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Perspectives in human brain plasticity sparked by glioma invasion: from intraoperative (re)mappings to neural reconfigurations

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Exploring the aptitude of the human brain to compensate functional consequences of a lesion damaging its structural architecture is a key challenge to improve patient care in various neurological diseases, to optimize neuroscientifically-informed strategies of postlesional rehabilitation, and ultimately to develop innovative neuro-regenerative therapies. The term 'plasticity', initially referring to the intrinsic propensity of neurons to modulate their synaptic transmission in a learning situation, was progressively transposed to brain injury research and clinical neurosciences. Indeed, in the event of brain damage, adaptive mechanisms of compensation allow a partial reshaping of the structure and activities of the central nervous system, thus permitting to some extent the maintenance of brain functions. Such findings have been observed in multiple clinical conditions, most notably in the context of diffuse low-grade gliomas (DLGGs) - a histopathological subgroup of slow-growing tumors that biologically integrates within the surrounding brain tissue, both at the synaptic (Venkatesh et al., 2019) and macro-structural levels (Numan et al., 2022). Contrary to acute neurological injuries such as stroke, where neurological recovery generally remains limited, patients with DLGGs can usually benefit from an extensive surgical excision without suffering from permanent neurological or cognitive deficits as long as critical neural structures are preserved thanks to modern intraoperative awake cognitive mapping (Lemaitre et al., 2022). Therefore, DLGGs may be viewed as a relevant model to grasp the neuroplastic mechanisms being deployed to counterbalance neuronal losses and to establish the neural fingerprints predictive of functional recovery in a lesion context. In this perspective article, the authors aimed to emphasize recent contributions investigating human brain plasticity in reaction to DLGG invasion. First, long-range axono-cortical connections are discussed as major substrates underlying spatial redeployments of brain functions. Second, the time-dependent and evolving aspects of cortical rewiring are reviewed in light of recent intraoperative direct electrical stimulation (DES) findings. Third, these spatiotemporal patterns are examined under the scope of global reconfigurations of the meta-networking brain, an emerging theory of brain functioning. Finally, a tentative dynamic and multilevel model of glioma-induced plasticity is proposed to pave the way to future research perspectives in the field.

Spatial reallocations of functions: a connectomic perspective: Several studies have highlighted structural and functional reshaping in patients with DLGG. For instance, the tumoral infiltration of the insular lobe has been shown to generate contralateral homotopic reorganizations, resulting in an increased homotopic functional connectivity based on resting-state functional magnetic resonance imaging (rsfMRI) measures (Almairac et al., 2021) and an inflation of the gray matter volume within the contralateral insular cortex in voxel-based morphometric analysis (Almairac et al., 2018). Overall, numerous works argue that the modulations of functional connectivity observed in patients with gliomas not only occur in the perilesional areas but also spread widely and bi-hemispherically in the entire functional connectome (Bartolomei et al., 2006). Further, a recent rsfMRI study reported that the global efficiency of network reshaping is associated with cognitive maintenance (Ng et al., 2022a), which supports the idea that brain-wide functional remodeling coincides with a functional compensation mechanism.

However, major constraints reduce the potential of functional reallocation following a brain injury. Inter-hemispheric commissural bundles and associative white matter tracts are presumed to act as major vehicles for the redeployment of brain activities by allowing the recruitment of perilesional latent subcircuits and long-distance parallel networks that generate cortico-subcortical functional relays. This view is remarkably supported by the low resectability potential of particular white matter tracts in the neurosurgical setting (Herbet et al., 2016), and is additionally corroborated by functional plasticity atlases based on causal anatomo-functional inferences obtained with intraoperative DES (Ius et al., 2011). Overall, these results highlight a functionally non-compensable core axono-cortical architecture with a low inter-individual variability index (described as the "minimal common brain") that is assumed to sustain locoregional and distant neuroplastic compensations.

Evolving patterns of neuroplasticity: a dynamic spatiotemporal framework: Diffuse gliomas are incurable tumors and patients with such a chronic disease will inevitably present with a tumor recurrence years (or even decades) after an initial surgery. In the context of DLGG recurrence, it is remarkable to note that a second brain surgery assisted by DES cortico-subcortical mapping in awake condition (often occurring several years after a first surgery performed under the same conditions) frequently allows an extra-resection of brain regions that were functionally responsive to electrical stimulations during the first surgery, with however no significant effects on neurological or cognitive status (Ng et al., 2022b).

Importantly, a recent study based on longitudinal intraoperative DES functional mappings in 101 patients who were operated on twice for a recurrent DLGG (about 2000 cortical functional sites were analyzed) demonstrated that there was a significant evolving neuroplasticity potential between the two surgeries (Ng et al., 2023). Of note, the propensity of cortical areas to be functionally redeployed followed a gradient and was spatially constrained by the underlying neuroanatomical structures. In particular, the evolutive potential for cortical redeployment remained restricted in unimodal cortical regions (primary sensorimotor cortex) but appeared to be extensive in transmodal regions such as the dorsolateral prefrontal cortex, despite the high centrality of this cortical hub in multiple high-level functions. Likewise, intragyral reconfigurations were also highlighted, especially regarding the left superior temporal gyrus, where a more posterior redeployment of functional responses was generally observed, and the ventral part of the premotor cortex, where significant shifts of functional responses (i.e., speech arrest and verbal apraxia responses) toward more dorso-lateral and posterior regions of the precentral gyrus were also reported. Moreover, the efficiency of cortical rearrangements tended to be domain-specific, with a remarkable reshaping of functions highly lateralized, including language and speech production, suggesting a compensatory recruitment of the contralateral hemisphere. Interestingly, the patterns of functional reconfiguration reported within the cerebral cortex were not strictly restricted to areas infiltrated by the tumor, but significantly expanded toward extra-lesional cortical areas, which strengthens the idea that long-term plastic reorganizations of cortico-subcortical subnetworks located within the whole hemisphere occur. These results not only provide critical clinical information to refine the selection and operability of patients with recurrent DLGG, but also pave the way for a time-dependent conception of lesion-induced neuroplastic potential, by incorporating spatial and temporal parameters into a dynamic and predictive framework.

Meta-network reconfigurations of the functional connectome: The meta-network theory of brain function (Herbet and Duffau, 2020), i.e., the context-sensitive recruitment of different systems of networks (networks of networks) that allows to optimally support moment-by-moment cognitive demands, has recently emerged to illustrate the constant interactions between the human brain and its environment but also the capacity of the brain to generate complex forms of behaviors. This framework may also be relevant to characterize the dynamic functional across-network reconfigurations induced by a brain tumor. In the context of DLGGs infiltrating the precuneus, a crucial functional hub in humans at the center of the so-called default mode network, several inter-network hyperconnectivity patterns (measured in rsfMRI prior to oncological surgical excision), appeared to be positive markers of postoperative cognitive maintenance (Ng et al., 2022a). This finding confirms that large-scale functional connectivity redeployments, including between-network reshaping, may be crucial markers of neuroplastic induction and may help to refine personalized therapeutical strategies in patients with DLGGs. Besides, a better understanding of the mechanistic aspects underlying context-sensitive across-network redeployments will allow a critical step in identifying and modeling the most efficient strategies implemented by the brain to maintain efficient interactions with the internal and external world during complex activities.

Toward a dynamic and multilevel model of glioma-induced plasticity: The study of neuroplasticity mechanisms in patients with DLGGs has been widely developed in the last twenty years. This has resulted not only in a drastic modification of clinical and surgical practices (a personalized assessment of brain functional compensations using intraoperative awake DES mapping is now the gold standard approach) but also in a substantial improvement of both quality of life (i.e., reduction of postoperative neurological deficits below 3%) and life expectancy in patients harboring a DLGG (with an overall survival now beyond 16 years in the median, that is strongly correlated with the extent of surgical excision). Here we propose a dynamic and multilevel model (**Figure 1**) to summarize macroscale features presumed to govern glioma-induced plasticity.

The dynamic dimension of this model accounts for the constantly evolving variables driving glioma-to-network interactions, including constant tumor growth and responsive network compensations (see below) that ensure the maintenance of global cognitive functioning. The time-dependent and non-linear dimension of glioma-induced plasticity mechanisms requires a constant adaptation of neuroplastic modulations (i.e., a modulation of Hebbian plasticity learning rules, in a pathological context) that is called meta-plasticity (i.e., plasticity of plasticity). Milestone events may indeed disturb the current course of plasticity redeployments; in this context, meta-plasticity will adjust neuroplasticity strategies to keep optimized ongoing functional compensations. These events may be (1) biological events (change of tumor velocity, modifications of tumoral patterns of diffusivity, e.g., proliferative *versus* diffusive, histomolecular

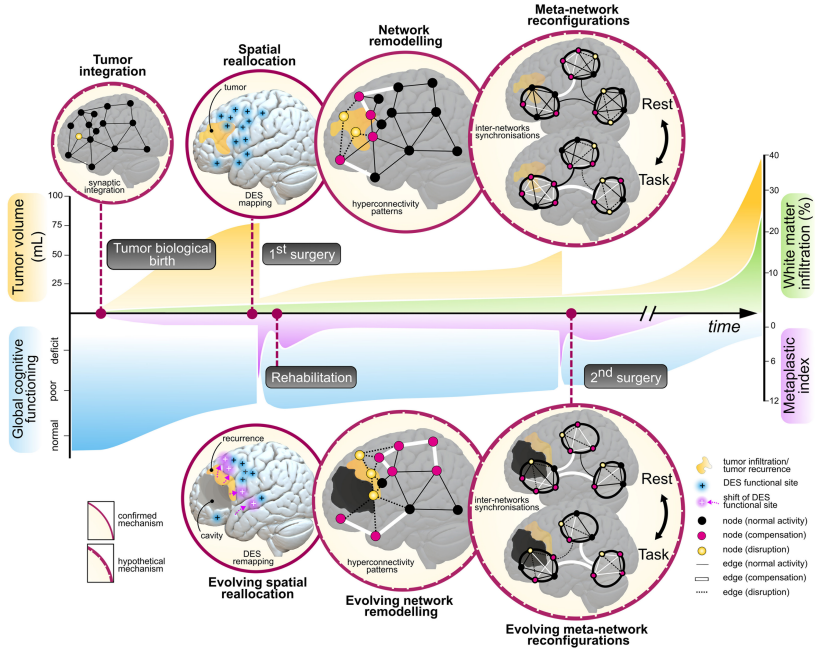

Figure 1 | **Toward a dynamic and multilevel model of glioma-induced plasticity.**
The dynamic dimension of the model is represented by a temporal framework (from left to right) along which different variables reflect the evolution of the disease (upper part, tumor volume in orange, white matter tract infiltration in green) and the resulting functional compensation in the same individual (lower part, global cognitive functioning in blue, and metaplastic index in purple). The multilevel dimension of the model includes at different time points of the temporal framework (here illustrated at first surgery and second surgery): (1) spatial reallocations, as attested by serial intraoperative functional mapping with direct electrostimulation, (2) a network remodeling of the functional connectome, and (3) a context-sensitive reconfiguration of the meta-network. The metaplastic index refers to the disruption of the natural course of plasticity redeployments, defined as modulations of previous plasticity learning rules (i.e., meta-plasticity) induced by milestone biological or therapeutic events (e.g., tumor birth, rehabilitation, surgery, modification of the glioma behavior). Created with Inkscape software (Inkscape.org, version 1.1.1). DES: Direct electrical stimulation.

changes, e.g., tumor hypermutation and anaplastic transformation), (2) current therapeutic approaches (e.g., neurorehabilitation, surgery, and chemotherapy) or (3) neuromodulation protocols currently under evaluation (e.g., transcranial direct current stimulation and repetitive transcranial magnetic stimulation).

The multilevel dimension of this model accounts for parallel mechanisms that sustain possible anatomo-functional rearrangements:

- A spatial reallocation potential is prominently located within the cerebral cortex and constrained by the underlying structural connectivity. Such functional reallocation may be loco-regional or distant (including within the contralateral hemisphere). This remodeling process may be purely driven by intracortical signaling but is thought to also rely on white matter connections. Critical lesions to determinant axono-cortical circuits (both related to the tumor infiltration and/or surgical accidental resection) may definitively disturb ongoing spatial rearrangements.
- A functional network remodeling process is observed both within a specific functional network and between multiple functional networks (both within the ipsilateral and contralateral hemispheres). The global efficiency of network modulations may participate in a better resilience to evolutive brain lesions.
- A compensatory reconfiguration of meta-networks i.e., modulations of context-sensitive network interactions to continue responding optimally to ongoing environmental demand (Herbet and Duffau, 2020). In normal physiological conditions, such meta-networks result from the abilities of the brain to switch and reformat their connections from one behavioral condition to another (e.g., from resting to task state).

In light of what has been developed above, the authors suggest that future efforts aiming at investigating glioma-induced plasticity should focus on the following lines:

- A multimodal assessment of structural and functional neuroplasticity patterns, involving combined methodologies (e.g., neuropsychological examinations, structural MRIs, tractography, fMRIs, non-invasive transcranial magnetic stimulation mapping, invasive cortico-subcortical DES mapping in awake condition) in a serial context (before/after a first surgery, a second surgery, before/after a cognitive rehabilitation); the combination of large datasets will be of the utmost importance to build strong predictive models of individual remodeling patterns, not only to anticipate the efficiency of connectome reorganization before a critical therapeutic choice, but also to provide backward projections on the dynamic interplay between connectome reconfigurations and the biological birth of the tumor.
- A better understanding of the mechanistic aspects underlying both macrostructural reconfigurations of the functional connectome at the network and meta-network levels, and ultrastructural changes of synaptic transmission and axonal rewiring, with the objective of identifying critical functional hubs and biological markers that could be targeted in future personalized neuromodulation protocols.
- A precise assessment of the effects of therapeutic tools currently available (including chemotherapy, radiation therapy, surgery, second or even third surgery) or under development (e.g., repetitive transcranial magnetic stimulation). Ultimately, the goal would be to boost and redirect the meta-plastic potential in order to optimize combined therapeutical approaches in a dynamic and integrated view.

The applications resulting from these complementary research fields could potentially contribute beyond the field of translational neuro-oncology and open the door to a new era of personalized neuro-regenerative medicine.

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