconnected community becomes more independent from the others. (**C**) Lesion of a community reduces the local integration of the network. Adapted from Sporns *et al.* (2013), with permission from Elsevier.

Organization and mapping of the connectome

The connectome is defined as a comprehensive map of all neural connections in the brain (Sporns *et al.*, 2005). It can be represented by brain graphs defined by a set of nodes and edges drawn between them (Bullmore and Bassett, 2011). However, the connectome is not simply defined by the random juxtaposition of networks. Indeed, the nodes and edges of the connectome are organized as a subtle balance between trade-off between economy and efficiency. The 'small-world' model maximizes local and global information processing between nodes of the network (Watts and Strogatz, 1998). It is recognizable by communities of highly connected nodes (Sporns, 2013) but with only few connections between nodes of different communities (Fig. 4). This organization promotes functional segregation between communities but preserves their functional integration (Sporns *et al.*, 2007). In this developing field, the importance of nodes and edges can be determined using various measures (Rubinov and Sporns, 2010). This complex brain architecture suggests that lesions in its structure induce widespread effects and therefore must be distinguished from a lesion in a single network.

The connectome can be assessed using structural and functional measures of connectivity (Table 3). Diffusion tensor imaging represents the most frequent form of structural imaging used to map the connectome. It estimates the tridimensional orientation of the

Table 3 Techniques to investigate connectional and connectomal diaschisis after focal lesions in humans

Electrophysiological studies	High density EEG (HdEEG)	Connectivity is determined by comparison between regional changes in neuronal activity. The recorded signal can be spectrally decomposed and connectivity assessed in distinct frequency bands. **Pro**: Non-invasive. High temporal resolution. Higher spatial resolution compared to standard EEG. **Con**: Spatial resolution lower than with imaging methods especially for subcortical networks.	A. Changes in brain networks in the beta band during motor imagery of the affected hand after cortical stroke. Adapted from De Vico *et al.* (2013), with permission from Elsevier.
	Magneto-encephalography (MEG)	Connectivity between two regions can be acquired over a broad frequency spectrum. Low and high frequency oscillations are mainly used for connectivity studies. **Pro**: Non-invasive. Higher spatial resolution than HdEEG (magnetic fields are less distorted by the skull than electric fields). **Con**: Technically complex technique. Limited spatial subcortical resolution.	B. Regions of high correlations between functional connectivity (fcMEG) and recovery after cortical stroke. Adapted from Westlake *et al.* (2012), with permission from Elsevier.
	Electrocortico-encephalography (EcoG)	EcoG may be a reliable approximation of local field potentials. **Pro**: Higher spatial resolution and higher signal-to-noise ratio than EEG.	
Imaging studies	Structural MRI	Diffusion tensor imaging and diffusion spector imaging use the properties of diffusion of water molecules in a constrained environnement to determine structural connectivity. **Pro**: Useful for white matter tracts structure studies. High spacial resolution, particularly useful for the study of network including subcortical nodes. **Con**: Assess structural connectivity which partially differs from functional connectivity.	C. Dynamic effects of a lesion (green cross) near the temporo-parietal junction. Adapted from Alstott *et al.* (2009).
	Functional MRI	Functional MRI represents a method to determine connectivity between two areas that share functional properties. Assessement of connectivity using functional MRI is based on the comparison of fluctuations in blood oxygenation signal (BOLD) between two regions. **Pro**: High spatial resolution. Reflects functional rather than structural connectivity. Helps define strength and direction of links between nodes. **Con**: Highly sensitive to head motion. Sensitive to differences in mental states. Does not necessary reflect anatomic structures. May vary across time.	D. Increased and decreased functional connectivity over time. Adapted from Wang *et al.* (2010).

(**A**) High density-EEG: scalp representation of connectivity (beta range) during movement of the affected hand. Blue and red lines denote the links within the unaffected (Uhemi) and the affected (Ahemi) hemispheres, respectively. Grey lines denote the interhemispheric links. Adapted from De Vico Fallani *et al.* (2013). (**B**) MEG: regions of high functional MEG and recovery score. Red and yellow regions indicate positive associations between baseline functional MEG and recovery. Blue/green regions indicate negative associations. Adapted from Westlake *et al.* (2012). (**C**) Structural MRI. Effects of temporo-parietal lesion on structural connectivity, red (weakened coupling) or blue (strengthened coupling) after lesion (green cross). Adapted from Alstott *et al.* (2009). (**D**) Functional MRI: weakened (blue lines) and strengthened (red lines) resting state functional MRI connectivity in the motor network are mainly located between ipsilesional primary cortex area and contralesional key motor areas, whereas the decreased connections involve ipsilesional subcortical areas and cerebellum. Adapted from (Wang *et al.*, 2010). IH = ipsilesional hemisphere; CH = contralesional hemisphere.

diffusion of water molecules for each brain voxel (Van Essen and Ugurbil, 2012). Diffusion tensor imaging is particularly helpful to determine white matter connections between grey matter regions. Diffusion spectrum imaging is a variant of diffusion tensor imaging whose merit is to determine fibre crossing, since imaging of multiple fibre orientation in a single voxel is possible (Hagmann *et al.*, 2008). Resting state functional MRI, EEG and MEG can all be used to describe comprehensive maps of functional networks. The functional coupling between brain regions can be determined with the study of temporal correlations between slow fluctuations of the neurovascular signal (functional MRI) or EEG and MEG signals (Deuker *et al.*, 2009; He and Evans, 2010; Power *et al.*, 2011). The main merit of electrophysiological measures (EEG and MEG) is the high temporal resolution that provides useful information about changes over time despite a lower spatial resolution. Organization of the connectome based on structural and functional connectivity are strongly interrelated (Honey *et al.*, 2009). However, there are notable differences. Connectome models based on structural connectivity exhibit lower variability than those based on functional connectivity. Furthermore, two brain regions may be functionally related with no direct structural connections. This is particularly important in the study of long-range connections responsible for integration between remote brain regions (Gallos *et al.*, 2012). Recent approaches intend to infer functional coupling based on structural connectivity (Goni *et al.*, 2014). As we will discuss later, it is important to notice at this point that both structural and functional connectivity measures do not inform on direction and strength of the relationship between brain regions and cannot differentiate excitatory and inhibitory polysynaptic effects (Park and Friston, 2013), which makes the mechanistic comprehension of brain function after focal lesions of the connectome problematic.

Impact of a lesion on brain organization

How does a lesion impact on the connectome and how may remote changes in the architecture of the connectome represent a 'new' form of diaschisis? The study of the remote effects of a lesion on brain graphs (i.e. connectomal diaschisis) is particularly useful when the resilience of the brain architecture is investigated. Structural and resting-state functional MRI studies recently demonstrated that the small-world organization is important for protecting the networks against an attack but differ depending on the characteristics of the hubs (Achard *et al.*, 2006). A deletion of a connector hub will disconnect the functional communities and increase the small-world index, whereas deletion of a provincial hub will affect the functional segregation of the community (Sporns *et al.*, 2007). Anatomically, the most widespread damage to the organization of the connectome (Alstott *et al.*, 2009) results from lesions of the cortical midline and in the temporo-parietal junction. This study, using diffusion spectral imaging sequences, is consistent with the modelling of lesions in the structural monkey CoCoMac database (Honey and Sporns, 2008). Using these data, lesions in the midline structure of the parietal (areas 5 and 7a) and frontal lobes (areas 46 and frontal eye field) had the greatest potential to disrupt the connectome and possibly in integrative aspects of neocortical function. These studies show that changes in the connectome are not restricted to changes in coupling in networks as part of the definition of 'connectional diaschisis'. Lesions in the connectome demonstrate complex changes in the relationship within and in-between modules or subgraphs providing information about integration and segregation.

Relationship between changes in the organization of the connectome and loss of function

Despite these promising results, one fundamental question remains unanswered: how may changes in the connectome influence clinical function? Indeed, the study of the functional impact of a lesion on the connectome faces several challenges: the first challenge relates to the techniques used for mapping of brain graphs. As we have seen, current descriptions are based on structural or functional connectivity measures under stationary assumptions. How can these techniques be used to determine the relationship between changes in the connectome distant to the lesion and loss of function? Despite being context-invariant, structural and functional connectivity techniques can estimate the impact of a lesion on virtually all neural connections/edges in the brain connectome. Based on brain graph measures, the effect of the lesion can additionally be determined on coupling within and between modules remote to the lesion. As a consequence, remote changes in the connectome may reflect more accurately the complexity of resulting cognitive and non-cognitive clinical deficits. Effective connectivity measures provide invaluable information about weight and directions of remote connections. However, these techniques are not sufficient to reflect the complexity of the whole clinical picture. They are limited by the number of nodes of the network of interest and therefore restrict the investigation to the task of interest. As developed currently, this method of investigation cannot replace the global information provided by the study of the connectome understood as the weighted average of all possible contexts. Nevertheless, future developments in the field will determine whether effective connectivity methods may be applied to systems with more than a limited number of nodes (Bullmore and Bassett, 2011). The use of dynamic causal modelling represents a promising approach to identify graph models for effective connectivity that best explain empirical data (Friston *et al.*, 2011; Seghier and Friston, 2013). These models derived from effective connectivity measures may be well suited for the understanding of brain function and complement current approaches of brain graphs using context-invariant structural and functional connectivity strategies. Finally, the study of the impact of changes in the connectome may extend its interest beyond its explanatory power in the management of patients suffering from focal brain lesions. The temporal changes in organization of the connectome remote to the lesion may represent a surrogate marker of recovery. Indeed, network dysfunction extends into the structurally intact hemisphere (Gratton *et al.*, 2012). It is not yet clear if the effects of a lesion on small world metrics could lead to a mechanistic conclusion about pathophysiology and functional brain architecture. To date, studies of brain graphs after focal lesions have been limited to specific networks. In rats, an increase in 'small-worldness' in the somatosensory network was found 3 days after stroke. This increase was more important following large strokes but shifted back to normal after 2 months (van Meer *et al.*, 2012). In a

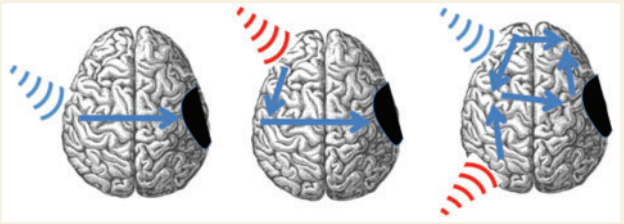

Figure 5 Strategies for brain stimulation/inhibition after cerebral brain lesions. Different strategies to target cortical areas after a focal cortical lesion (black). Inhibition (**A**) or stimulation (**B**) of contralateral cortical areas. (**C**) Concomitant stimulation and inhibition of multiple cortical areas.

longitudinal study in humans, no change in small-world organization was observed within 2 weeks after stroke (Wang *et al.*, 2010). Surprisingly, the network then gradually shifted towards a random mode, suggesting that the small-world architecture is not necessary during the recovery process.

Based on these considerations, we think there is enough evidence to propose a new subtype of diaschisis: 'connectomal diaschisis' could be defined as the 'remote changes in the structural and functional connectome, including disconnections and reorganization of subgraphs'. In the near future, new studies are required to investigate the clinical interest of 'connectomal diaschisis'. If of proven clinical value, these studies may then form the basis of treatments focusing on restoring the functional integrity of the connectome.

Diaschisis as a target for neuromodulation

In this review, we have seen that the clinical interest of diaschisis is debated when based on observational studies only. The interest in the topic may increase if treatment, based on physiological changes remote to the lesion, improves the short- and long-term clinical outcome. Different techniques are now available for neuromodulation. Non-invasive brain stimulation techniques include repetitive TMS and transcranial direct current stimulation (DCS) (Fig. 5). They are potentially useful techniques for the neuromodulation of diaschisis, as they directly affect local cortical activity. Furthermore, the immediate effect on cortical excitability persists for several hours/days. In the context of diaschisis, the first studies using non-invasive brain stimulation after focal lesions were based on the observation that the contralateral hemisphere was disinhinited after cortical or subcortical motor strokes. This is an attempt to modulate "focal diaschisis". Repetitive TMS or transcranial DCS were used to induce an inhibition of the contralateral dishinibited primary motor cortex (M1) to decrease the inhibition of the ipsilesional hemisphere (Nowak *et al.*, 2008; Ameli *et al.*, 2009; Grefkes and Fink, 2012). This modulation of contralateral M1 focusing on 'normalization' of activation showed conflicting results, with no clear benefit on outcome. This variability between studies may be due to the different parameters (number, frequency and duration of pulses) used for brain stimulation or inhibition. Furthermore, TMS pulses may affect excitability of adjacent areas (Miranda *et al.*, 2013). Finally, the comparison between studies is limited because patients were examined at different stages of recovery. Nevertheless, these limitations may be overcome by using different alternative strategies. For instance, repetitive TMS and transcranial DCS can be used to modulate other nodes of the motor network including the dorsal premotor cortex, the superior parietal lobe or the cerebellum (Lotze *et al.*, 2006).

The modulation of remote coupling between cortical regions is a strategy to modulate 'connectional diaschisis'. In a recent study based on effective connectivity and dynamic causal modelling in patients with subcortical strokes, repetitive TMS, when applied to the contralesional M1, not only induced restoration of the inhibition of the contralesional M1 regions, but also increased the effect of ipsilesional supplementary motor area to the ipsilesional M1 (Grefkes *et al.*, 2010). In the future, concomitant use of MRI and repetitive TMS may allow individualized treatment based on coupling changes after stroke 'bridging the neuronal and network level' (Grefkes and Fink, 2014; Raffin and Siebner, 2014). The development of robotic-based therapy, based on the analysis of brain connectivity measures, may also help target critical pathways for recovery. The association of neuromodulatory strategies with drug treatment or physical therapy may improve the efficacy of repetitive TMS or transcranial DCS. In the future, it will be important to determine whether restoration of original networks or modulation of alternative circuits is the best strategy to improve recovery.

Conclusion

As we have seen, diaschisis is a multiform, open concept. Over more than a century, diaschisis has evolved in parallel with our understanding of brain function and the development of new tools to assess brain function. Although the location and characteristics of the distant changes may vary, they all represent remote alterations directly provoked by a focal lesion. As discussed in this review, there is mounting evidence that diaschisis may have an importance in accounting for clinical findings that cannot be explained by local changes. Nevertheless, the key point in testing the validity of the concept of diaschisis in humans will be to determine whether neuromodulation of physiological changes distant to the lesion may promote clinical recovery. This is particularly true for the treatment of cerebrovascular diseases, for which therapeutic options remain limited.

Acknowledgements

The authors thank Professor Jean-Claude Baron for helpful discussions and suggestions and Professor Andreas Kleinschmidt for his comments and remarks.

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