Brain plasticity and tumors

H. DUFFAU

Department of Neurosurgery, Hôpital Gui de Chauliac, CHU de Montpellier, Montpellier Cedex, France and Laboratoire de Psychologie et Neurosciences Cognitives (CNRS FRE 2987/Université de Paris V René Descartes), Institut de Psychologie, Boulogne Billancourt, France

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Abstract

Brain plasticity is the potential of the nervous system to reshape itself during ontogeny, learning or following injuries. The first part of this article reviews the pathophysiological mechanisms underlying plasticity at different functional levels. Such plastic potential means that the anatomo-functional organization of the brain in humans, both physiological and pathological, has flexibility. Patterns of reorganization may differ according to the time-course of cerebral damage, with better functional compensation in more slowly growing lesions. The second part of this review analyzes the interactions between tumor growth and brain reshaping, using non-invasive (neuroimaging) and invasive (electrophysiological) methods of functional mapping. Finally, the therapeutic implications provided by a greater understanding of these mechanisms of cerebral redistribution are explored from a surgical point of view. Enhanced preoperative prediction of an individual's potential for reorganization might be integrated into surgical planning and preserving quality of life through tailored rehabilitation programmes to optimize functional recovery following resection of a brain tumor.

Keywords: Brain plasticity; sensorimotor; language; functional neuroimaging; electrical stimulation mapping; brain tumor; neuro-oncology; low-grade glioma.

Introduction

As early as the beginning of the XIXth century, two opposing concepts of the functioning of the central nervous system were suggested. First, the theory of "equipotentiality" hypothesized that the entire brain, or at least one complete hemisphere, was involved in the performance of a functional task. In contrast, the theory of "localizationism", supposed that each part of the brain corresponded to a specific function, so called "phrenology". Reports of lesion studies led to an intermediate view, namely a brain organized (1) into highly specialized functional areas called "eloquent" regions (such as the central, Broca's and Wernicke's areas), in which any lesion gives rise to major irrevocable neurological deficits, and (2) into "non-functional" structures, with no apparent clinical consequence when injured.

Based on these initial anatomo-functional correlations and despite the description by some pioneers of several examples of post-lesional recovery [9, 138], the dogma of a static functional organization of the brain was secure for a long time, with no ability to compensate for any injury involving the so-called eloquent areas. However, through regular reports of improvement of the functional status following damage to cortical and/or subcortical structures considered as "critical", this view of a "fixed" central nervous system has been called into question. In particular, slow-growing cerebral tumors such as low grade gliomas (LGG), have demonstrated that large amounts of cerebral tissue

may be removed, inside or outside the so-called eloquent areas, with impressive recovery and often no detectable permanent functional consequences [37]. This finding parallels some old reports in humans and animals. In humans, for instance, it was shown that large brain tumors did not prevent patients from living a normal life [69, 138]. As a consequence, a growing number of investigations have recently been performed, not only in vitro and in animals, but also in humans since the development of non-invasive neuroimaging methods, in order to study the mechanisms underlying these compensatory phenomena: the concept of cerebral plasticity was born.

The goal of this article is to link enhanced understanding of the pathophysiology of cerebral plasticity (at sub-cellular, cellular, up to the topographical level) to the possible use of this dynamic potential for clinical applications in neuro-oncology.

Cerebral plasticity: fundamental considerations

Definitions

Cerebral plasticity is a continuous process allowing short-term, middle-term and long-term remodelling of the neural organization, with the aim of optimizing the functioning of brain networks [49]. Plastic changes constitute fundamental events which underly various kinds of brain development (1) during phylogenesis, with structural and functional cerebral maturation throughout evolution of the species; (2) during ontogeny and ageing, with the elaboration of new circuits induced by learning, and also with the maintenance of neural networks in adults into old age [63]: these physiological processes constitute "natural plasticity"; (3) after injury of the peripheral or central nervous system, with functional reshaping underlying a partial or complete clinical recovery: this is the "post-lesional plasticity" [146]. In all cases, these dynamic phenomena have to be stabilized in order to allow the functioning of the system: these mechanisms of regulation represent "homeostatic plasticity" [133].

Pathophysiological mechanisms subserving cerebral plasticity

Several mechanisms underlying brain plasticity have been reported, from the ultrastuctural to the topographical levels [14, 47] (Table 1).

At the ultrastructural scale, beyond the processing involved in development [66] and potentiated by learning according to Hebbian's concept [22], the other mechanisms advocated are: modifications of synaptic weight [15, 87], synchrony [75], unmasking of latent connections and networks [70, 81], glial modulation [52, 61], regulation by the extracellular matrix [26], phenotypic changes [74, 102, 134] and neurogenesis [57, 60, 79, 112] – which might also play a role in glioma genesis [114].

Table 1. *Mechanisms subserving brain plasticity at ultrastructural and macroscopic levels*

Microscopic level	Map level
Modification of synaptic weight	Resolution of diaschisis
Synchrony	within-area reshaping via recruitment of functional redundancies
Unmasking of latent connections and networks	Redistribution within eloquent network
Glial modulation	Cross-modal plasticity
Phenotypic changes	Macroscopic changes
Neurogenesis	Compensatory strategies

These ultrastructural changes may lead to a functional reorganization at a macroscopic scale, via the following mechanisms: resolution of diaschisis [121]; within-area reshaping via recruitment of functional redundancies [29, 31], redistribution within eloquent network [104] – especially through the recruitment of contralateral homologue areas [72] – cross-modal plasticity [6, 54, 93], compensatory strategies [107] and macroscopic structural changes [28, 80, 97].

Moreover, numerous experiments over the past twenty years in animals have demonstrated that functional cortical organization could be modulated not only by experience, but also by lesions of the peripheral [117, 144] and central nervous system [94]. This plastic potential was observed within the visual, auditory, and above all, sensorimotor cortex [78, 108]. Furthermore, the possibility that functional recovery is modulated by the kinetics of the lesion inflicted on the brain has been addressed in a series of animal studies [1, 53, 89, 96, 105, 125, 139]. Such factors are very important in order to better understand the variability with regard to the functional compensation in humans with cerebral lesions, according to the time-course of the injury (acute versus slow-growing lesions) – thus to adapt the therapeutic strategy, as will be detailed later [25]. In addition to studies showing that the cortical motor map could be modulated by skill acquisition with specific learning-dependent enlargement of cortical representation, animal studies suggested that, after local damage to the motor cortex, rehabilitative training such as constraint-therapy could shape subsequent reorganization in the adjacent intact cortex and could favor the recruitment of the undamaged motor cortex, which might play an important role in motor recovery [94]. These first results in animals have provided the basis for the elaboration of specific retraining in humans following nervous system injury (see below). Potentiation of post-lesional plasticity using pharmacological agents was also tested in animals, especially with the demonstration of a neuroprotective effect on the somatotopic map with chronic treatments such as piracetam [146].

In summary, the better understanding of the pathophysiological mechanisms underlying the functional and morphological changes (and their stabilization) at the microscopic and macroscopic levels, as studied in vitro, in vivo in animals and also in silico, have provided the basis for analyzing the behavioural plasticity in humans.

Natural plasticity in humans

Despite a static "point by point" view of the somatotopic organization of the homonculus since its description by Penfield in humans [100], recent studies in healthy volunteers have demonstrated the existence of multiple representions of movements within the primary sensorimotor cortex [115], with an overlap and a likely hierarchical organization of the functional redundancies [65]. It has been advocated that some cortical sites within the primary motor area could correspond to a representation of muscle, while other sites might rather correspond to a representation of postures, and even of more complex movements [56, 59]. Moreover, this cortical representation of the muscles and movements seems to be organized as a "mosaic" [118], which may facilitate an intrinsic reshaping of this primary area during learning and following an injury (see below). These concepts are in accordance with neurofunctional imaging studies performed in healthy volunteers during skill learning [10]: extension of activation was observed, most likely corresponding to a recruitment of adjacent sites in order to favor the acquisition of new motor sequences. Interestingly, this phenomenon can be durable, particularly in musicians [92].

In addition to this "spatial" distribution based on multiple functional representations, the "temporal" organization of this mosaic must also be considered. Numerous electrophysiological recording studies, notably using magnetoencephalography in humans, have shown changes in neural activity in the sensorimotor cortex following skill learning, and changes in oscillations of neural activity in this same region during motor action [111]. These oscillations could reflect the synchronous cortical activity of many neurons, and might allow the rapid modification of the ensemble of neurons involved in the execution of a motor task, through a modulation of their temporal relationships [75]. Therefore, these mechanisms could contribute to sensorimotor plasticity.

Beyond this dynamic organization of the primary sensorimotor cortex with its ability to reshape, such plasticity mechanisms also imply possible changes (a) in activity within the other "non-primary" structures implicated in the sensorimotor network, and (b) in the effective connectivity within this whole network – as revealed by measurement of the coherence of the activity between the distinct areas involved in the sensorimotor function [2].

Finally, this recent progress in human brain mapping methods has also led to a revised view of the neural basis of language, i.e. a spatio-temporal func-

tioning of parallel distributed cortico-cortical and cortico-subcortical networks, with the simultaneous and/or successive involvement of a mosaic of hierarchically organized areas, some of them essential and others compensatable, with an inter-individual variability [136].

Plasticity in acute brain lesions

Post-lesional sensorimotor plasticity

In cases of acute cerebral lesions, especially stroke, plasticity mechanisms frequently include both intrinsic reorganization of the primary sensorimotor cortex, and also the recruitment of other "non-primary" regions implicated in the functional network. Indeed, remodelling of the primary sensorimotor area was first observed following damage to the corticospinal pathway, in particular in cases of deep stroke: the cortical representation of the paretic hand expanded laterally, within the face representation [141]. Second, due to the fact that reorganization within the primary sensorimotor cortex is often insufficient to insure a (complete) functional compensation, numerous neurofunctional studies performed in patients who recovered following a lesion of the sensorimotor network showed activations of other ipsi-hemispheric regions – such as the premotor areas [18], supplementary motor area [16], retrocentral areas including the posterior parietal cortex [32], and the insula [19]. Furthermore, the participation of the contralateral hemisphere, in particular the "mirror" primary sensorimotor area was also suggested [16, 84, 98, 104]. In the same way, in cases of damage involving the primary somatosensory area, several works showed the recruitment of the contralateral homologue [57], in addition to the ipsilateral posterior insula and to the secondary somatosensory areas bilaterally [32]. However, it is worth noting that, in recent longitudinal studies following stroke, with repeated neurofunctional imaging performed in the same patients throughout their recovery, the exact role of the contralateral homologue was questioned [51, 86].

Post-lesional language plasticity

In cases of acute brain lesions involving the language network, as for the sensorimotor function, plasticity mechanisms seem to be based: first on intrinsic reorganisation within injured language areas (indice of favorable outcome) [62, 64, 106]; second, when this reshaping is insufficient, other regions implicated in the language circuits will be recruited, in the ipsilateral hemisphere (close and even remote to the damaged area) then in the contralateral hemisphere [142] – even in this case however, the functional recovery is usually poor [122].

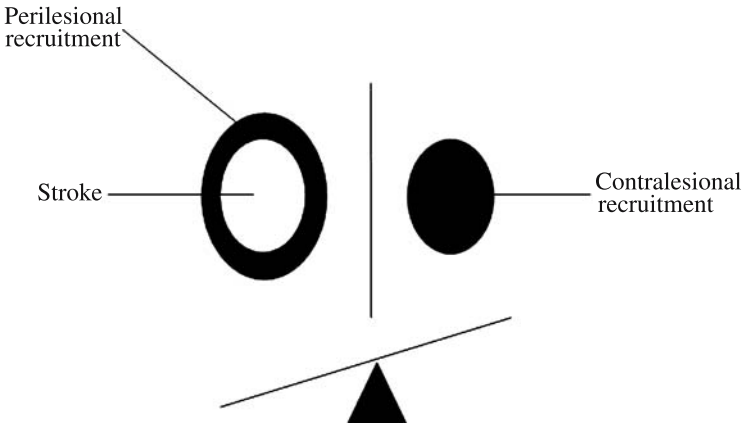

Fig. 1. Hierarchical model of functional compensation following acute stroke, with a recruitment of ipsilesional (especially peri-lesional) areas before the recruitment of contralateral homologous. Remote compensations are a marker of poor recovery

In summary, numerous observations of functional improvement following acute brain lesions have been reported, most of the time in stroke studies, underlining the existence of a post-lesional plasticity. Moreover, recent advances in non-invasive neurofunctional imaging has allowed a better understanding of the mechanisms of cerebral remapping. These data suggest that functional recovery is better when occurring within the limits 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 of recovery is usually observed when neural reorganizations involve the intact (contralateral) hemisphere (Fig. 1).

Nevertheless, due to the acute nature of this kind of lesion, it was impossible to compare the redistributed maps to the functional organization before the damage – because of the lack of neuroimaging examination in the patient before the brain injury. Furthermore, the recovery was incomplete in many patients. As a consequence, it seems that stroke represents a limited model of the study of cerebral plasticity. Interestingly, more recently, researches have been performed in slow-growing brain tumors, especially in low-grade gliomas (LGG): these works have provided new insights into the brain's capacity of functional compensation.

Plasticity in slow-growing brain tumors: the example of low-grade glioma

LGG – gliomas WHO grade II – are slow-growing primary tumors of the central nervous system, which represent approximately 15% of gliomas [140]. They can evolve in three ways: (1) local growth (2) invasion (3) anaplastic

transformation. First, recent works demonstrated that before any anaplastic degeneration, LGG showed a continuous, constant growth of it mean tumor diameter over time, with an average of around 4 mm per year [82]. Second, invasion of LGG along the main white matter pathways within the lesional hemisphere or even contralaterally via the corpus callosum has also been extensively described [83]. Third, it is currently well-known that LGG systematically changes its biological nature and evolves to a high grade glioma, with a median of anaplastic transformation of around 7 to 8 years, a process which proves fatal (median survival around 10 years) [143].

Interestingly, during the long stage before the transformation of the tumor, in spite of some possible slight cognitive disorders (in particular involving working memory) found only using extensive neuropsychological assessments [127, 129], the patient presents most of the time with a normal neurological examination and has a normal socio-professional life. Indeed, more than 80% of LGG are revealed by seizures, usually efficiently treated by antiepileptic drugs [23]. Thus, due to the recent advances in the field of functional mapping, many authors have studied brain plasticity in patients harboring a LGG, with the goal (1) to better understand the mechanisms of cerebral reorganization induced by these slow-growing tumors, explaining the frequent lack of deficit despite an invasion of the so-called "eloquent areas" and (2) to try to use this dynamic potential in order to improve the functional and neurooncological result in treatment of LGG, especially surgical resection [25, 42].

Functional reorganization induced by LGG

Numerous preoperative neurofunctional imaging studies have recently shown that LGG induced a progressive redistribution of the eloquent sites, explaining why most of these patients have a normal neurological examination or only a slight deficit [37].

Interestingly, the patterns of reorganization may differ between patients [42] (Fig. 2).

In the first one, due to the infiltrative feature of gliomas, function still persists within the tumor. This LGG invasion to functional sensorimotor and language cortices was reported as possibly occurring in up to 36% of cases in some recent series using magnetoencephalography [55].

In the second possible pattern of reshaping, eloquent areas are redistributed immediately around the tumor, according to a mechanism of "within-area" reorganization. With reference to sensorimotor function, preoperative neuroimaging showed that the activated areas on the tumor side could be broader than in normal volunteers and/or could be displaced compared with that in the normal contralateral hemisphere – with a functional shift which cannot be explained by the anatomical deformation of the central sulcus [3]. As

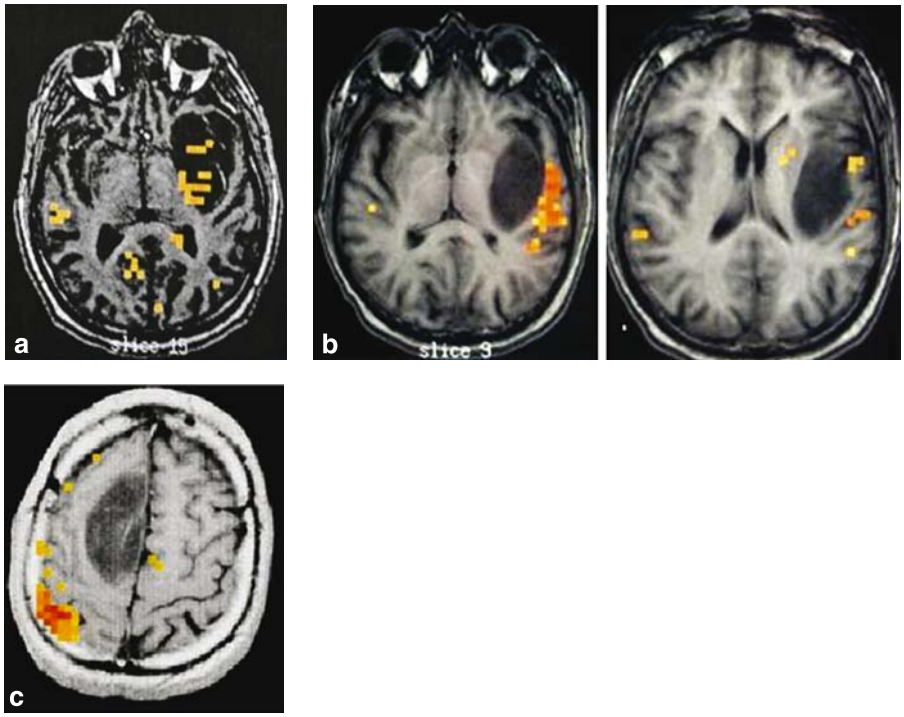

Fig. 2. Different patterns of remapping induced by slow-growing LGG, as shown by preoperative fMRI (a) intralesional activations during fluency task in a patient with no deficit harboring a left insular LGG (b) perilesional language reshaping during fluency task in a patient with no deficit harboring a left insular LGG (c) recruitment of contralateral homologous, with activation of the left contrahemispheric SMA during movement of the left hand (in addition to the activation of the right primary motor cortex), in a patient with no deficit harboring a right mesio-premotor LGG

regards language, activation of the adjacent left inferior frontal cortex was demonstrated for patients without aphasic symptoms harboring glioma located within the classical Broca's area [90].

In the third pattern of compensation, there is a recruitment of a widely distributed network within the lesion hemisphere. Typically, concerning motor function, activation of the "secondary motor areas", including the supplementary motor area, the premotor cortex and even the superior parietal lobe was frequently observed in patients performing a simple (and not complex) motor task [3, 73]. Concerning the recruitment of the other regions implicated in the language circuit, activation of the left superior temporal gyrus was shown for a glioma within Broca's area [62, 90], while an activation of the Broca's area was observed in left temporoparietal tumor [90]. Moreover, patients with slowly evolving gliomas regularly recruited frontolateral regions other than "classic" language areas, such as left BA 46, BA 47, supplementary motor area (and left

cerebellum) [90, 131]. Finally, the left insula, a structure known to be involved in the complex planning of speech, when invaded by a LGG, was demonstrated to be compensated for by the recruitment of a network involving not only Broca's area and the left superior temporal gyrus, but also the left putamen [33].

There is also possible compensation by the contralateral hemisphere, likely due to a decrease of the transcallosal inhibition on the opposite homologous area. In glioma located within the rolandic region, several reports found activations within the contralesional primary motor cortex [5, 109], the contralesional premotor area [50] and contralateral supplementary motor area [72]. Concerning language function, both translocation of Broca's area to the contralateral hemisphere as the result of the growth of left inferior frontal glioma [67] and translocation of Wernicke's area to the right hemisphere in left temporo-parietal glioma [101] have been demonstrated.

Finally, association of different patterns was reported, in particular with combination of peritumoral and contra-hemispheric activations, both for sensorimotor [50] and language [62, 90] functions. In the largest activation study to date in patients with gliomas of the left hemisphere, in addition to left activations, right inferior frontal activations were reported in 60% of patients [131].

Therefore, sensorimotor and language plasticity mechanisms in slow-growing LGG seem to be based on an hierarchically organized model, similar to the one previously described in stroke, i.e.: first, with intrinsic reorganization within injured areas, the perilesional structures playing a major role in the functional compensation [62, 131]; when this reshaping is not sufficient, with recruitment of other regions implicated in the functional network, in the ipsilateral hemisphere (remote to the damaged area) then in the contralateral hemisphere. Indeed, some works even stated that in cases of bilateral activations, langage performances could be worse than after possible regression of the right activations [62]. However, the debate concerning the actual role of the recruitment of the contralateral homologuous area through a decrease of the transcallosal inhibition [123] – inhibition essential during language learning – is still open [67, 104]. The use of new techniques such as TMS might provide further information [132], in particular taking account of additional parameters such as the inter-individual variability of the hemispheric specialization for language [136] and the timing of occurrence of the lesion during language acquisition [91]. In this way, a recent combined PET and TMS study in right-handed patients with a left glioma, showed that all subjects had a significant activation of the left inferior frontal gyrus, and that they were all susceptible to TMS over this left IFG. Moreover, 50% had an associated right IFG activity during verb generation: these patients had also significantly longer language latencies during TMS over the right IFG. These results have indicated that in all patients, but especially in those with left IFG activation only, the residual language function

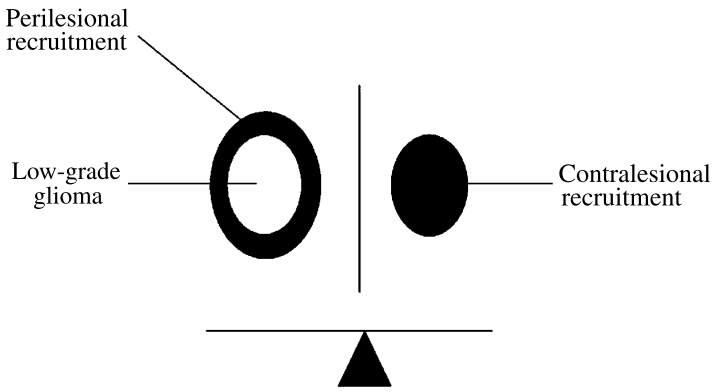

Fig. 3. Hierarchical model of functional compensation in case of slow-growing LGG, with a recruitment of ipsilesional (especially peri-lesional) areas before the recruitment of contralateral homologous. However, in this pathology, remote compensations are not a marker of poor recovery. Thus, bilateral recruitments are frequent in patients with a normal clinical examination

of the left hemisphere was responsible for maintenance of language function – reinforcing the hypothesis which emphasized the importance of the residual language capacity of the left hemisphere for quality of language compensation. However, this study also demonstrated relevant language function of the right IFG in right-handed patients with gliomas of the left hemisphere [132].

In summary, the data above suggest that different plastic processes compensate for LGG invasion. 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 [131]). Second, remote compensations in the intact or lesioned hemisphere are not a marker of poor recovery (Fig. 3). 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 tumoral 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 tissue around the tumor to increase the likelihood of obtaining a more complete resection [44].

Functional reorganization induced by LGG resection

While controversial for a long time, maximal resection of brain glioma, especially LGG, when possible, appears currently to be a valuable treatment to

influence the natural history of this tumor [7, 21, 44]. Thus, the double goal of surgery is to maximize the quality of resection while minimizing the operative risk [46]. Nonetheless, due to the frequent location of supratentorial gliomas near or within so-called "eloquent" areas [40], and due to their infiltrative feature previously mentioned, it was considered that the chances to perform an extensive glioma removal were low, whereas the risk of inducing post-operative sequelae was high. Indeed, many surgical series have reported a rate of permanent and severe deficit between 13% and 27.5% following removal of intra-axial tumors [12, 119, 137]. Therefore, to optimize the benefit to risk ratio of surgery, functional mapping methods have been used extensively in the last decade. We have already detailed that slow-growing LGG induced brain reshaping with a considerable interindividual anatomofunctional variability [42]. It is thus mandatory to study for each patient the cortical functional organization, the effective connectivity and the brain plastic potential, in order to tailor the resection according to both oncological and also cortico-subcortical functional boundaries.

Methodological considerations

The knowledge of such a preoperative functional reorganization is very important for both surgical indication and planning [55]. Indeed, if function still persists within the tumor, there is very limited chance to perform a good resection without inducing postoperative sequelae [120]. Conversely, if eloquent areas are redistributed around the tumor [90], there is a reasonable chance of performing a near-total resection despite a likely immediate transient deficit – but with secondary recovery within some weeks to some months (see below). Finally, if there is already a preoperative compensation by ispsilesional remote areas [62] and/or by the contra-hemispheric homologuous area [5, 67, 72, 109], the chances to perform a real total resection are high, with only a slight and very transient deficit.

Nevertheless, accumulating evidence seems to indicate that the BOLD response in the vicinity of brain tumors does not reflect the neuronal signal as accurately as it does in healthy tissue, – with the sensitivity still too low [110]. Although poorly understood, the mechanisms seem not to result from reduced neuronal activity, but rather from an alteration of neurovascular and metabolic coupling [4]. Consequently, glioma-induced neurovascular uncoupling may cause reduced fMRI signal in perilesional eloquent cortex, in conjunction with normal or increased activity in homologous brain regions: this phenomenon can simulate a pseudo-reorganization of the function, namely can mimic a false functional transfer to the opposite side of the lesion preoperatively [135].

This is the reason why the additional use of intraoperative direct electrical stimulation (DES) has been widely advocated, under general or local anesthesia, during surgery of glioma in eloquent areas [8, 44]. DES allows the mapping

of motor function (possibly under general anesthesia, by inducing involuntary movement if stimulation of a motor site), somatosensory function (by eliciting dysesthesia described by the patient himself), and also cognitive functions such as language (spontaneaous speech, object naming, comprehension, etc. . . .), calculation, memory, reading or writing, performed in these cases on awake patients – by generating transient disturbances if DES is applied at the level of a functional "epicenter" [95].

Furthermore, DES also permits the study of the anatomo-functional connectivity by directly stimulating the white matter tracts all along the resection [43, 46]. A speech therapist must be present in the operative room, in order to interpret accurately the kind of disorders induced by the cortical and subcortical stimulations, e.g. speech arrest, anarthria, speech apraxia, phonological disturbances, semantic paraphasia, perseveration, anomia, and so on [45]. Such on-line intraoperative anatomo-functional correlations give a unique opportunity to study the individual connectivity, as demonstrated concerning (1) motor pathways and their somatotopy from the corona radiata to the internal capsule and the mesencephalic peduncles [38], (2) thalamo-cortical somatosensory pathways [37], (3) subcortical visual pathways [43], (4) pathway subserving the spatial cognition, that is, the superior fronto-occipital fasciculus [130] and right superior longitudinal fasciculus [124], as well as (5) and language pathways – concerning loco-regional connectivity, cortico-cortical connections such as the phonological loop, striato-cortical loop such as the subcallosal medialis fasciculus, as well as long-distance association language bundles such as the arcuate fasciculus [34] or the inferior fronto-occiptal fasciculus involved in the semantic connectivity [45].

Therefore, DES represents an accurate, reliable and safe technique for the on-line detection of the cortical and subcortical regions essential for the function, at each place and each moment of the resection. Consequently, any functional disturbance induced by DES with reproducibility must lead to interruption of the resection at this level, both for cortical and subcortical structures. The tumor removal is then performed according to functional boundaries, in order to optimize the quality of resection while minimizing the risk of postoperative permanent deficit [44].

Intra-operative plasticity

Thus, DES during surgery for LGG within or near the sensorimotor areas, has allowed the study of brain plasticity in humans. In this way, cortical stimulation after brain exposure and before any resection confirmed the frequent existence of a peri-lesional redistribution of the eloquent areas, due to the slow-growing LGG, as suggested by preoperative neurofunctional imaging [37, 42].

These observations were also confirmed using DES under local anesthesia during resection of LGG within language areas, in patients with no or slight

previous deficit. Indeed, as preoperative functional neuroimaging, stimulations also found essential language sites (i.e. eliciting language disturbances when stimulated) preferentially located in the immediate vicinity of the lesion, sup-

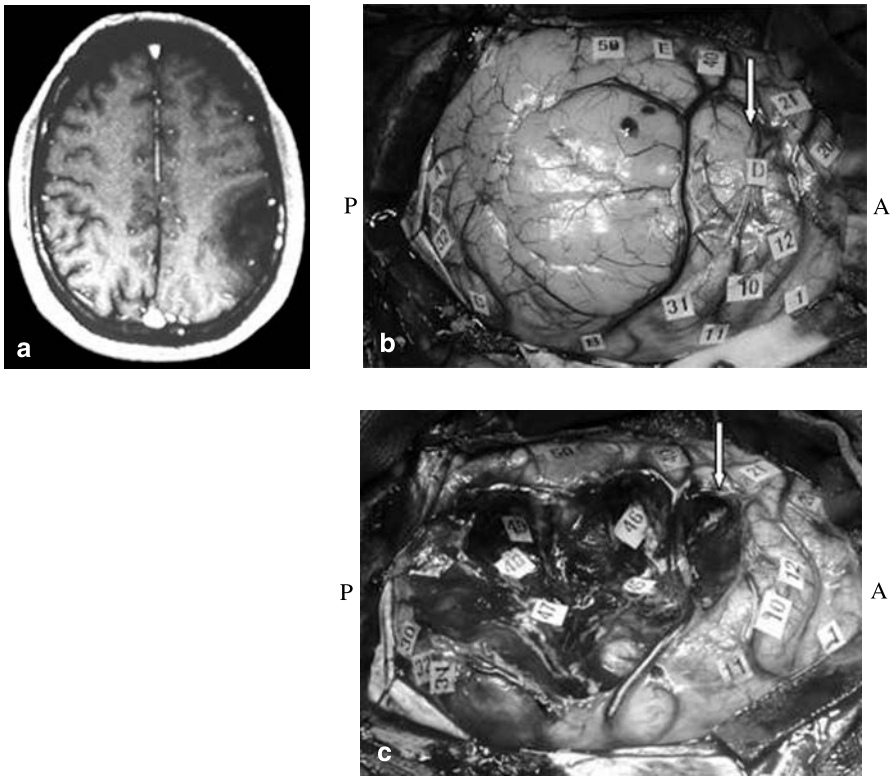

Fig. 4. Language reorganization induced by a LGG located within the left supramarginal gyrus (a) Preoperative axial T1-weighted enhanced MRI (b) Intraoperative view before resection of the tumor, delineated by letter tags. Electrical cortical mapping shows a reshaping of the eloquent maps, with a recruitment of perilesional language sites, i.e. the rolandic operculum (tags 20 and 21), angular gyrus (tags 30 and 32) and posterior part of the superior temporal gyrus (tags 40 and 50). The straight arrow shows the lateral part of the retrocentral sulcus. (c) Intraoperative view after resection of the tumor. Electrical subcortical mapping has enabled to study the individual anatomo-functional language connectivity. Indeed, deeply and posteriorly, the postero-superior loop of the arcuate fasciculus was identified, by eliciting phonological paraphasia during each stimulation (tag 40, 47 and 49). More anteriorly, the lateral part of the superior longitudinal fasciculus was detected, by inducing speech apraxia (articulatory disturbances) (tag 45 and 46). It is worth noting that in the depth, the resection was continued up to the contact of these language pathways, in order to optimize the quality of resection while preserving the eloquent white matter tracts. The arrow shows the lateral part of the retrocentral sulcus. The straight arrow shows the lateral part of the retrocentral sulcus. *A* Anterior, *P* posterior

porting the hypothesis of the major contribution of the intrinsic reshaping mechanisms [25, 37, 42]. For instance, reshaping of the language sites was observed around the Broca's area invaded by a LGG, with a functional compensation related to recruitment of adjacent regions such as the left ventral premotor cortex, the middle frontal gyrus (BA 46) and the pars orbitaris of the IFG (BA 47). Also, the compensation of left insular involvement by LGG, owing to the recruitment of Broca's area, the left superior temporal gyrus and the putamen, was demonstrated intraoperatively by DES [33]. In addition, DES showed a language reshaping of the left supramarginal gyrus, with a recruitment of perilesional sites, i.e. the rolandic operculum, angular gyrus and posterior part of the superior temporal gyrus (Fig. 4). These results fit very well with those reported using neurofunctional imaging previously reviewed.

Furthermore, the persistence of structures still functional within LGG was equally confirmed using DES [46]. Indeed, paresthesias were induced during stimulation of the primary somatosensory cortex despite its tumoral invasion, and motor face responses were elicited during stimulation of the primary motor area involved by LGG [37]. Also, DES regurlarly induced speech disorders when applied over the left insular cortex, even when invaded [30].

It is worth noting that because brain exposure is performed only around the invaded area, DES is generally not relevant for investigating distant compensations.

Regarding intra-surgical plasticity, a very puzzling observation concerns the existence of acute functional remapping triggered by the resection itself that takes place within 15 to 60 minutes of beginning the surgical act. This type of acute reorganization has been very well documented in the motor system (for areview [32]). For instance, it was reported in a 39 old patient with a left precentral lesion and normal pre-operative neurological evaluation [29]. Intraoperative DES performed caudally to the lesion, prior to any resection, allowed identification of three functional sites in M1: one for the forearm, one for the wrist and one for the fingers. No other response was found. Cortical stimulations performed during and after resection replicated the three motor responses identified intraoperatively (of course stimulation parameters were kept constant throughout surgery). Interestingly, two new functional sites were also detected in regions that did not show any response before resection. These sites induced hand and arm movements. They were located in the precentral gyrus, in front of the three original sites. Identical observations were reported in other patients in a subsequent study [31]. Similar acute reorganizations were also found after postcentral resections [32]. The origin of these changes remains poorly understood. The most likely hypothesis suggests that a local increase of cortical excitability allows an acute unmasking of latent functional redundancies (i.e. multiple cortical representation of the same function), via a decrease of intracortical inhibition [29, 31]. 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 [13]. Likewise, human studies have provided evidence that the level of intracortical inhibition is reduced in the damaged hemisphere in stroke patients [20]. 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. This idea fits well with the importance of adjacent reorganizations for behavioral recuperation.

Post-operative plasticity

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. 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 (MEG), it has been reported that resections of the somatosensory cortex (S1) caused perilesional sites to be recruited around the cavity, within the postcentral gyrus [88]. In addition to this local remapping, contributions of S2, the posterior parietal cortex, and the primary motor cortex were also reported using post-operative DES [32]. 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 orbitaris of the inferior frontal gyrus, and the insula [37].

Probably, the best evidence for efficient postoperative compensations in remote structures comes from SMA resections. Ablation of this area usually produces an SMA syndrome, due to the removal of the SMA-proper [71]. This syndrome regresses spontaneously within 10 days. Postoperative fMRI images taken after the regression of this surgically-induced SMA syndrome suggest that plastic functional compensations involve the contralesional SMA, the controlesional premotor cortex [72] and, potentially, the ipsilesional primary motor cortex [37]. Unfortunately, to date, no study has tried to directly investigate the functional role of these structures using, for instance, TMS. This direct approach was however exercised in a recent study involving two patients with a large resection of the posterior parietal cortex [11]. In these patients, TMS delivered over the intact parietal cortex did impair the accuracy and kinematic characteristics of reaching movements performed without vision of the arm. No TMS-related effect was observed for healthy subjects, as had already been reported in a previous study [24].

Therapeutic implications for LGG

It was recently proposed to incorporate such better understanding of the individual plastic potential in the surgical strategy for LGG, with the goal (1) to extent the indications for resection in eloquent structures so far considered as "inoperable" (2) to maximize the quality of glioma removal, by performing the resection according to (not fixed) functional boundaries (3) while minimizing the risk of postoperative permanent neurological deficit [44] (Fig. 5).

Consequently, several surgical series showed that it was possible to remove LGG invading the following "eloquent" brain structures:

- SMA resection: it induces the occurrence of an SMA syndrome [148], spatially and temporally due to the removal of the SMA-proper [71]. As previously mentioned, postoperative fMRI after such a surgical SMA syndrome recovery argue in favor of a compensation by the controlateral SMA and premotor cortex [72], and also by the ipsilesional primary motor cortex [37].
- Insular resection: despite a hemiparesis after right insula removal, likely because this region is a non-primary motor area, and transient speech disturbances following left dominant insula resection, all patients recovered [147] – except in rare cases of deep stroke [30, 48]. Moreover, it was possible in right non-dominant fronto-temporo-insular LGG involving the deep grey nuclei, to remove the clautrum without any cognitive disorders (despite its role suggested in consciousness), and to also to remove the invaded striatum without inducing any motor deficit not movement disorders [35].
- S1 resection: the first results using pre- and post-operative MEG suggest the possible recruitment of 'redundant' eloquent sites around the cavity, within the postcentral gyrus [88]. It is in accordance with the DES data, showing unmasking of redundant somatosensory sites during resection, likely explained by the decrease of the cortico-cortical inhibition [31]. The recruitment of the second somatosensory area or posterior parietal cortex, M1 (due to strong anatomo-functional connections between the pre- and retrocentral gyri), and the controlateral S1 are also possible (for a review, see [32]). These plastic phenomena likely explain the recovery of the frequent transient postoperative sensory deficit.
- In addition, the resection of the (dominant) parietal posterior lobe can be performed without inducing any sequelae, and even with a possible improvement in comparaison to the preoperative status, especially using pointing task [11].
- Resection of non-dominant M1 of the face: the recovery of the usual transient central facial palsy [76], with a potential Foix-Chavany-Marie syndrome when the insula is also involved [39], is likely explained by the disinhibition of the contralateral homologous sites, via the transcallosal pathways.

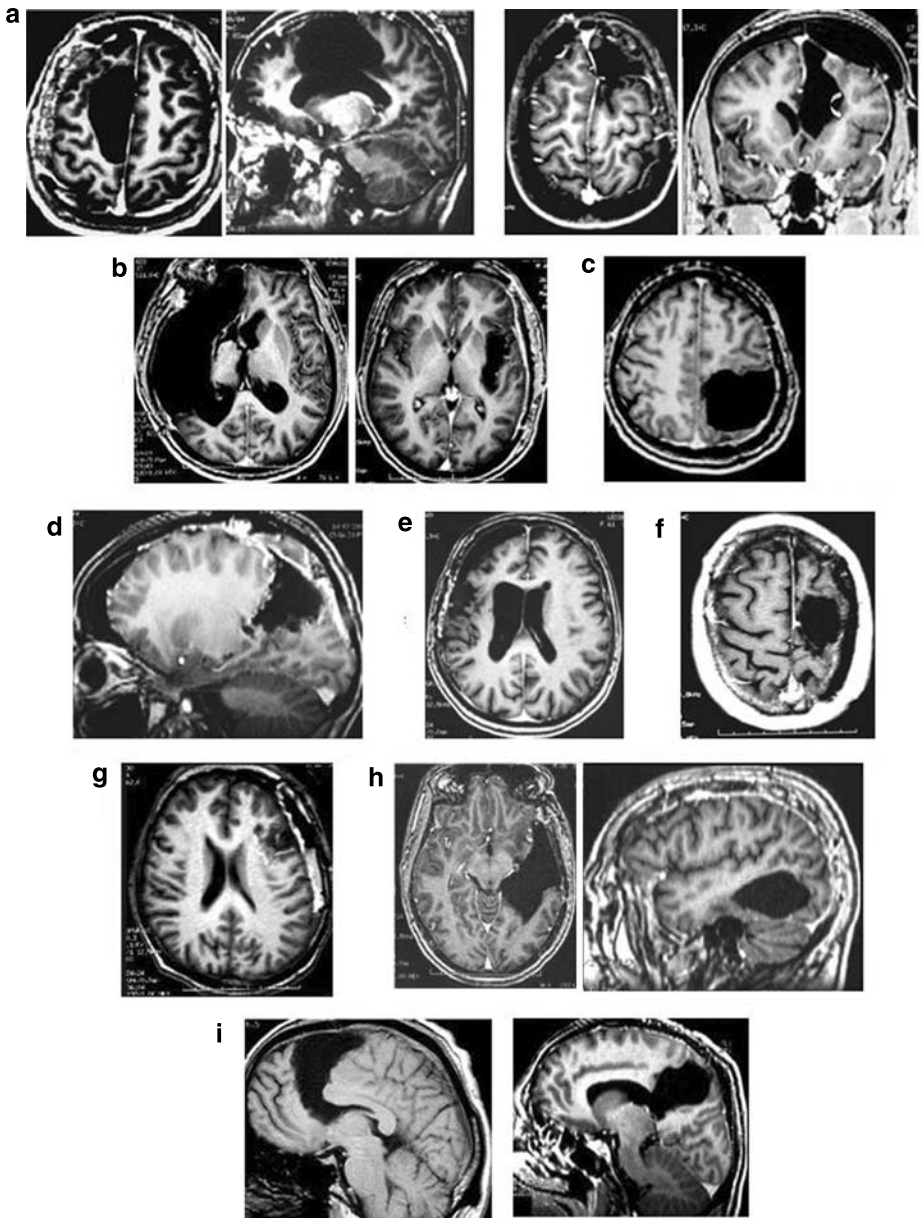

Fig. 5. Examples of complete resections of LGG (according to MRI criteria) within classical ''eloquent'' areas, with preservation of the quality of life, owing to the mechanisms of brain plasticity (a) resection involving the right and left supplementary motor areas (b) resection involving the right paralimbic system with the claustrum as well as the striatum (left) and involving the left insula (right) (c) resection involving the primary somatosensory area and the parietal posterior lobe (d) resection involving the left inferior parietal lobule (e) resection involving the primary sensorimotor cortex of the face (f) resection involving the primary motor area of the hand (g) resection involving Broca's area (h) resection involving the anterior and mid- (left) and posterior (right) left dominant temporal lobe (i) resection involving the corpus callosum

– Resection of M1 of the upper limb: on the basis of the existence of multiple cortical motor representations in humans using fMRI [116], and DES [31], the compensation of the motor function could be explained by the recruitment of parallel networks within M1 – allowing the superior limb area removal, eventually using two consecutive surgeries in order to induce durable remapping following the first one [36] (see below).
– Broca's area resection: any language compensation may reflect the recruitment of adjacent regions, in particular BA 46, BA 47 and the insula [42, 90, 131].
– Temporal language area resection: language compensation following left dominant temporal resection could be explained by the fact that this function seems to be organized with multiple parallel networks [136]. Consequently, beyond the recruitment of areas adjacent to the surgical cavity, the long term reshaping could be related to progressive involvement of first remote regions within the left dominant hemisphere – such as the posterior part of the superior temporal gyrus, the pars triangularis of inferior frontal gyrus or other left frontolateral regions (BA 46 and BA 47) [131] – second the contralateral right non-dominant hemisphere due to a transcallosal disinhibition phenomenon [62].
– Finally, a recent study showed that the resection of a part of the corpus callosum invaded by a LGG is possible without motor, language or cognitive deficit [41].

Improvement of the functional and oncological results of LGG surgery

–Functional results

Thus, the integration of the study of individual plasticity provided by preoperative functional neuroimaging and intraoperative DES in the surgical decision and planning has enabled firstly extention of the indications for surgery for gliomas located in areas considered until now as "inoperable" [44]. Moreover, despite a frequent but transient immediate postoperative functional worsening (due to the attempt to perform a maximal tumor removal according to cortico-subcortical functional limits using IES), in a delay of 3 months following the surgery, more than 95% of patients recovered a normal neurological examination, even with a possible improvement in comparison with their preoperative status – and also with a significant decrease of seizures in 80% of patients with preoperative chronic epilepsia. It is important to underline that all patients returned to a normal socio-professional life, and have been extensively evaluated by repeated neurological examinations, combined with language assessment (in particular using the Boston Diagnostic Aphasia Examination) and neuropsychological assessment [38, 129]. This rate of less than 5% of sequelae is very reproducible among the teams using DES worlwide (for a review, see Ref. [44]).

Interestingly, in comparison, in series which did not use DES, the rate of sequelae ranged from 13 to 27.5%, with a mean of around 19% [12, 119, 137].

–Neuro-oncological results

Since DES allows identification of the cortical and subcortical eloquent structures individually, it seems logical to perform a resection according to *functional boundaries*. Indeed, it has been suggested to continue the resection until the functional structures are detected by DES, *and not before*, in order to optimize the quality of resection – without increasing the risk of permanent deficit [46]. This surgical strategy enables a significative improvement of the quality of glioma removal, despite a higher number of surgeries within critical areas, and a parallel decrease of the rate of sequelae. Indeed, in a recent study comparing LGG resected without or with DES in the same institution, it was demonstrated on control MRI that (1) 62% of gliomas selected for surgery were located within eloquent area with the use of DES, instead of only 35% without IES (2) only 37% of resections were subtotal (less than 10 cc of residue according to the classification from Ref. [7]) and 6% total (with no signal abnormality) without DES, whereas 50.8% of resections were subtotal and 25.4% subtotal with the use of DES ($p < 0.001$) [44].

Moreover, while extensive resection is still controversial in neuro-oncology, especially concerning LGG, current surgical results support the positive impact of such a "maximal" treatment strategy, i.e. with a benefit on the natural history of the tumors which seems to be directly related to the quality of resection. Indeed, it was recently shown in a consecutive series of low-grade gliomas operated on according to functional boundaries using DES that the mortality rate was 20.6% in cases of partial resection, instead of 8% in cases of subtotal resection and 0% in cases of total resection (follow-up 48 months) ($p = 0.02$) [44].

Conclusions

The current view of the spatio-temporal functioning of the nervous system has dramatically changed. Indeed, the brain is now considered as a morphological and functional dynamic structure, influenced by the environment, and constituted of interactive distributed glio-neunoro-synaptic networks. Each of them comprises several essential and/or modulatory epicenters, with behavioral consequences depending on their effective connectivity, itself modulated by their synchrony. Moreover, this whole dynamic system is stabilized by a homeostatic plasticity.

The better understanding of these phenomena enables us to begin to guide this plastic potential, in order to favorably regulate the dynamic of the eloquent networks – with the aim of facilitating functional recovery following brain damage. Such a linkage between an improved knowledge of the pathophysiological mechanisms underlying cerebral plasticity and its focussed use opens

now a large field of new therapeutic perspectives, applied to the functional restoration and the optimization of the quality of life in patients with brain tumors.

Perspectives

Individual plastic potential could be better understood using repeated intraoperative mappings combined with post-surgical neurofunctional imaging, and *guided by specific post-operative rehabilitation program* in order to optimize the quality of functional recovery. Indeed, functional rehabilitation can be matched to specific (re-)training based on the repetition of the tasks, with the goal of facilitating plasticity phenomena leading to positive reinforcement while inhibiting the others. With regard to sensorimotor rehabilitation, functional neuroimaging studies have shown that (re-)activations of the brain structures may be induced by the mental imagery of the movement alone, by its observation, or by passive training [17]. In addition, a single session of physiotherapy seems to produce a use-dependent enlargement of motor cortex representations paralleled by an improvement in motor function in stroke patients, but with variable durability [77]. The principle of constraint-induced movement therapy is currently extensively used [128]. This method seems to generate (re-)expansion of the cortical motor areas, correlated to the functional recovery, on condition that such therapy is performed 6 hours instead of 3 hours per day [126]. Conversely, immobilization induces a decrease of the size of the cortical motor area. Finally, the timing of rehabilitation following the damage is still controversial, since some studies have suggested that 'precocious' physiotherapy might exacerbate brain injury due to an early postlesional vulnerable period.

With regard to aphasia therapy, while some randomized works have not demonstrated any significant difference between groups of patients with and without training, other trials have shown a favorable impact of language therapy [27]. This discrepancy may be due to differences in the intensity of training. Indeed, aphasia therapy has given strong arguments in favor of its efficacy on condition that the program comprised at least one hour of training per day in the three months following the lesion, namely a minimum of 90 hours (i.e. "constraint-induced therapy") [103]. Furthermore, recent neurofunctional imaging studies performed before and after training have shown a reshaping of the language map, in particular with a re-activation of the Broca's area and left supramarginal gyrus, and even with possible recruitment of the right non-dominant hemisphere [99]. Currently it is proposed that intensive language therapy should be specifically adapted to each aphasic symptom. For instance, semantic training seems more efficient than phonological therapy in patients with a semantic or mixed aphasia.

In patients with LGG, the functional status is now more systematically assessed using extensive neurological and neuropsychological examinations

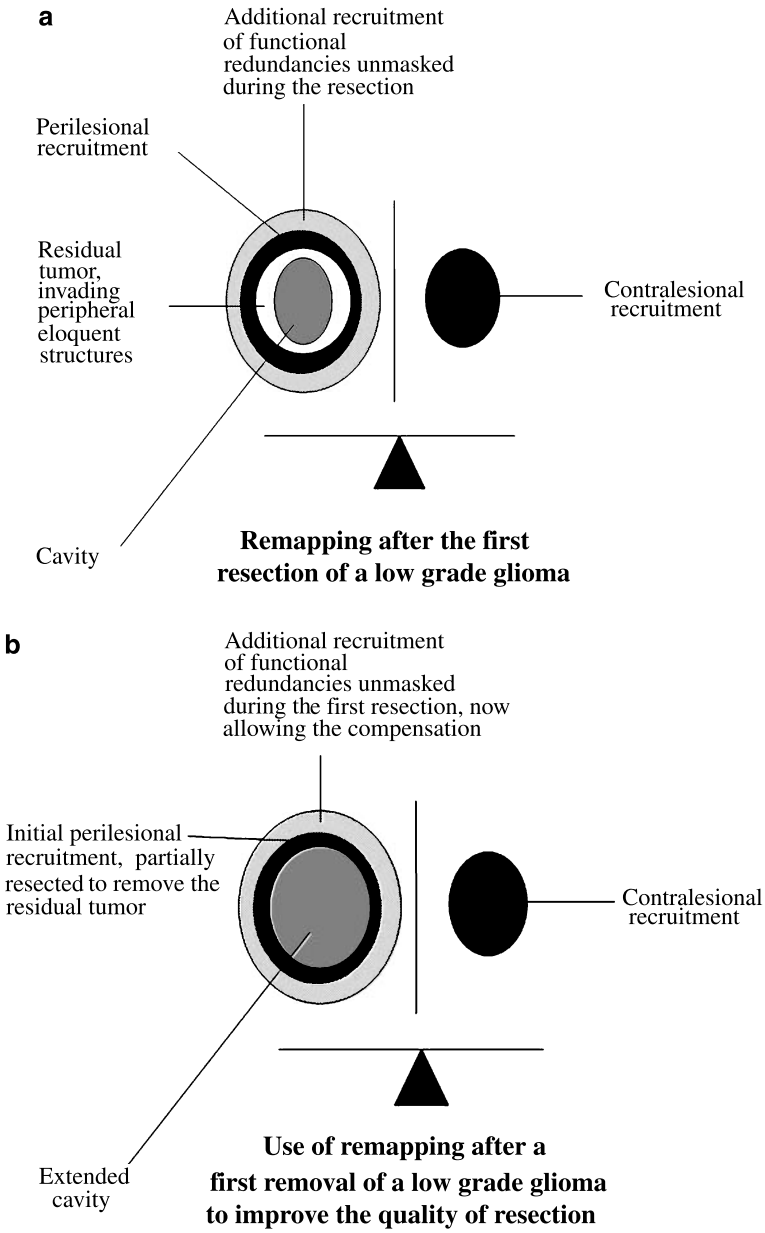

Fig. 6. (a) Model of acute plasticity induced by a first surgical resection, underlied by unmasking of additional perilesional functional redundancies (b) use of this remapping, once stabilized, in order to increase the quality of tumor removal while preserving the function, even if the residue involves the areas which have initially been implicated in the compensation of the slow-growing LGG

as well as using subjective scales – with the goal to precisely evaluate the quality of life. Such studies have demonstrated that specific rehabilitation was able to improve the postoperative functional status in comparison to the preoperative one, in particular with regard to cognitive functions such as working memory – in spite of frequent immediate postsurgical deterioration [129].

Long-term functional reorganization might be integrated into a dynamic surgical schedule [25], that is, by considering a second operation in order to increase the quality of resection, when LGG removal was not possible during the first surgery – on the basis of the reshaping of eloquent areas. Indeed, in cases of second surgery in patients with tumor regrowth, a novel intraoperative electrical mapping demonstrated the occurrence of a long-term reshaping of the sensorimotor and language regions [36]. These observations support the fact that the short-term plasticity induced by the first surgical resection can lead to a durable remapping, with an actual functional value, thereby allowing the subsequent removal of the residual tumor without sequelae [42]. Thus, there is the possibility of "dynamic planning" of surgery, by performing multiple resections if the complete removal of the LGG was not initially possible due to the involvement of essential eloquent areas, by eliciting plastic phenomena through the first operation itself [36] (Fig. 6) in addition to a specific rehabilitation program. As a consequence, it may prove possible to provide a more reliable and comprehensive pre-operative prediction of the potential for reorganization and its limitation for each patient using a biomethamatical model based on non-invasive neurofunctional imaging [85] to be integrated into the surgical strategy.

Such advances may enable optimization of the risk/benefit ratio of surgery for brain tumor surgery maximizing the impact on the natural history of the tumor while preserving the quality of life. It is nevertheless mandatory to validate all these new concepts via extensive multi-centre prospective studies.

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