Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: Towards a “minimal common brain”

Tamara Ius a, Elsa Angelini b, Michel Thiebaut de Schotten c,d, Emmanuel Mandonnet e,f, Hugues Duffau g,h,⁎

A R T I C L E   I N F O

Article history:
Received 22 December 2010
Revised 6 March 2011
Accepted 8 March 2011
Available online xxxx

Keywords:
Brain plasticity
Direct electrical stimulation
Glioma surgery
Intraoperative functional mapping
Probabilistic atlas
White matter connectivity

A B S T R A C T

Despite recent advances in non-invasive brain mapping imaging, the resectability of a given area in a patient harboring a WHO grade II glioma cannot be predicted preoperatively with high reliability, due to mechanisms of functional reorganization. Therefore, intraoperative mapping by direct electrical stimulation remains the gold standard for detection and preservation of eloquent areas during glioma surgery, because it enables to perform on-line anatomic-functional correlations. To study potentials and limitations of brain plasticity, we gathered 58 postoperative MRI of patients operated on for a WHO grade II glioma under direct electrical cortico-subcortical stimulation. Postoperative images were registered on the MNI template to construct an atlas of functional resectability for which each voxel represents the probability to observe residual non-resectable tumor, that is, non-compensable area. The resulting atlas offers a rigorous framework to identify areas with high plastic potential (i.e. with probabilities of residual tumor close to 0), with low compensatory capabilities (i.e. probabilities of residual tumor close to 1) and with intermediate level of resectability (probability around 0.5). The resulting atlas highlights the utmost importance of preserving a core of connectivity through the main associative pathways, namely, it supports the existence of a “minimal common brain” among patients.

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Axonal pathways also play a crucial role in glioma surgery, considering their integrative growth patterns along white matter fiber tracks (Chen et al., 2010; Mandonnet et al., 2006; Pallud et al., 2005). Recent developments in DTI have allowed to track non-invasively in vivo subcortical fibers (Catani et al., 2002; Catani and Thiebaut de Schotten, 2008) providing information on displacements, inclusions or disruptions of fibers induced by the tumor (Witwer et al., 2002). Nevertheless, tracking algorithms may strongly influence the anatomical data of DTI (Kinoshita et al., 2005), even if some reports have provided some validation on postmortem studies (de Schotten et al., 2011; Lawes et al., 2008). Finally, DTI is not yet able to highlight the functional role of the tracts.

Considering (1) the large variability in structural and functional networks among healthy volunteers (Brett et al., 2002; Tzourio-Mazoyer et al., 2004), (2) functional limitations in neuroimaging, and (3) functional modifications induced by tumoral growing patterns both at cortical and axonal levels (Duffau, 2006a), the study of the brain functional cortical organization and connectivity is needed for individual patients to both select the best indications for surgery and to perform a resection with the optimal benefit/risk ratio. As a consequence, the use of intraoperative direct electrical stimulation (DES) is considered as the “gold standard” to detect both the eloquent cortical areas and subcortical pathways at the individual level (Duffau et al., 2008b; Mandonnet et al., 2010b). Indeed, DES provides accurate and real-time data on the distribution not only of the cortical eloquent areas (Ojemann et al., 1989; Sanai et al., 2008), but also of the functional white matter bundles (Bello et al., 2007; Duffau et al., 2008b; Sanai and Berger, 2010). Thus, DES allows to tailor the tumor resection according to individual functional boundaries, maximizing the extent of resection while minimizing the risk of permanent neurological deficits.

Combining intraoperative anatomofunctional data with pre and post-operative MRI and DTI imaging is currently the best approach to assess the functional role of the cortical areas and the white matter fiber tracts (Kamada et al., 2007). For this reason, we propose in this paper the elaboration of a probabilistic postsurgical residue atlas computed on a series of patients who underwent incomplete tumor resection on the basis of intraoperative DES brain mapping. The anatomofunctional correlations we obtained by combining the DES data with postoperative anatomical MRI findings will provide a greater understanding of the functional limits of surgical removal, and will provide new insights into the potentials and limitations of brain plasticity. Especially, this probabilistic atlas highlights the crucial role of the axonal pathways in the reshaping and reorganization of the brain after a lesion. Finally, beyond its fundamental interest, we hope this atlas will be an essential tool for surgery planning, by allowing an objective pre-operative estimation of the expected extent of the resection.

Materials and methods

Patients

In this retrospective study, we analyzed a homogenous group, for radiological and neuropathological features, of 58 patients who underwent surgery for WHO grade II glioma (low-grade glioma, LGG) between 2005 and 2009. All the procedures were performed by the same neurosurgeon (H.D.). All patients had a lesion in eloquent regions, which required intraoperative functional mapping achieved with both cortical and subcortical stimulations. Considering that the aim of this study is to evaluate the limitations of brain plasticity, we focused our analysis on cases in which the tumor removal was subtotal (residual volume < 10 cm³) or partial (residual volume > 10 cm³) for functional reasons (i.e. presence of cerebral structures still eloquent as demonstrated by intraoperative electrostimulation mapping while already invaded by the glioma), according to the classification method reported by Berger et al. (Berger et al., 1994; Sanai and Berger, 2008).

The preoperative volume and the postoperative tumoral residual volume were computed on FLAIR-weighted MRI images.

Patients included 30 men and 28 women, ranging in age from 19 to 61 years (average age 38 years). The presenting symptoms were seizures in all cases (34 generalized, 24 partial). The preoperative neurological clinical examination was normal in 56 patients. Two patients, harboring lesions in the tempo-parieto-occipital junction, presented a preoperative visual field deficit.

Intraoperative direct cerebral stimulation

All patients had a tumor located near or within so-called “eloquent” areas. In consideration of individual anatomofunctional variability, intraoperative electrocortical and subcortical white matter stimulations were employed in all cases in order to define real-time functional maps and tailor LGG resection in accordance with functional boundaries. In this process, techniques previously described by one of the authors (H.D.) (Duffau et al., 2002) and based on the methodology of Berger and Ojemann (1992), Berger et al. (1990) and Ojemann et al. (1989) were used. Patients with lesions located in somatosensory area and in the dominant temporal, premotor lobe as well as the insula and inferior parietal lobule were operated under local anaesthesia (43 cases) while intraoperative sensori-motor and language mapping were performed. Conversely, patients harboring lesions involving non-dominant supplementary, primary motor area, insular and temporal lobes underwent surgery under general anaesthesia (15 cases) in which cortical and subcortical DES enabled the detection of cortico-spinal pathways. Cortical and subcortical brain mapping were performed using direct electrical stimulations with a bipolar electrode with 5 mm spaced tips delivering a biphasic current (pulse frequency of 60 Hz; single-pulse phase duration of 1 ms; amplitude between 1 and 8 mA). (Nimbus*, Newmedic, Hémôdia, Labège, France). In the first phase of the surgical procedure, cortical mapping was performed before resection to avoid any damage to the eloquent cortical areas. The current intensity was adapted to each patient and was determined by progressively increasing the amplitude by 0.5 mA steps, from a baseline of 1 mA, until a sensory-motor response was elicited. Usually, 4 mA was the maximum stimulus needed to localize the eloquent areas in awake patients, whereas up to 8 mA was needed to localize the motor cortex under general anesthesia. The upper amplitude limit was set to 8 mA, to avoid the generation of seizures. Sensori-motor mapping was systematically tested to confirm a positive response (e.g. the induction of movement and/or paresthesia in the contralateral hemibody when the primary sensory motor areas were stimulated in a patient at rest). In addition to motor mapping, for patients under local anesthesia, counting, picture naming, and reading tests were systematically performed, so that the essential cortical language sites, known to be inhibited by stimulation, could be identified. Moreover a calculation task was added if a patient harbored a lesion in the left angular and supramarginal gyri, a repetition and/or semantic task if the lesion was within left mid-posterior temporal lobe, and a bisection line task when the tumor involved the tempo-parieto-occipital region.

Patients were not informed of the timing of stimulation. Stimulations lasted less than 4 s. For the picture-naming task, at least one picture presentation without stimulation separated each stimulation, and no site was stimulated twice in succession in order to avoid seizures. In accordance with previous studies (Ojemann et al., 1989), a cortical site was considered essential for language when its stimulation induced speech disturbance during the three trials. In the second surgical phase, direct stimulation with the same electrical parameters as those used at the cortical level was continuously applied during lesion removal at the subcortical level to detect and preserve the subcortical pathways in order to tailor the deep functional limits of...
In summary, the methodological procedure is very similar to the one used in our previous work (Mandonnet et al., 2007a), with the following modifications:

- all segmentations are now performed on FLAIR images, and the registration algorithms have been modified accordingly,
- the resulting atlas can be superimposed on an atlas of white matter tracts (obtained from a DTI atlas), allowing to analyze the resectability of each pathway.

**Results**

**Patients**

Among the 58 lesions, the right hemisphere was involved in 25 cases and the left in 33 cases. The median preoperative tumoral volume was 65 cm³ (range: 15–202 cm³). Patients with right-sided lesions displayed a right dominant hemisphere in 10 cases. The hemispheric dominance was established using the Edinburgh test and the index of dominance was calculated on the basis of MRI findings (Gaillard et al., 2002). In particular preoperative MRI revealed 24 precentral lesions (8 on the right side and 16 on the left side), 3 right postcentral lesions, 23 lesions with the involvement of the insular lobes (10 on the right side and 13 on the left side), 3 lesions in temporoparieto-occipital junctions (2 on the right side and 1 on the left side) and 5 in the temporal lobes (2 on the right side and 3 on the left side). The map of tumor overlap (Fig. 1, top) confirms that in this series, tumors were predominantly located in frontal, temporal and insular lobes. Lesions were exclusively located within or near functional areas. Thus, during intraoperative functional mapping, sensory-motor functions were systematically tested, and language functions were tested for 43 patients. According to the Berger’s classification (Berger et al., 1994; Sanai and Berger, 2008), the postoperative FLAIR-weighted MRI showed a subtotal removal in 39 cases (65.5%), and a partial resection in 20 cases (34.5%). The median residual volume was 9.7 cm³ (range, 2–25 cm³).

**Probabilistic atlas**

**Fig. 1** illustrates the resulting probabilistic map on the cortical surface. Probabilities are encoded in a chromatic scale. The probability of leaving a functional tumoral residue, according to the color code, increases as the color changes from green to yellow and finally to red. In particular, regions in red color correspond to the sites that can never be resected, because of their invariant functional role. Regions in green color refer to areas that are resectable. Yellow regions represent areas with an intermediate probability of resectability. Finally, transparent regions indicate areas where no preoperative tumor was observed, that is without any information about resectability.

Analyzing the results in greater detail at the cortical level, the atlas indicates a high probability of residual tumor (i.e. a very low functional resectability) in the following areas:

- on the left side: the primary motor and somatosensory areas for upper and lower limbs, the ventral premotor cortex (vPMC), the posterior part of superior temporal gyrus (Wernike's area), the supramarginal gyrus, and the angular gyrus,
- on the right side: the primary motor and somatosensory areas for superior and inferior limbs and the angular gyrus.
All other cortical areas appear to be resectable, including the left and right Supplementary Motor Areas (SMA) and the primary non-dominant sensorimotor area of the face (regions visualized in green), and to a lesser extent, Broca’s area and insular lobes (represented in yellow).

Fig. 2 superimposes the residual atlas to the fiber tracts atlas. Few pathways appear to be resectable:

- the anterior part of the corpus callosum and cingulate area (on both sides),
- right and left uncinate fasciculus,
- anterior part of right and left longitudinal fasciculus.

All other tracts, on both sides, appear to be non-resectable (or at least, of intermediate resectability).
- the cortico-spinal tract, just under the primary motor area, and deeply at the level of the corona radiata (posterior limits of resection in patients with a frontal precentral glioma) and in correspondence to both the internal capsule and the superior part of the mesencephalic peduncles (which represent the depth of resection in patients with fronto-temporo-insular glioma),
- the thalamo-cortical tract (anterior limit of resection in patients with a parietal glioma),
- the stratum sagittale (including optic radiations, posterior part of inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), defining the medial functional boundaries during the resection of temporo-parietal gliomas,
- the anterior part of the inferior fronto-occipital fasciculus, that represents the deep limit of resection in patients with gliomas involving tumors in the left insular lobe, in the pars orbitalis of the left inferior frontal gyrus and in the dorsolateral prefrontal area,
- the perisylvian network, both on the left and right sides (see Duffau et al. (2002, 2008a); Thiebaut de Schotten et al. (2005) for extensive discussion on the glioma locations for which these network will be detected by DES).

Discussion

A new tool to study the potentialities and limitations of interindividual variability and plasticity in patients with LGG

Low-grade gliomas are slow-growing tumors, but hamper functional prognosis, as they infiltrate functional areas, and are ultimately prone to undergo anaplastic transformation (Wessels et al., 2003). Numerous pre-operative neurofunctional imaging studies have shown that tumor invasion triggers a neural reorganization, explaining the fact that 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). Four main plastic patterns have been reported: first, the infiltrative character of LGG makes it possible for the function to persist within...
the tumor; second, eloquent areas can be redistributed immediately around the tumor; third, a distributed network of areas can be recruited within the lesioned hemisphere; finally, a network of areas can be recruited in the contralateral hemisphere (Duffau, 2006b).

Therefore, slow growing tumors represent an accurate model to study in vivo the interactions between the tumor growth and the capability of the whole cerebral network to reorganize itself (Desmurget et al., 2007).

Combinations of different neurofunctional imaging methods (such as fMRI, PET, and MEG) have enhanced our understanding of the preoperative functional reorganization. This has allowed for the identification of functional areas that can be preserved during surgery because of their language networks similar to that observed in left dominant networks. Thus, the symmetrical aspect of the non-resectable areas to be roughly symmetrical. This can be explained by a selection bias:

- Pallud et al., (2005), they constitute the main obstacle to radical surgery.
- In line with our previous work (Mandonnet et al., 2007a), we observed that the functional deficit elicited by their electrical stimulation, the observed transient disturbances can nevertheless be inferred for each case from the operative report. Tables 1 and 2 report the effects of electrical stimulation for these non-resectable areas, for cortical and axonal sites, respectively.

Two questions arise on why there is no inter-individual variability for these areas and why their resection cannot be efficiently compensated by plasticity phenomena. For some of these areas, the explanation could be that they act as input or output areas: input sites convey or are the first relay of information entering the brain, whereas output sites are the last relay or the fiber tracts sending information outside the brain. These areas include the primary motor and somatosensory areas, the cortico-spinal and thalamo-cortical tracts and the optic radiations, that is, the projection fibers. These areas are mainly unimodal and probably organized serially. The absence of parallel alternative pathway explains the impossibility to restore their function after any damage (Duffau, 2009b).

For all other areas, their non-resectability should be analyzed within a network perspective. High-order cognitive processes are mediated by short- and long-range networks, with cortical epicenters connected by U-shaped fibers, associative and commissural pathways and a particular network topology (like the “small word” one) is required to allow proper synchronization between several distant areas (Stam, 2010). The link between the function and the anatomy is not as simple as for input–output areas: here, a local lesion will disturb a whole network topology, which in turn could ultimately hamper the function sustained by this network. It can be hypothesized that structures like the Wernike’s area, supramarginal and angular gyri, the inferior-fronto-occipital fasciculus and the arcuate fasciculus are non-resectable because their lesion would cause major changes in the network topology that the dynamical plasticity potential would be overwhelmed. Interestingly, these areas are considered as “hubs” in revisited models of cognition — e.g. the posterior part of the left dominant superior temporal gyrus and its junction with the inferior parietal lobule (Hickson and Poeppe, 2017). Indeed, these functional epicenters allow a plurimodal integration of multiple data coming from the unimodal areas. In a step forward, this

Table 1: Functional responses of electrical stimulation for non-resectable cortical areas.

<table>
<thead>
<tr>
<th>Location of stimulation</th>
<th>Task</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary motor area (left or right)</td>
<td>Rest</td>
<td>Unvoluntary movement of contralateral limb</td>
</tr>
<tr>
<td>Primary somatosensory area (left or right)</td>
<td>Rest</td>
<td>Paresthesia in the contralateral limb</td>
</tr>
<tr>
<td>Left ventral premotor cortex</td>
<td>Counting</td>
<td>Speech arrest (counting)</td>
</tr>
<tr>
<td>Left posterior part of superior temporal gyrus (Wernike’s area)</td>
<td>Picture naming</td>
<td>Anoma/phonological paraphasias</td>
</tr>
<tr>
<td>Left supramarginal gyrus</td>
<td>Picture naming</td>
<td>Speech arrest/phonological paraphasias</td>
</tr>
<tr>
<td>Left angular gyrus</td>
<td>Picture naming</td>
<td>Phonemic paraphasias/ leftward deviation</td>
</tr>
<tr>
<td>Right angular gyrus</td>
<td>Line bisection</td>
<td>Rightward deviation</td>
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Analysis of non-resectable areas: the limitations of inter-individual variability and plasticity

Although the present methodology does not give direct access to the functional deficit elicited by their electrical stimulation, the observed transient disturbances can nevertheless be inferred for each case from the operative report. Tables 1 and 2 report the effects of electrical stimulation for these non-resectable areas, for cortical and axonal sites, respectively.

Two questions arise on why there is no inter-individual variability for these areas and why their resection cannot be efficiently compensated by plasticity phenomena. For some of these areas, the explanation could be that they act as input or output areas: input sites convey or are the first relay of information entering the brain, whereas output sites are the last relay or the fiber tracts sending information outside the brain. These areas include the primary motor and somatosensory areas, the cortico-spinal and thalamo-cortical tracts and the optic radiations, that is, the projection fibers. These areas are mainly unimodal and probably organized serially. The absence of parallel alternative pathway explains the impossibility to restore their function after any damage (Duffau, 2009b).

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1 The dynamical plasticity is the ability of brain networks to redistribute, after a focal injury, their global dynamical behavior over the intact areas, on a time scale ranging from seconds to hours. It is different from the biological plasticity, where biological changes in the properties of neurons and axons and their branching will allow brain function changes on a time scale from days to months.
529 tumor in the SMA. It has been shown by longitudinal fMRI studies that 530 involuntary movement of the contralateral limb.
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532 For example, the possibility to remove the primary non-dominant 533 visual hemisphere.
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535 Sensory-motor area of the face without inducing permanent central 536 phonological paraphasias.
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538 The reproducibility of these results, despite the inter-individual 539 semantic paraphasias.
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541 The intermediate resectability of some areas should be considered 542 line bisection.
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544 Analysis of resectable areas: the role of interindividual 545 bisection.
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547 Analysis of resectable areas: the potential of plasticity
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549 Regarding resectable areas, it should be kept in mind that the 550 task effect.
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552 Methodological procedure
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554 To compute this atlas we have improved a previously reported 555
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557 A first issue of the proposed method arises from the limitations 558
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Several ways can be foreseen to improve the quality of the present work:

- to enhance the accuracy of the registration procedure in order to optimize the spatial resolution of the atlas, for example by using algorithms based on biomathematical models of tumoral growth (Gooya et al., 2010).
- to increase the number of included patients, providing a higher confidence in the statistical results. To achieve this purpose, an online tool could be created to facilitate inclusion of patients from several collaborative centers.
- to correlate for each patient the intraoperative errors elicited by DES in the white matter pathway with the location of the residues, providing a new tool for lesion-behavior mapping (Kinkingnehun et al., 2007; Rorden et al., 2009).

Finally, apart from its fundamental interest in terms of lesion-behavior mapping, the present atlas can be used to predict individually, before surgery, the expected extent of the resection, by computing the overlap between the atlas and the preoperative MRI. Such a tool could play a role in the design of clinical trials — for example, to guide the decision between surgery or chemotherapy as first line of treatment.

References


