Introducing the concept of brain metaplasticity in glioma: how to reorient the pattern of neural reconfiguration to optimize the therapeutic strategy

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Gliomas, which represent about half of all primary cerebral tumors, generate functional disturbances by progressing within the brain, with patient survival time still short even with treatment, especially in glioblastomas (survival less than 2 years). Nonetheless, in low-grade glioma (LGG) patients, who usually experience no or only slight neurological deficits, the lifespan is more prolonged (more than 10 years). Because LGG will unavoidably evolve to a higher grade of malignancy if left untreated, the purpose of an early therapeutic approach is to postpone tumor transformation, while enabling patients to carry out normal familial and socioprofessional activities with a chronic tumoral disease. To this end, multiple treatments are commonly administered over years, with maximal resection(s), several lines of chemotherapy, and radiation therapy adapted to the glioma course. Quality of life (QOL) however, should be preserved, on one hand by controlling the growth of the neoplasm, which will otherwise lead to cognitive deterioration if still able to migrate along the cerebral connectivity, and on the other hand by preventing treatment-induced neurological morbidity. To achieve this ambitious aim, a new way of thinking would be to tailor the management of ongoing glioma treatment based on the understanding of the dynamic organization of the individual brain, i.e., to study the functional “connectome.”

A Meta-Networking Brain

Contrary to what was thought for more than a century according to the localizationist theory, namely, that there is an inflexible cerebral architecture relying on discrete specialized areas, with each of them being supposed to correspond to a specific function, the nervous system is in fact underpinned by parallel and interactive large-scale neural networks. Such circuits that subserve conation, cognition, and behavior comprise a mosaic of cortical regions, interconnected by white matter tracts. This connectivity permits multiple patterns of synchronization which result in various brain functions. Moreover, the overall processing of the neural circuitry is based on a continuous succession of equilibrium states founded on interactions across these functional systems, enabling behavior adapted to moment to moment environmental demands. Such a dynamic “meta-networking” (network of networks) framework with perpetual modulation of within- and between-circuit spatiotemporal integration opens the door to neuroplasticity. Plasticity is an adaptive phenomenon made possible thanks to changes of neural properties in response to internal stimuli, the environment, and cerebral insult. This considerable potential of cerebral reconfiguration is critical in physiology (e.g., experience-dependent plasticity mediating development and learning) and in brain-damaged patients, because it can enable postlesional neurological recovery. This potential is stronger in patients with slow-growing lesions, which explains why LGG patients exhibit so few functional disorders, at least at the initial
phase of the disease. Indeed, noninvasive functional neuroimaging (FNI) studies performed before any treatment in glioma patients have evidenced neural circuit reallocation that is progressively generated by diffusion of the tumor and sustains functional compensation. Based on such brain reshaping, large resections of LGG were achieved using intraoperative electrical mapping in awake patients, with postoperative recovery and return to a normal life, even for tumors within structures thought to be “eloquent” according to the localizationist dogma (e.g., Broca’s area). Intrasurgical direct electrical stimulation of the brain allowed the identification and preservation of critical cortical and white matter fibers, confirming functional redistribution elicited by the glioma, and resulting in an optimization of the extent of resection and longer survival. Interestingly, postoperative FNI demonstrated further degrees of remapping elicited by surgery and by postsurgical rehabilitation. This additional reorganization led to reoperation in case of glioma relapse, with improvement of the tumor resection while preserving the patient’s QOL, as replicated by multiple centers. Furthermore, a recent series demonstrated that further degrees of functional reshaping may occur even after a second LGG resection, opening the door to a third surgery with an overall survival of 17.8 years. Such a multistage surgical approach also enabled patients to postpone adjuvant treatment, especially radiotherapy, which entails exposure to a risk of delayed cognitive disturbances, in particular due to radiation of the white matter fibers. Despite factors leading to such positive outcomes, brain neuroplasticity is nonetheless limited in some locations, i.e., the unimodal cortical areas (such as the primary motor or visual cortex) and at the level of subcortical connectivity. Therefore, with the goal of avoiding QOL deterioration, it is not always possible to propose repeated resection(s) or reradiation in the event of glioma regrowth in these critical neural structures which cannot be functionally compensated.

The Concept of Metaplasitcity

Such constant changes in the meta-network organization are commonly conceived as simply reflecting mechanisms of Hebbian synaptic plasticity, which promotes strong or synchronous firing among neurons. In fact, because the Hebbian learning rule allows synaptic strength to grow infinitely, this process is intrinsically unstable and must be counterbalanced by mechanisms able to maintain the global stability of the neural circuitry. This so-called homeostatic plasticity, which modulates the synaptic weights and permits restoration of overall firing rates or excitability within a network, dynamically interplays with Hebbian plasticity to avoid synaptic saturation and to preserve the equilibrium in the system. Metaplasitcity, i.e., the plasticity of the synaptic plasticity itself, is a higher-order plastic mechanism that regulates the learning rule as a function of the dynamical context. According to this concept, the past history of the activity of a neuron may determine its capability to undergo future update of synaptic rules. Activation of synapses in particular directions may affect their abilities to subsequently elicit long-term potentiation or long-term depression. Therefore, metaplasticity changes the properties of synaptic plasticity, with a delay between the initial neural activity that generates metaplasticity (“priming”) and the subsequent induction of synaptic plasticity.

Such an ability for the plasticity itself to slowly adapt at the cellular level may have a profound effect on behavioral plasticity, by enabling learning to learn. The brain network which encodes memory may take account of prior experience to impact future learning. Past events such as enriched environments or stress can affect memory, learning, and coping behavior later on. Learning capacities are dependent on the background of the repertoire of the neural circuit based on prior training and behavioral experiences. For example, metaplasticity allowed more rapid and persistent skill acquisition in subjects who had a history of prior musical training.

An improved knowledge of the mechanisms underlying dynamic changes in neuroplastic functions can be of utmost importance in clinical practice. Indeed, dysregulation of synaptic plasticity with aberrant plastic mechanisms has been demonstrated in various psychiatric or neurological diseases such as depression, Parkinson’s disease, stroke, and Alzheimer’s disease. Saturation of synaptic potentiation can be avoided with regulatory metaplasticity, a process that may have contributed to prevention of epilepsy; prevention of maladaptive modifications in neural circuits, such as focal dystonia in musicians; and restoration of associativity in animal models of Alzheimer’s disease.

Metaplasitcity and Gliomas

The purpose here is to introduce the concept of metaplasticity as a factor that may influence the multistage therapeutic management of LGG patients in order to optimize both their overall survival and their QOL over years of treatment. Because gliomas are diffuse neoplasms infiltrating the cerebral parenchyma, treatments such as surgery and radiation therapy must be tailored to optimize the interactions between tumor progression and adapted neuroplastic phenomena, which allow functional compensation. As mentioned, awake functional mapping–based resection represents the first therapeutic option to increase survival while preserving critical neural networks already reorganized in reaction to the prior glioma diffusion. However, due to the diffuse feature of gliomas, complete resection is not possible during the first surgery in all cases, for functional reasons. Yet, repeated resections can be considered in the event of further plastic changes occurring after the first operation—and also provide an option allowing postponement of adjuvant radiation in order to minimize the risk of early cognitive decline. Metaplasticity could be helpful to reorient the pattern of neural reconfiguration at the individual level, i.e., to use the past history of the disease and previous treatment(s) to canalize subsequent plastic mechanisms. A potentially fruitful avenue would be to guide functional reallocation evoked by the initial surgery. At the cellular level, resection, which can be assimilated to brain injury, may impact synaptic plasticity. Furthermore, at the connectomal level, FNI investigations following glioma removal have found evidence of additional mechanisms of circuitry rearrangement compared with preoperative
In a metaplastic view of brain processing, in which prior experience affects future behavioral learning, it might be hypothesized that presurgical reshaping elicited by tumor progression before diagnosis acted as a “priming effect” able to facilitate further neural reorganization after resection. Longitudinal FNI studies showed considerable variability across glioma patients in the patterns of postoperative redistribution, with various contributions of perilesional versus contralesmipheric compensatory structures. These different individual fingerprints can result in distinct therapeutic strategies, since prominent recruitment of functional areas around the surgical cavity will prevent subsequent connectome-based reoperation and will increase the risks of neurocognitive deficits in cases of adjacent locoregional radiation therapy. By contrast, if the functional compensation is mainly sustained by the contralesional hemisphere, repeated operation(s) with optimization of the extent of resection while preserving QOL could be considered in the event of glioma relapse. Thus, the ultimate goal would be to change the preoperative plastic pattern in case of peritumoral reorganization, by shifting to a more distributed reorganization after surgery, predominantly based on contralateral recruitment.

Functional rehabilitation may play a key role in the reorientation of individual mechanisms of neuroplasticity. The benefit of programs of cognitive remediation has been evidenced after glioma resection, especially by improving executive functions. Furthermore, serial FNI investigations before and after rehabilitation following brain surgery have demonstrated shifts of cerebral activation which were correlated with improvement of cognitive scores. Based on the meta-networking principle that relies on interaction between distinct eloquent circuits, adapted cognitive remediation programs can be elaborated to facilitate strategies of functional compensation, e.g., by using intact nonverbal memory abilities to compensate for verbal memory troubles. Postoperative FNI also showed language compensation by means of attentional resources, allowing the patient to name a pictured object thanks to the recruitment of the frontoparietal attention circuit. Interestingly, metaplasticity, which can stabilize the activity of neural networks, may increase or decrease the synergistic effect of functional remediation depending on the timing of combined neurorehabilitation therapies that are used, as demonstrated in stroke patients. According to this concept, and because prior training seems to facilitate faster and more robust learning, it might be advantageous to envision preoperative rehabilitation as a “preconditioning effect” in order to potentiate postoperative functional remediation in glioma patients.

Furthermore, at the cellular level, since the metaplastic potential is founded on the fact that the current state of the neuron depends on past states induced by separate prior events, an original strategy to enhance outcomes might be the application of a period of transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) as priming effects, before a subsequent period of neuromodulation by means of tDCS or TMS. Promising preliminary results have shown that protocols that included tDCS/TMS priming led to improved functional outcomes in comparison with protocols without priming. Such a heightened benefit from tDCS/TMS priming, mediated by regulatory metaplastic mechanisms in which the state elicited by the priming impacts the effects during the second stimulation period, could be applied to glioma patients. Indeed, tDCS/TMS might be used to catalyze neural reorganization, in isolation or by potentiating concomitant cognitive rehabilitation, not only after surgery but also before (re)operation to constrain the pattern of functional reallocation in order to facilitate subsequent resection(s).

Conclusions

Introducing the concept of metaplasticity in a meta-networking account of neural organization may open the window to new attitudes regarding the treatment of glioma patients, especially those with chronic tumor disease such as LGG, by proposing repeated treatments over years, and by adapting the next therapy to the previous one and its effects on individual brain reshaping. This approach could be considered to take into account several parameters able to modulate intra- and internetwork dynamic redistribution, such as 1) the natural history of the glioma before and after each treatment (e.g., possible changes in the tumor behavior, growth rate, or proliferative versus migratory pattern), 2) the impact of a prior resection performed according to functional boundaries and itself based on previous rearrangement induced by the glioma progression before diagnosis, 3) the effect of postoperative (or even preoperative) cognitive rehabilitation, able to elicit further degrees of neural reallocation, not only within a function-specific circuit (e.g., devoted to language) but also across circuits by developing compensatory strategies (e.g., rehabilitation of altered verbal memory by means of preserved nonverbal capacities), and 4) the use of tDCS or TMS priming protocols to boost outcomes. By incorporating interplay among these ever-changing variables, the ultimate aim would be to redirect the mechanisms of neural reorganization in order to induce a shift from a prior prominent pattern of perilesional recruitment to a pattern of predominantly recruiting remote networks (ideally contralateral homologous areas) (Fig. 1). Interestingly, computational models of plasticity and metaplasticity might be helpful to predict homeostasis in synaptic weights. Such metaplastic changes in the mechanisms of neuroplasticity knowingly generated by guiding interactions over time between tumor course and brain reaction, and made possible owing to perpetual modifications in the meta-networking equilibrium, could allow improvements of both survival and QOL of glioma patients. Because the heterogeneous group of LGGs is composed of different tumor types based on genetics, in order to tailor personalized medical therapies to successfully treat patients, the next step could be to explore whether molecular profiles of the glioma are correlated with the patterns of neuroplasticity. To favor a multidisciplinary approach optimizing the management of glioma patients, it is time to bridge the gap between basic neurosciences dedicated to the field of connectomics and metaplasticity; fundamental oncology, which explores tumor behavior; and clinical neurooncology, with the aims of developing original multimodal and
multistep therapeutic strategies. Prospective multicenter studies should be designed to validate this new theory.

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Disclosures
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