Contrasting acute and slow-growing lesions: a new door to brain plasticity

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The concept of plasticity describes the mechanisms that rearrange cerebral organization following a brain injury. During the last century, plasticity has been mainly investigated in humans with acute strokes. It was then shown: (i) that the brain is organized into highly specialized functional areas, often designated 'eloquent' areas and (ii) that a lesion within the eloquent area gives rise to major irrevocable deficits. However, in sharp contrast with these observations, it was recently found that patients with low-grade gliomas were able to undergo massive cerebral resections without detectable functional consequence. In this paper, we tackle this puzzling observation and address the idea that brain plasticity cannot be fully understood and fruitfully studied without considering the temporal pattern of the injury inflicted to the brain. To achieve this goal, we first review experimental evidence showing that functional recovery is considerably better in the context of slow-growing injuries than after acute lesions. Both human and animal data are considered. In a second step, we emphasize that slow and acute lesions involve very different patterns of reorganization. In agreement with this idea, we show that the recruitment of remote brain areas in the ipsi- and contralesional hemispheres is much more efficient in slow growing than acute lesions. Finally in a last section, we briefly discuss the main implications of these results.

Keywords: brain plasticity; stroke; low-grade glioma; brain surgery; functional mapping

Abbreviations: DES = direct electrical stimulation; LGG = low grade gliomas; SMA = supplementary motor area; TMS = transcranial magnetic stimulation


Introduction

In 1861, P. Broca reported the case of a patient who became unable to speak after a lesion of the rostral part of the left inferior frontal convolution. A few years later, in 1874, C. Wernicke described a 'mirror' subject whose lesion, in the posterior part of the left superior temporal gyrus, prevented any word comprehension. These two cases proved very influential. They established the methods and hypotheses of our modern neurophysiology. They suggested in particular that: (i) the brain is organized into highly specialized functional areas, often designated 'eloquent' areas; (ii) a lesion within the eloquent areas gives rise to major irrevocable deficits. Based on these premises, patients with ischaemic strokes were extensively studied during the last few decades. It was then found, in agreement with the original finding of Broca and Wernicke, that only a minority of stroke patients completely recovered. In most cases ischaemic injuries were reported to induce mild to severe permanent deficits (Stallones et al., 1972; Varona et al., 2004). This result gave rise to the idea that cerebral plasticity has very limited healing potential in the context of brain injuries. However, recent data on slow-growing lesions have called the generality of this conclusion into question by showing impressive recovery after massive cerebral lesions. In particular, the field of low-grade gliomas (LGG) have...
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demonstrated that large amounts of cerebral tissue could be removed, inside or outside the so-called eloquent areas, without detectable functional consequences (Duffau et al., 2003a). This finding nicely parallels some old reports in humans and animals. In humans, for instance, it was shown that large brain tumors did not prevent the patients from living a normal life (Jackson 1879, von Monakow, 1914). In monkeys, it was demonstrated that functional recovery was much better in slow-growing cerebral lesions than in acute brain destructions (Finger, 1978; Finger and Stein, 1982). Although these animal studies have been widely disregarded, they are of primary importance. Indeed, they indicate that the difference between acute and progressively growing lesions cannot be dismissed by simply arguing that strokes cause undetected damages in the peri-lesional tissue, that acute infarcts are more likely to occur in older patients, or that the surgical release of a tumour-related compression explains the good post-operative recovery (an often mentioned idea which does, in fact, not even apply to the non-compressive nature of LGG; Daumas-Duport et al., 2005). When all the potentially confounding factors are controlled, as can be done in animal studies, functional recovery remains considerably better in slow growing than in acute lesions.

Previous publications have addressed the issue of functional recovery in the context of slow-growing injuries or acute strokes. The specificity and originality of this review is to directly compare the neural and behavioural outcomes of these two types of lesions. We believe that such a direct comparison is needed for at least two reasons. First, it shows that neural plasticity cannot be fully understood and fruitfully studied without considering the temporal pattern of the injury inflicted to the brain. Second, it creates a bridge between two fields of research that should ‘feed’ each other but generally unfold along parallel paths. Regarding this second point, one may note that the literature on slow-growing lesions has not yet abandoned the comfortable nest of neurooncology to become an established experimental paradigm. As observed by the authors of this review in two recent meetings, lesion data associated with slow-growing lesions lead often to skepticism or even distrust, when presented outside the field of neurooncology. The reason for these negative reactions is probably that slow-growing lesions tend to question and challenge our classical, modular view of brain architecture (Finger, 1978).

For the sake of clarity, the present review is organized in three sections. The first section focuses on behavioural observations. It shows that functional recovery is substantially better in the context of slow-growing injuries than after acute lesions. Both human and animal data are considered. The second section deals with the neural processes of brain plasticity. It shows that slow and acute lesions give rise to very different patterns of reorganization. The last section discusses briefly the fundamental and clinical implications of these results.

Acute strokes and slow-growing lesions: behavioural observations

Clinical observations in humans

Strokes

Strokes occur with high frequency, at least in occidental countries. For every million people, 2400 strokes are observed every year (Hankey and Warlow, 1999). Almost 50% of the 2400 stroke victims are unable to return to work. More than 70% of the patients still exhibit mild to severe functional deficits after 11 years (Varona et al., 2004). These numbers agree with more ancient observations provided by Stallones et al. (1972). According to these authors, of every 100 survivors of the acute phase of a stroke, 10 will return to work without disability, 40 will have ‘mild’ disability, 40 will be severely disabled and 10 will require institutionalization. At the scale of the United States (300 million inhabitants), these values predict that 720,000 subjects will suffer a stroke every year. Among these subjects, 72,000 will recover totally, 288,000 will keep ‘mild’ functional deficits, 288,000 will be left with severe irreversible disabilities and 72,000 will require placement in a medical institution.

Low-grade gliomas

LGG (WHO Grade II gliomas) are slow-growing primary tumours of the CNS. In comparison to ischaemic strokes, these gliomas have a relatively rare occurrence. For instance, within a population of one million people only 10–20 individuals will be diagnosed with a LGG every year (Wessels et al., 2003; Walker and Kaye, 2003). This means 3000–6000 cases at the scale of the United States. LGG progress slowly (4 mm per year on average Mandonnet et al., 2003) for 7–8 years, until undertaking a fatal anaplastic transformation (Walker and Kaye, 2003). During this slow progression, a majority of LGG patients exhibit normal clinical exams (Walker and Kaye, 2003), even if slight cognitive disorders can be detected using extensive assessments (Taphoorn and Klein, 2004). In fact, in 80% of the patients, LGG are not revealed by behavioural deficits, but by the sudden occurrence of seizures (DeAngelis, 2001).

During the last decade, preventive resection of LGG has become a major therapeutic option. It was then found that major ‘eloquent’ regions could be removed without inducing permanent deficits. These regions include Broca’s area (Fig. 1; Duffau et al., 2000a, 2001c, 2002b), the left (Duffau et al., 2001c) and right insula (Fig. 2; Duffau et al., 2003c), the sensorimotor cortex (Duffau et al., 1999; Duffau and Capelle, 2001b; Duffau, 2001, Fig. 3), the supplementary motor area (SMA, Kraynik et al., 2001; Fig. 4), the striatum (Duffau et al., 2002c), the corpus callosum (Duffau et al., 2004), the frontal eye fields (Milea et al., 2002), the left angular gyrus (Duffau et al., 2002d), the left posterior parietal cortex (Duffau et al., 1999, 2002a, d; Fig. 5) and the right (Fig. 6) and left (Fig. 7) temporal lobes (Duffau et al., 2002a, b; Gatignol et al., 2004).
data, a recent meta-analysis reported that 93% of 103 patients harbouring LGG in various regions were both able to return to work within a year and free of identifiable functional deficits when submitted to classical clinical and neurological evaluations. The remaining patients (7%) showed only mild deficits (Duffau et al., 2003a).

The results above are even more impressive when contrasted with a similar, already mentioned, meta-analysis performed in stroke patients (Varona et al., 2004, Fig. 8). In this analysis, 74% of patients presented mild to severe neurological deficits 11 years after the stroke. A complete recovery was only observed in 26% of the subjects. Only 30% of the patients were able to return to a normal professional life. An additional 20% were able to do so in an adapted environment. These high proportions of permanent deficits may seem puzzling when contrasted with stroke literature as a whole. Indeed, substantial levels of recovery are reported in many studies. This discrepancy is relatively easy to explain if one considers that stroke studies often aim to identify the neural processes underlying post-lesional plasticity. This leads to two biases: (i) focusing on very specific functions (e.g. language) without describing other non-relevant deficits (e.g. motor) potentially exhibited by the patients (e.g. Cao et al., 1999; Calvert et al., 2000; de Boissezon et al., 2005; Longworth et al., 2005); (ii) selecting patients for whom a good recovery is observed (e.g. Chollet et al., 1991; Weiller et al., 1993; Cao et al., 1998; Cramer et al., 2000; Johansen-Berg et al., 2002a; Foltys et al., 2003; Fridman et al., 2004). As observed by Rijntjes and Weiller (2002) with respect to this latter point, ‘for both the motor and language systems, it should be pointed out that usually only patients who have recovered well are reported. There is hardly any information about activation patterns in patients that recover poorly’ (Rijntjes and Weiller 2002, p. 115).

**Experimental observations in animals**

The possibility that functional recovery is modulated by kinetic factors has been addressed in a series of animal...
Acute strokes and slow-growing lesions: neurophysiological correlates

In the paragraphs above, we have shown that functional recovery is directly influenced by the kinetics of the lesion inflicted to the brain. In this study, in contrast, complete recovery was found. The same type of disassociation was observed in monkeys. Acute ablations of the prefrontal cortex were found to induce functional deficits that were much more severe than those produced by serial lesions (Rosen et al., 1971).

Probably, the most direct demonstration that functional recovery is directly influenced by the kinetics of the lesion inflicted to the brain has been provided by Patrissi and Stein (1975). These authors trained a group of rats to retrieve water alternatively located in the right or the left branch of a conventional T-maze. Following a period of training, the rats were divided in four sub-groups: (i) one-stage bilateral resection of the frontal cortex; (ii) two-stage bilateral resection of the frontal cortex (one hemisphere per operation); (iii) one or two-stage sham operations (control group). For the two-stage groups, three inter-lesion intervals were considered: 10, 20 or 30 days. As shown in Fig. 9, the rats given sequential (two-stage) frontal lesions with either a 20 or 30 day inter-operative interval could not be differentiated from the sham-operated controls. Animals with two-stage lesions, produced 10 days apart, exhibited substantial deficits when contrasted with the sham-operated, the 20 or the 30 day two-stage groups. However, the two-stage 10 day animals performed significantly better than the one-stage rats. Similar results were found in other studies involving resections of the frontal cortex (Glick and Zimmerberg, 1972), the visual cortex (Meyer et al., 1958) and the superior temporal gyri (Stewart and Ades, 1951). In all these studies, the animals were reported to exhibit a complete recovery when the different surgeries were spaced by a sufficient interval. This interval varied from study to study but it was never smaller than 6 days. Whatever the inter-lesion interval, the level of recovery was always better for the multi-stage surgeries than for the one-stage operations.

Of course, the positive effect of sequential lesions on functional recovery depends strongly on the amount of tissue resected at each surgical stage. This was clearly shown by Stein et al. (1977) in a monkey study involving the resection of the sulcus principalis. In this study, the total amount of tissue resected was kept constant. It was reported that four partial lesions performed three weeks apart produced a greater level of recovery than two partial lesions performed 10 weeks apart. This result pleads directly for the idea that the progressiveness of neural destruction is a key predictor of functional recuperation.

**Stroke data**

During the last decades, numerous studies have been performed with the purpose of identifying the functional anatomy of post-lesional recovery in stroke patients. At a first level, these studies have distinguished between passive and active recovery mechanisms (Seitz, 1997). Passive mechanisms refer to the non-plastic changes that take place during the acute phase of the infarct. With respect to this point, spontaneous reperfusions with subsequent regression of oxygen depletion, the progressive resolution of the injury response (oedema, inflammation) and the resolution of diaschisis have been shown to play an
important role in recovery (Inoue et al., 1980; Kuhl et al., 1980; Hakim et al., 1987; Sakashita et al., 1993; Heiss et al., 1993; Furlan et al., 1996; Cappa et al., 1997; Toni et al., 1997; Cramer and Bastings 2000; Croquelois et al., 2003). Because the present review aims to investigate active brain plasticity, we will not discuss these passive recovery mechanisms any further.

Following the acute post-ischaemic phase, functional compensations start to take place. Of course, the nature of these reorganizations depends on the original architecture of the lesioned network. With respect to this point, the main message of the stroke literature may be that recovery is always substantially better when performed within the boundaries of the original (non-lesioned) network. For instance, language functions rely heavily on the left (dominant) hemisphere. As shown in several studies, when the left hemisphere regions are destroyed, some compensation occurs in the homologous structures of the right hemisphere (Gainotti 1993; Cao et al., 1998; Heiss et al., 2003). In this case however, the functional recovery is usually poor (Karbe et al., 1998; Heiss et al., 1999, 2003). As emphasized by Selnes (1999, p. 419), ‘recruitment of right-hemisphere structures for language recovery is a last-resort type of strategy and one that yields a less than satisfactory overall degree of language recovery in most instances’.

Within this context, it is not surprising that the best level of recovery is generally observed, in language functions, when compensatory recruitments take place in the peri-lesional area, along the rim of the injured tissue (Heiss et al., 1993; Miura et al., 1999; Herholtz et al., 2000; Rosen et al., 2000). It is worth mentioning, however, that some patients display good levels of recovery in the presence of non-dominant activations. For instance, Clavert et al. (2000) described the case of a patient who suffered a stroke in Broca’s area and recovered well while showing an increased activation within the right homologous region. This type of compensation is usually thought to reflect the existence of an atypical, relatively large, bilateral language representation before the stroke (Rijntjes and Weiller, 2002).

Another well-documented example of ‘intrinsic reorganizations’ is provided by the motor system. In this case, functional control is not lateralized and the ‘dominant’ hemisphere is the one that is contralateral to the moving segment. After a stroke, physiological changes occurring in the damaged hemisphere seem to be more efficient in producing a good level of recovery than physiological changes occurring in the undamaged hemisphere. As emphasized by Hallett (2001, p. 172) ‘contralateral control, even if reorganized, seems superior to ipsilateral control in recovery’. In agreement with this claim, transcranial magnetic stimulation (TMS) studies have repeatedly reported that the ability to trigger motor evoked potentials (MEP) from the lesioned hemisphere was the most reliable marker of good recovery (Heald et al., 1993; Catano et al., 1995, 1996; Misra et al., 1995; Binkofski et al., 1996; Rapisarda et al., 1996; Turton et al., 1996; Escudero et al., 1998; Pennisi et al., 1999; Bastings et al., 2002; Ziemann, 2005). This observation is compatible with other data showing that
(i) contralesional TMS does not interfere with the performance of simple motor tasks, while ipsilesional TMS does (Werhahn et al., 2003; Fridman et al., 2004); (ii) motor maps are enlarged and/or displaced in the lesioned hemisphere of hemiparetic patients (Cicinelli et al., 1997; Traversa et al., 1997; Rossini et al., 1998); (iii) motor improvements are associated with plastic reorganizations of the lesioned hemisphere during rehabilitative therapy (Liepert et al., 2000; Johansen-Berg et al., 2002a; Cramer, 2003). In line with this latter observation, several imaging studies have reported that the early recruitment of the contralesional sensorimotor cortex tended to vanish over time, as the paretic hand regained function (Marshall et al., 2000; Calaustti et al., 2001). However, a recent study failed to reproduce this result (Feydy et al., 2002).

Probably the best evidence for an intrinsic plasticity involving the original ipsilesional motor network comes from animal studies in which localized injuries were performed within the motor system. A good example of such studies is provided by Rouiller and colleagues who recently investigated the functional and neural consequences of brain lesions positioned within the hand territory of M1. Two experiments were conducted in newborn (Rouiller et al., 1998) and mature (Liu and Rouiller, 1999) monkeys. In these experiments, the experimental lesions were combined with reversible inactivations to investigate cerebral reorganizations. As could be expected, very different results were obtained in the two studies. In the newborn investigation, the monkeys showed substantial, although partial, recovery.

Fig. 5 (A) Pre-operative axial FLAIR-weighted MRI, showing a left LGG involving the superior parietal lobule. (B) Post-operative axial FLAIR-weighted MRI after surgery, showing a total tumour removal, with resection of the entire superior parietal lobule. The patient neurological examination was normal before and after tumour removal.

Fig. 6 (A) Pre-operative axial T1-weighted MRI, showing a right fronto-temporo-insular LGG. (B) Post-operative axial T1-weighted MRI, showing a total glioma removal, with resection of the entire right paralimbic system. The patient had an immediate post-surgical hemiparesia, and completely recovered within 3 months.
(the functional score was >50% lower with the paretic than with the normal hand). This recovery was mediated by the development of a ‘new’ hand area in M1, adjacent to the lesioned territory. When this adjacent region was inactivated, the monkeys were no longer able to perform the prehension task for which they had been trained. In the adult study, more dramatic long-lasting deficits were observed. Nine months after the lesion, the functional

**Fig. 7** (A) Pre-operative T1-weighted axial and sagittal MRI showing a left temporal LGG. (B) Post-operative axial and sagittal MRI showing a total glioma resection. The patient neurological examination was normal before and after tumour removal. (from Duffau et al., 2002b).

**Fig. 8** Functional deficits as a percentage of the patient population following a stroke (dark grey) or a slow-growing tumoural invasion (black: LGG patients prior to resection; light-grey: LGG patients 3 months after resection). From Duffau et al. (2003a; 103 patients; mean age 36) and Varona et al. (2004; 272 patients; mean age 36).
score for the paretic hand reached a plateau at ~30% of the pre lesion score. This partial recovery was found to be sustained by the non-primary motor areas within the lesioned hemisphere (premotor cortex and probably the supplementary and cingulate motor areas). In contrast to what had been observed in newborns, no reorganization was found within M1, around the lesioned area. Compatible results were provided by Frost et al. (2003) in an experiment requiring adult monkeys to retrieve pellets in wells of five different diameters. A peri-lesional re-mapping was however reported in another experiment in which the animals were submitted to a specific rehabilitative training (Nudo et al., 1996).

In contrast with the human and animal data reported above, imaging studies have provided repeated indications that contralesional pathways are significantly involved in post-stroke recovery of motor functions. For instance, Chollet et al. (1991) used PET to investigate neural reorganizations in six patients who had recovered substantially from a capsular infraction. When motor activations associated with the recovered and normal hands were compared, increased responses were detected in the contralesional hemisphere in the sensorimotor cortex, the insula and the inferior parietal cortex. A significant signal was also identified in the cerebellum on the ipsilesional side. These data were replicated and generalized in subsequent studies. It was then shown, in hemiparetic patients, that the hand representation was displaced and/or enlarged bilaterally in most motor territories, including M1, the premotor cortex, the SMA, the retrocentral areas, the posterior parietal cortex and the insula (Weiller et al., 1993; Maegaki et al., 1995; Cramer et al., 1997, 2000; Cao et al., 1998; Seitz et al., 1998; Chassoux et al., 1999; Vandermeeren et al., 2002; Pinedo et al., 2001; Cramer, 1999). Three hypotheses have been proposed to account for these bilateral responses. First, some contralesional activations might be associated with the existence of mirror movements in the intact hand when intending to move the paretic hand (Weiller et al., 1993; Marshall et al., 2000). Second, the fact that ipsilesional motor regions play a dominant role in recovery does not mean that contralesional structures have no role to play. As emphasized in the previous paragraph, the contribution of distant contralesional structures may become more important, as a last-resort strategy, when the size of the infarct prevents ipsilesional recovery (Kolb, 1995; Kolb et al., 2000; Hallett, 2001; Johansen-Berg et al., 2002b; Ward, 2004). Third, contralesional activations may result from the suppression of transcallosal inhibition. The activations observed within the intact motor cortex in hemiparetic patients provide the best illustration for this idea. For M1, it has been shown that (i) the magnitude of the activations observed within the intact cortex did not correlate with functional recovery (Cao et al., 1998); (ii) the neural activity in the contralesional M1 did occur after the onset of the motor response (Verleger et al., 2003); (iii) a TMS-triggered disruption of the functioning of the contralesional M1 did not affect the response of the paretic hand in patients with various degrees of impairments (Werhahn et al., 2003; Fridman et al., 2004); (iv) the MEPs resulting from contralesional TMS did not correlate with the clinical improvement exhibited by the patients (Netz et al., 1997). With respect to this latter point, it was even reported that contralesional MEPs were more prevalent in the patients who exhibited the poorest level of recovery (Turton et al., 1996). When considered together, these observations suggest that the cortical activation observed in the contralesional M1 (i.e. ipsilateral to the limb) is reflective of a suppression of transcallosal inhibition (Liepert et al., 2000; Feydy et al., 2002; Shimizu et al., 2002).

In summary, the data above suggest that functional recovery is substantially better when occurring within the boundaries of the original (non-lesioned) network. The best outcome is found when plastic neural reorganizations take place within the regions adjacent to the infarct zone. A poor
level recovery is generally observed when neural reorganizations involve the intact hemisphere.

**LGG data**

**Pre-operative reorganizations**

Numerous pre-operative neurofunctional imaging studies have shown that tumour invasions trigger major neural reorganizations. These reorganizations explain why most LGG patients appear either normal or only slightly impaired under standard neurological assessments (Duffau and Capelle, 2001a; Duffau et al., 2003b; Duffau, 2005) (Fig. 8). Unsurprisingly, the nature of the reorganizations induced by slow-growing lesions has been shown to differ from patient to patient (Carpentier et al., 2001). However, beyond individual variations four main plastic patterns have been reported.

First, the infiltrative character of LGG makes it possible for the function to persist within the tumour. Recently, magneto-encephalography studies have suggested that this intra-tumoural activity was present in up to 36% of the patients (Ganslandt et al., 1997, 2004; Schiffbauer et al., 2001, 2002; Daumas-Duport et al., 2003). Similar results have been obtained in fMRI studies. For instance, Krainik et al. (2003) demonstrated that BOLD activation of the SMA did occur despite infiltration by an LGG. These authors reported that surgical resection of this region induced, for 50% of the patients, a 'SMA syndrome', in agreement with the idea that the fMRI activation really reflected a functional persistence within the glioma for these patients.

Second, eloquent areas can be redistributed immediately around the tumour. For instance, pre-operative neuroimaging techniques have revealed, for LGG located within the central region, that the hand representation was displaced and enlarged around the tumoural tissue (Youssry et al., 1995). Anatomic deformations associated with the presence of the tumour were not able to account for these changes, suggesting that a true functional re-mapping had taken place (Atlas et al., 1996; Mueller et al., 1996; Righini et al., 1996). Similar observations were described in the language domain. Non-aphasic patients harbouring a glioma within Broca’s area were reported to exhibit speech-related activations in the left inferior frontal cortex adjacent to the tumour (Meyer et al., 2003a).

Third, a distributed network of areas can be recruited within the lesioned hemisphere. For instance, in patients harbouring intracerebral gliomas within the motor system, activations of ‘secondary motor areas’ have often been reported during simple tasks such as finger tapping or grip force modulation. These activations commonly concern the SMA, the premotor cortex and the superior parietal lobe (Seitz et al., 1995; Atlas et al., 1996; Wunderlich et al., 1998; Krings et al., 2002; Meyer et al., 2003b). A similar type of ‘remote plasticity’ was observed in patients harbouring intracerebral gliomas within the language system. In this case, speech-related activations were observed (i) in the left superior temporal gyrus following tumoural invasions of Broca’s area (Heiss et al., 2003; Meyer et al., 2003a); (ii) in Broca’s area following tumoural invasions of the left temporo-parietal region (Meyer et al., 2003a). Interestingly, some patients with slowly evolving gliomas affecting language functions were also reported to recruit ‘non typical’ language areas in the left frontotemporal regions, including Brodmann areas (BA) 46 and 47, and the SMA (Thiel et al., 1998, 2001; Meyer et al., 2003a). A recruitment of remote areas not typically involved in language functions was also observed following lesions of the left insula (a structure known to contribute to the planning of speech; Ackermann and Riecker, 2004). In this case, compensatory activations were reported, not only in Broca’s area and the left superior temporal gyrus, but also in the left putamen (Duffau et al., 2001c).

Finally, a network of areas can be recruited in the contralateral hemisphere. For instance, for LGG located within the rolandic region, several studies have reported activations within the contralesional primary motor cortex (Yoshiura et al., 1997; Caramia et al., 1998; Fandino et al., 1999; Roux et al., 2000; Baciu et al., 2003), the contralesional premotor area (Fandino et al., 1999) and the contralesional SMA (Krainik et al., 2004). For language function, translocations of Broca’s area to the right hemisphere were observed following the development of a LGG within the left inferior frontal cortex (Holodny et al., 2002). Likewise, translocations of Wernicke’s area to the contralesional hemisphere were reported in the context of left temporo-parietal tumours (Petrovitch et al., 2004). However, the significance of these translocations is often questioned. A frequent criticism suggests, in particular, that the recruitment of the intact contralesional homologous reflects a decrease of transcallosal inhibition (Netz et al., 1995; Heiss et al., 2003; see above) or a compromised BOLD signal at the vicinity of the tumoural tissue (Ulmer et al., 2003, 2004). A recent study seems to convincingly rebut these concerns by showing that TMS induces speech disruption when applied over the contralesional activation sites (Thiel et al., 2005). Of course, the different plastic patterns reported above rarely occur in isolation. Generally, recovery takes the form of a mix between different types of compensatory recruitments. For instance, recent studies have reported a combination of peri-tumoural and contra-hemispheric activations in patients harbouring intracerebral gliomas within the sensorimotor (Fandino et al., 1999) and language systems (Thiel et al., 1998; Heiss et al., 2003; Meyer et al., 2003a). In the largest study to date, PET was used to study the plasticity of the language network in 61 patients harbouring gliomas in the left hemisphere (Thiel et al., 2001). A combination of inter- and intra-hemispheric compensations was observed in >60% of these patients. Interestingly, while some patients exhibited pure intra-hemispheric compensations, no example of unmixed contralesional recruitment was provided. This suggests that the four different patterns of compensation described above are organized in a hierarchical manner.
According to this view, intrinsic reorganizations occurring within the injured and perilesional structures are the first factor of compensation (Thiel et al., 2001; Heiss et al., 2003). Remote recruitments in the ipsi- and contralesional hemispheres occur only at a second level, when local reorganizations become insufficient. In agreement with this model, it has been reported that activations in the contratumoural hemisphere were associated with a less complete recovery (Heiss et al., 2003 for a discussion).

In summary, the data above suggest that different plastic processes compensate for LGG invasions. These processes seem to follow a hierarchical model similar to the one previously discussed in the context of acute strokes: local compensations take place before the occurrence of remote recruitments. Beyond this analogy, however, LGG recovery presents two major specificities. First, compensations can involve areas that are not part of the typical functional network (e.g. BA 46, BA 47, for speech; Thiel et al., 2001). Second, remote compensations in the intact or lesioned hemisphere are not a marker of poor recovery. Concerning this latter point, one may argue that LGG resections would be impossible if this was not the case. Indeed, if efficient plastic compensations were only possible within and around the glioma, it would be impossible to resect the tumoural tissue without generating major functional deficits. With respect to this point, it may be noticed that neurosurgeons usually tend to remove a small layer of sound tissue around the tumour to increase the likelihood of obtaining a complete resection and decrease the probability of tumoural recurrence (Duffau et al., 2005; Duffau, 2005).

**Intra-operative reorganizations**

LGG resection is bounded by two constraints: (i) removing as much as possible of the invaded tissue; (ii) minimizing functional sequelae. Unfortunately, this equation cannot be solved pre-operatively only, using imaging techniques. Indeed, the IMRI BOLD signal seems compromised at the vicinity of LGG (Holodny et al., 1999, 2000; Roux et al., 2003; Fujiwara et al., 2004), which may both prevent reliable identification of significant responses in the peri-lesional region (Schreiber et al., 2000; Murata, 2004; Aubert et al., 2002) and lead to the observation of a false functional response in the intact hemisphere (Ulmr et al., 2003, 2004).

In addition, with imaging techniques it is not always possible to distinguish between essential (non-removable) and compensable (removable) structures (Price et al., 1999; Duffau, 2005). These problems explain why the use of intra-operative DES is widely advocated during surgical resections (Berger and Rostomily, 1997; Keles and Berger, 2004a; Keles et al., 2004b; Duffau, 2005). DES generates transient disturbances when applied on a neural epicentre essential for the function (Ojemann et al., 1989). These disturbances allow to map functional systems in the motor (by inducing involuntary movements), somatosensory (by eliciting dyasesthesia) and cognitive domains (by inhibiting the function). In this latter case, functions such as language (spontaneous speech, object naming, comprehension, etc), calculation, memory, reading or writing can be investigated. Of course, most of these investigations require the surgery to be performed under local anaesthesia in an awake patient. Under this framework, the rule is quite simple: any reproducible functional disturbance induced by DES provokes the interruption of the resection (Duffau, 2005).

From a theoretical point of view, the major difference between DES and the pre-operative approaches (evoked potentials, electrocortical recordings, imaging) lies in the fact that DES is a technique, not of neural recording, but of ‘active’ functional perturbation. This technique achieves a transient virtual lesion, thus allowing to isolate, at each stage of the resection, the structures that are essential for the function (Duffau, 2004). DES has been shown to propagate only along the stimulated white matter pathways (Matsumoto et al., 2004; Thiebaut de Schotten et al., 2005) and to induce a marginal amount of cortical spreading (Haglund et al., 1993).

During the last decade, DES performed just before and during the resection has confirmed the possible persistence of functional responses within LGG (Ojemann et al., 1996; Skirboll et al., 1996; Danks et al., 2000). For instance, when the somatosensory motor cortex is stimulated with DES, paraesthesias and facial movements can still be observed, despite tumoural invasions (Duffau et al., 2003b). Likewise, speech disorders can be evident when DES is applied over the invaded surface of the left insular cortex (Duffau et al., 2000a) or the left paralimbic cortex (Duffau et al., 2006). Similar results were reported for invasions involving the subcortical white matter pathways (Skirboll et al., 1996; Duffau et al., 2003a). In fact, the most direct evidence of functional response within the tumoural tissue comes from the observation that the surgical resections driven by DES remain sub-optimal in >50% of the cases (Mandonnet et al., 2006b). This result can be explained by the fact that LGG are not bulkiy but infiltrative lesions, which tend to travel along the white matter tracts (Mandonnet et al., 2006a).

In most patients, DES reveals the existence of a redistribution of the eloquent areas in the regions just adjacent to the lesion (Duffau et al., 2003b). This was shown, in particular, in patients harbouring ‘silent’ tumours within language structures. In these patients, peri-tumoural DES is generally able to induce language disturbances that are not present pre-operatively. For instance, a local reshaping of the language network is often observed following a tumoural invasion of Broca’s area. In this case, functional compensations recruit adjacent regions including the left ventral premotor cortex, the middle frontal gyrus (BA 46) and the pars orbitalis of the inferior frontal gyrus (BA 47) (Duffau, 2003; Duffau et al., 2003b).

Because brain exposure is performed around the invaded area, DES is generally not relevant for investigating distant compensations. However, a small set of data seems to
support the functional validity of remote recruitments for behavioural recovery. For instance, in patients harbouring a silent tumour within the left insula, compensations were found in the damaged hemisphere in Broca’s area, the left superior temporal gyrus and the putamen (Duffau et al., 2001). These results support the conclusions of pre- (see above) and post- (see below) operative imaging studies.

Regarding intra-surgical plasticity, a very puzzling observation concerns the existence of acute functional re-mapping triggered by the resection itself and taking place within 15–60 min of beginning the surgical act. This type of acute reorganization is illustrated in Fig. 10. It has been very well documented in the sensorimotor system (Duffau et al., 2000b; Duffau, 2001; Duffau and Capelle, 2001b; for a review see Duffau and Capelle, 2001a). The origin of these changes remains unfortunately unknown. The most likely hypothesis suggests that a local increase of cortical excitability allows to unmask latent intracortical connections (Duffau et al., 2000b; Duffau, 2001). In agreement with this idea, animal models have shown that focal brain damages induce large zones of enhanced cortical excitability in both the lesioned and the intact hemisphere (Buchkremer-Ratzmann et al., 1996). Likewise, human studies have provided evidence that the level of intracortical inhibition is reduced in the damaged hemisphere in stroke patients (Gicinelli et al., 2003).

Whether or not this hypothesis of increased excitability is true, it is tempting to speculate that the latent redundant networks revealed by the resection process participate in functional recovery (Nii et al., 1996). This idea fits well with the importance of adjacent reorganizations for behavioural recuperation.

**Post-operative reorganizations**

While mechanisms of post-stroke recuperation have been thoroughly investigated during the last 50 years, the processes of post-resection recovery in slow-growing lesions have emerged only recently as a major subject of research. This explains why data associated with this topic remain scarce. However, this scarcity is counterbalanced by the existence of a relative consensus among studies. Schematically, the post-operative literature reinforces the pre-surgical observations by suggesting that functional recovery involves a large array of complementary mechanisms. For instance, using magneto-encephalography, it has been reported that resections of the somatosensory cortex (S1) caused peri-lesional sites to be recruited around the cavity, within the postcentral gyrus (Meunier et al., 2000). In addition to this local re-mapping, contributions of S2, the posterior parietal cortex and the primary motor cortex were also reported.
using post-operative DES (Duffau and Capelle 2001b). Similar combinations of local and remote reorganizations were found in the language domain, after resections of Broca’s area. In this case, DES performed right at the end of the resection showed that plasticity involved a reorganization of the neural networks within the premotor cortex, the pars orbitalis of the inferior frontal gyrus and the insula (Duffau et al., 2003b). These data are compatible with other results showing that the language networks evolve from surgery to surgery when successive operations have to be performed (Duffau et al., 2002b). They also agree with the rapid regression of the functional deficits observed when the SMA proper is removed (Krainik et al., 2003). Postoperative fMRI images taken after the regression of these deficits suggest that plastic functional compensations involve the contralesional SMA, the contralesional premotor cortex (Krainik et al., 2004) and, potentially, the ipsilesional primary motor cortex (Duffau et al., 2003b). Unfortunately, to date, no study has tried to directly investigate the actual functional role of these regions using, for instance, TMS.

Implications
At a therapeutic level, the most obvious message of the present review is clearly that LGG can be treated surgically without generating detectable functional deficits, even when the tumour is located in the so-called ‘eloquent areas’. Another promising implication points to the possible development of iterative surgeries for LGG patients. Because these clinical issues have been discussed elsewhere they will not be examined here any further (Duffau, 2005).

At a fundamental level, the present review questions the growing localizationist trend of our modern neurophysiology. The anatomo-functional model has become so powerful that the issue of ‘functional localization’ has penetrated even our most complex human faculties. For instance, recent reports have claimed that visuomotor adaptation is mediated by the parietal area PEG (Clower et al., 1996), that saccadic adaptation relies on the medio-posterior cerebellar cortex (Desmurget et al., 1999, 2000), that imitation (Iacoboni et al., 1999) and understanding (Gallese and Goldman, 1998) of actions depends on Broca’s area, that our moral sense originates in the prefrontal cortex (Anderson et al., 1999), that religious experience is built into our nervous system within a restricted frontal-parietal network (Azari et al., 2001) and that romantic and maternal love engages the medial insula and the anterior cingulate cortex (Bartels and Zeki, 2000, 2004). During the last decade, a handful of authors have questioned the theoretical and methodological significance of these results (for a review see Farah, 1994; Uttal, 2001). The present review supports their effort. Indeed, both clinical data in LGG patients and experimental observations in brain lesioned animals demonstrate that the brain is not a rigid mosaic of independently encapsulated modules. Massive brain lesions within almost any area of the brain, including the supposedly untouchable eloquent areas, can often be effectively counterbalanced by adjacent and remote changes in neural organizations. Of course, this astonishing plasticity does not mean that the brain is equipotent and that it can compensate for any type of lesion, as was once suggested by Lashley (1950). Rather, it indicates that functional specializations are not the inevitable byproduct of local architectonic differences. The ability of ‘non-canonical’ speech areas (BA 46 and 47) to compensate for LGG invasion located in Broca’s area provides an especially convincing support for this idea.

Beyond the remarks above, one major issue remains to be addressed: why is functional plasticity so limited following acute infarcts and so remarkable following slow tumoural invasions? Although this question cannot be answered irrefutably at this point, it is tempting to speculate that a gradual learning process mediates brain plasticity. According to this idea, plastic adaptations take place through supervised learning. Eloquent areas would then play the role of a ‘distant teacher’ (Jordan and Rumelhart, 1992). This teacher would instruct intact regions through direct or indirect pathways, providing these regions with new functional competences. Acute destruction would prevent this gradual learning process from taking place, thus leading to a poor recovery. Of course, further investigations are required to test this appealing, but still conjectural hypothesis.

Conclusions and perspectives
The take-home message of the present review might be summarized as follows. While major irrevocable functional impairments are generally reported following acute injuries, a complete or nearly complete recovery is commonly observed in the context of slow-growing lesions. Here, we have shown this latter conclusion to be true for slow tumoural invasions in humans and multiple surgical resections in animals. Although this is beyond the scope of the present paper, it may be worth mentioning that data associated with slow degenerative disease are also compatible with the idea that our brain possesses a very high potential for plasticity. For instance, in patients with Parkinson’s disease, no behavioural symptom is observed until the neural destruction reaches 80% among the dopaminergic cells of the substantia niagra pars compacta (Bernheimer et al., 1973). This ‘preclinical period’ has been estimated to last between 3 and 7 years (Morrish et al., 1996, 1998), even if some older reports have suggested that the presymptomatic state could, in fact, unfold over several decades (Vingerhoets et al., 1994). It is now widely admitted that powerful adaptive mechanisms are responsible for the existence of this prolonged preclinical period (for a review see Bezard et al., 2003). In agreement with this idea, it has been shown, in monkeys, that acute and chronic lesions of the niagra dopaminergic system were associated with very different patterns of behavioural deficits (Hantraye et al., 1993; Bezard et al., 1997).
With respect to the present review, the relevant (and probably trivial) message carried by the degenerative disease literature is that never-ending slow-growing lesions exhaust progressively the plastic potential of the brain. When a certain threshold is reached, the system can no longer cope with the neural destruction and behavioural deficits start to appear. It is very plausible that the same sort of mechanism is at work in ageing. In agreement with this idea, it has been shown that cognitive performance is maintained in older adults through the recruitment of neural networks that are more distributed and more bilateral than the networks recruited by younger subjects (Cabeza et al., 2001, 2004). As the years pass by, however, the effects of small acute injuries and normal neural death add up making plastic compensations more and more uncertain. If one admits this premise as plausible, two important inferences follow. First, tumoural resections tax the plastic potential of the brain, leaving open the possibility that ageing will have a dramatic effect on the health of the patients. Because the systematic resection of LGG is a recent practice, it will unfortunately not be possible to investigate the validity of this concern for at least a second. Second, the massive plastic potential revealed by slow-growing tumoural models might be critical, not only in pathological situations, but also in the context of ‘normal’ ageing. According to this view, plastic mechanisms would act, throughout our lives, to counterbalance the deleterious effects of time. This idea is compatible with the observation that slow-growing lesions, that mimic the effect of ageing, are compensated for much more efficiently than acute lesions. Of course, further investigations remain necessary to investigate the validity of these ideas.

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References


Duffau H, Capelle L. Functional recuperation after resection of gliomas.


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Meunier S, Duffau H, Garnier L, Capelle L, Ducorps A. Comparison of the somatosensory cortical mapping of the fingers using a whole head magnetoencephalography (MEG) and direct electrical stimulations during surgery in awake patients. Neuroimage 2001; 15: 5868.


Schiffbauer H, Berger MS, Ferrari P, Freudenstein D, Rowley HA, Roberts TP. Preoperative magnetic source imaging for brain tumor surgery: a


von Monakow C. Die Lokalisation im Groshirn und der Abbau der Funktion durch kortikale Herde. Wiesbaden, Germany: Bergman; 1914.


