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Opinions

Hodotopy, neuroplasticity and diffuse gliomas

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ABSTRACT

Background and purpose. – The historical approach in neurooncology is used to mainly investigate the tumor, with very few considerations regarding the brain itself. Nonetheless, to select the best personalized therapeutic management for each patient with a diffuse glioma, i.e. to optimize the "onco-functional balance", the brain reaction induced by glioma growth and migration should be studied. Indeed, due to strong interactions between the glioma and the brain, cerebral adaptive phenomena often occur in order to maintain neurological and cognitive functions, as well as to compensate glioma spreading. Here, the goal is to detail mechanisms underlying neuroplasticity and its implications for surgical neurooncology.
Methods. – Data issues from cerebral mapping and functional outcomes in patients who underwent awake surgery for gliomas were discussed.
Results. – Massive resections of the brain, including so-called "eloquent areas", are possible without generating permanent neurological deficits in adult patients harbouring a diffuse glioma.
Conclusion. – From a fundamental point of view, these findings open the door to a hodotopical anatomo-functional organization of the brain, i.e. organized in dynamic and interactive parallel large-scale distributed networks, able to compensate for each other. Furthermore, cognitive neurosciences represent valuable help to neuro-oncology, by leading to the elaboration of new treatment strategies, such as multistage surgical approach, made possible thanks to cerebral remapping over years. In other words, understanding neuroplasticity in a connectomal account of brain processing permitted a dramatic improvement of both quality of life as well as overall survival in glioma patients, and resulted in the proposal of an "individualized functional neurooncology".

1. Introduction

The classical approach in neuro-oncology is mainly to investigate the tumor, with few considerations regarding the host, namely, the brain. Yet, the "onco-functional balance" must be taken into account when selecting the best therapeutic strategy for each patient with a diffuse glioma (DG). Although understanding of the natural history of the disease is compulsory, this is not sufficient. One should also study the reactions of the central nervous system (CNS) generated by the glioma growth and migration. Due to strong tumor–brain interactions, cerebral adaptive phenomena often occur in order to maintain neurological and cognitive functions, i.e. to compensate the DG spread [1].

In this opinion article, the aim was to study mechanisms underlying such neuroplasticity, based on lessons provided by cerebral mapping and functional outcomes in adult patients who underwent awake surgery for DG. The purpose is to switch from a localizationist view to a dynamic hodopical framework of neural processing. This knowledge has led to the adjustment of optimal therapeutic management according to the dynamic relationships between glioma course and adaptation of cerebral functional reorganization at the individual level.

2. The concept of neuroplasticity

2.1. History

Two opposite conceptions of CNS functioning were historically suggested. Firstly, the theory of "equipotentiality" hypothesized that the whole brain was involved in a functional task. In contrast, the theory of "localizationism" (built on the historical basis of the "phrenology") postulates that each cerebral area corresponds

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to a specific function. Progressively, an intermediate view emerged, namely a brain organized (i) in highly specialized functional areas, called "eloquent" regions (e.g. the Rolandic, Broca's and Wernicke's areas), for which any lesion generates major permanent neurological deficits, and (ii) in "non-eloquent" regions, with no functional consequences when damaged. Then, the dogma of a static CNS organization, with the inability to compensate any injury involving the "eloquent" areas, was settled for a long time. However, through regular reports of functional improvement following damage of structures considered as "critical", this view of a "fixed" CNS was called in question. Consequently, many investigations studied the mechanisms underpinning these adaptation phenomena: the concept of neuroplasticity was born (for a review, see [2]). Current developments in functional mapping and neuroimaging techniques have radically changed the classical modular model for a new dynamic and distributed perspective of organization of the brain, able to reorganize itself both during everyday life (learning) and after a pathological event [3].

2.2. Definition and mechanisms

Neuroplasticity is a continuous processing allowing short, middle and long-term remodelling of the neurono-synaptic organization, in order to optimize the functioning of neural networks – during phylogenesis, ontogeny, physiological learning and following brain injury. On a microscopic scale, pathophysiological mechanisms underlying plasticity are mainly represented by synaptic efficacy modulations, unmasking of latent connections, phenotypic modifications, synchrony changes and neurogenesis. On a macroscopic scale, diaschisis, functional redundancies, cross-modal plasticity with sensory substitution and morphological changes are involved. The behavioral consequences of these phenomena were analyzed, especially the ability to recover after cerebral damages (post-lesional plasticity), and the underlying patterns of functional remapping were investigated [4]. Neuroplasticity is only conceivable in a dynamic account of CNS organization. The brain is an ensemble of complex networks that form, reshape and flush information dynamically. Thus, reorganization is made possible by the existence of multiple and overlapping redundancies hierarchically organized. These findings have testified that neuronal aggregates, beside or outlying a lesion, can increasingly adopt the function of the damaged area and switch their own activation pattern to substitute the lesioned structure while facilitating functional recovery [5].

In this setting, the concept of the brain connectome has recently emerged. Its aim is to capture the characteristics of spatially-distributed dynamical neural processes at multiple spatial and temporal scales [6]. The new science of brain "connectomics" is contributing both to theoretical and computational models of the brain as a complex system, and experimentally, to new indices and metrics (e.g. nodes, hubs, efficiency, modularity) in order to characterize and scale the functional organization of the healthy and diseased CNS [3]. In pathology, neuroplasticity is nonetheless possible only on the condition that the subcortical connectivity is preserved, to allow spatial communication and temporal synchronization among large interconnected networks. In fact, although distinct patterns of subcortical plasticity were identified, namely unmasking of perilesional latent networks, recruitment of accessory pathways, introduction of additional relays within neuron-synaptic circuits, and involvement of parallel long-distance association pathways, the real capacity to build a new structural connectivity ("rewiring") leading to functional recovery has not yet been demonstrated in humans [7].

3. The time course of DG and its impact on cerebral remodelling

Conversely to glioblastomas, diffuse low-grade glioma (DLGG, WHO grade II glioma) is a slow-growing tumor, which progressively invades the brain over years. This slow time course explains why DLGG patients usually have no or only mild functional deficits, despite the frequent involvement of "eloquent" structures [8]. Moreover, these lesions induced progressive functional brain reshaping. Thus, neuroplasticity cannot be fully understood without considering the temporal pattern of the cerebral injury. In acute lesion such as stroke, even if many patients improved within the months following the damage, only around 25% of patients totally recovered, while more than 90% of DLGG patients (similar location than stroke) had a normal neurological examination [2].

Interestingly, a neurocomputational model based on a training of parallel-distributed processing neural networks simulated acute versus slow-growing injuries [9]. The results showed a very different pattern emerging in the simulation of DLGG in comparison with the simulation of stroke, with slow decay of the links within the same subnetwork leading to minimal performance decline in DLGG, in agreement with clinical observations. Moreover, at the end of the decay regime, the entire affected hidden layer could be "removed" on the simulation with no effect on performance – which closely matches the lack of major impairment from DLGG resection. It is likely due to the fact that abrupt stroke occasions rapid neuronal death in some minutes, while DLGG initially spares neuronal tissue and thus gives time for cerebral remapping over years. Thus, the functional status at the time of diagnosis might be a good reflect of the natural history of the disease.

4. The patterns of presurgical functional reorganization in DG

The patterns of reshaping may differ between DG patients. Preoperative functional neuroimaging found four kinds of remapping in patients without deficit [1]:

- function still persists within DG, thus with a very limited chance to perform a fair resection;
- eloquent areas are redistributed around the tumor, thus with a reasonable chance to perform at least a near-total resection despite a likely immediate transient deficit and a subsequent recovery;
- a preoperative compensation by remote areas within the lesional hemisphere occurred;
- areas are recruited in the contralateral hemisphere: in the two last patterns, the chances to achieve a total resection are very high, with only a slight and very transient worsening. These different patterns can be associated.

Therefore, in DG involving eloquent areas, plasticity mechanisms seem to be based on an hierarchically organized model, i.e., first with intrinsic reorganization within injured areas (index of favorable outcome); second, when this reshaping is not sufficient, other regions implicated in the functional network are recruited, in the ipsilateral hemisphere (close or even remote to the tumoral site) then in the contralateral hemisphere if necessary [10].

Interestingly, magnetoencephalography studies showed that a focal tumor disturbs the functional and effective connectivity within the whole brain, and not only in restricted area around the tumor [11]. These network dysfunctions are related to cognitive