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Predictors of cognition after glioma surgery: connectotomy, structure-function phenotype, plasticity

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Determining preoperatively the maximal extent of resection that would preserve cognitive functions is the core challenge of brain tumour surgery. Over the past decade, the methodological framework to achieve this goal has been thoroughly renewed: the population-level topographically-focused voxel-based lesion-symptom mapping has been progressively overshadowed by machine learning (ML) algorithmics, in which the problem is framed as predicting cognitive outcomes in a patient-specific manner from a typically large set of variables. However, the choice of these predictors is of utmost importance, as they should be both informative and parsimonious.

In this perspective, we first introduce the concept of connectotomy: instead of parameterizing resection topography through the status (intact/resected) of a huge number of voxels (or parcels) paving the whole brain in the Cartesian 3D-space, the connectotomy models the resection in the connectivity space, by computing a handful number of networks disconnection indices, measuring how the structural connectivity sustaining each network of interest was hit by the resection. This connectivity-informed reduction of dimensionality is a necessary step for efficiently implementing ML tools, given the relatively small number of patient-examples in available training datasets.

We further argue that two other major sources of interindividual variability must be considered to improve the accuracy with which outcomes are predicted: the underlying structure-function phenotype and neuroplasticity, for which we provide an in-depth review and propose new ways of determining relevant predictors. We finally discuss the benefits of our approach for precision surgery of glioma.

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Introduction

In the field of glioma surgery, it is now firmly established that the larger the resection, the better the survival.[1-3] On the other hand, pushing the resection too far bears the risk of inducing permanent neurological deficits. Surgery with sensorimotor and language mapping is thought to be the best approach for minimizing the risks of resection-induced long-lasting neurological deficits,[4] thus allowing to achieve so called 'maximal safe resection', that is to optimize the onco-functional balance.[5] But if sparing of language and sensorimotor functions is relatively well controlled, very little is known about the risks regarding other more complex cognitive functions—such as executive functions, emotional processing, mentalizing or decision making—all functions which are not systematically tested intraoperatively. It could be argued that the preservation of executive functions or emotion recognition does not need to be part of the onco-functional balance, as there is very limited data regarding the ecological value of putative deficits, that is regarding their real impact in daily life. However, preliminary studies suggested a strong link in glioma patients between integrity of executive functions and health-related quality of life or work resumption,[6-8] and one report demonstrated in brain trauma patients that impaired emotion recognition correlated and with impaired self-awareness and with behavioural problem as rated by proxies.[9] Furthermore, the availability of a tool capable of accurately predicting which cognitive functions may be at risk with an increased extent of resection would serve to enrich the preoperative dialogue between the surgeon/neuropsychologist and the patient. This, in turn, would facilitate a genuinely informed preplanning of the 'ideal' resection—one that maximally preserves functions considered essential by the patient himself. (See also the associated concept of 'à la carte' cognitive mapping.[10])

The goal of this paper will thus be to review how machine learning advances resulted in a recent paradigmatic shift to tackle the challenge of making accurate prediction of cognitive outcomes during preoperative surgical planning. Importantly, making accurate predictions is all the more challenging that cognitive functions are complex: indeed, the more complex a function, the more distributed, variable, and malleable its neural basis.[11,12] It is essential to highlight that the relevance of preserving these functions is contingent upon patients being free of preoperative deficits. This consideration applies to any type of glioma, although grade 2 and 3 IDH-mutated gliomas represent the most prevalent scenario. Furthermore, predictors of cognitive outcomes in high-grade gliomas also include additional confounding factors, such as the nature of the oedema surrounding the tumour mass (vasogenic versus infiltrative) and the type of adjuvant treatments. As a result, the framework we present in this paper will primarily focus on lower-grade gliomas. However, it can be readily extended to high-grade gliomas (For instance, the dosimetry of radiation therapy planning can be converted into a concise set of features using the same process as the one applied to resection topography.)

In the first part, we will briefly review the literature about the deficits reported in executive functions and emotional processing after (low-grade) glioma surgery. The commonalities in the outcomes observed for these two functions will help us to grasp why the old but still relevant question of lesion-symptom mapping should be now formulated as a prediction problem rather than as a simple correlational study between a resection topography and a cognitive deficit (Fig. 1). Nonetheless, resection topography plays without any doubt an essential role in the prediction, as each resection topography has its own signature on the connectome. The second part will be thus devoted to explain why lesion topography, which is highly variable at the voxel level in the geometrical 3D-space (as two patients never have exactly the same surgical cavity), needs to be compressed in a limited set of relevant parameters computed in the connectivity space, thus allowing to reach an adequacy between the number of predictors (dimensionality) and training examples, as required for efficient implementation of machine learning algorithms.

Next, we will focus on the interindividual variability in structural and functional anatomy, an issue that initially motivated the introduction of intraoperative mapping, to individually map essential areas to be preserved. We will mention some new and very recent methodological advances in imaging processing that enable to personalize brain functional parcellation, paving the way towards a better understanding of the role played by this variability in the quality of the prediction.

Finally, plasticity constitutes the third source of interindividual variability in cognitive outcomes. We will emphasize that this is the most critical point, because currently, we do not have any available tool to preoperatively measure how much the brain of a patient is plastic, i.e. its 'neuromalleability'. Situating plasticity in the wider framework illustrated in Fig. 2, we will thus review the literature about the different forms of plasticity, with the aim to find a way to measure individual neuromalleability, or at least, to identify relevant proxies of it.

Last but not least, we will explore two opposite but complementary avenues to make the prediction more accurate, heading towards its implementation in clinical practice.

Do we observe long-term deficits of complex cognitive functions after glioma surgery?

To address this question from literature data, we selected, among the large spectrum of cognitive functions, the two that could be viewed as opposite poles—reason and the heart: executive functions and emotion processing. Through their interaction in decision making processes,[13,14] allowing individuals to make a decision adapted to the context, they play an essential role in daily life.

Executive functions

Over the past few years, the number of studies exploring the impact of lower-grade glioma resection on executive function suddenly increased[15-24] (see also two recent meta-analyses[25,26]). Comparison between studies is complicated by the fact that there is no standardized way to measure the different components of executive functions (which are, in the original model by Miyake *et al.*,[27] updating, inhibition and shifting). Each neurosurgical team includes different tasks in its battery, including but not limited to the Stroop test, the trail making test, object matching by shape or colour, verbal fluencies and digit span forward and backward. Moreover, the thresholds defining pathological performance or postoperative decline can also vary from one study to another. Nonetheless, reviewing studies focusing on set-shifting[19,20,22,28-31] (Table 1), we found that a small to moderate fraction of patients (7% to 26%) are still impaired and/or have declined performances compared to their preoperative level at follow-up examination (i.e. >3 months after surgery). Unfortunately, we found very few data regarding the postoperative period (i.e. in the days following the surgery), but the percentage seems much higher here (up to 60% in one study[19]). No clear anatomical correlates emerged from these studies when using standard

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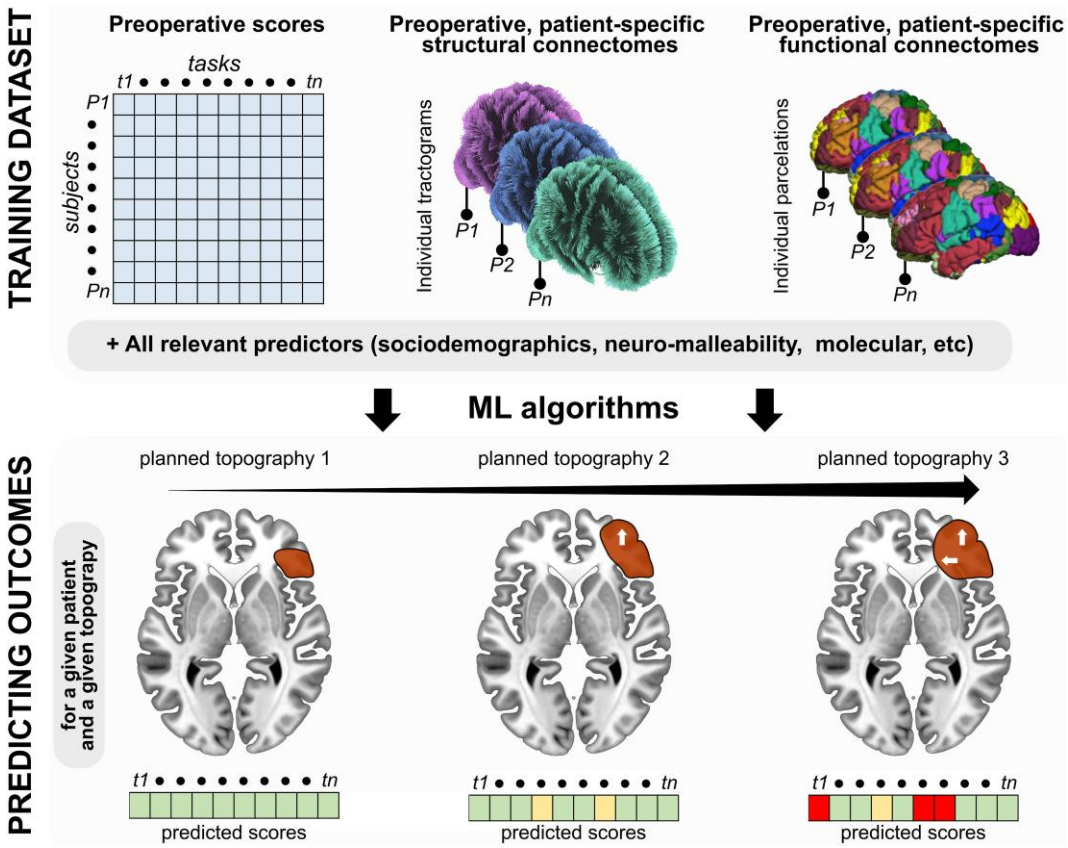


Figure 1 A global framework to address the challenge of accurately predicting postoperative cognitive outcomes. *Top*: Multimodal data are collected, including the preoperative and postoperative scores, patient (P)-specific structural and functional connectomes, and the surgical cavity. Note that the preoperative scores can be incorporated into the predictors, the goal being to predict the delta (postoperative-preoperative). Once condensed to a limited set of predictors, these data serve as the training dataset for a machine learning (ML) algorithm. *Bottom*: The trained algorithm is used to predict the postoperative scores for intended topographies of resection. The optimal topography can then be selected, depending on the functional, personalized strategy developed by the patient and neurosurgeon.

voxel-based lesion-symptom mapping (VLSM). One study associated the deficits with right frontal location,[28] another with right white matter of temporo-parietal junction[30] and a final one did not evidence any effect of resection side.[29] In addition, another study applying VLSM to disconnection maps mainly ascribed impairments to the second branch of the left superior longitudinal fasciculus.[22] Such inconsistencies are in a whole coherent with the hodotopic view according to which complex cognitive functions rely on brain-wide interacting networks, thus making the link between lesion and deficit intractable with standard lesion-symptom mapping methods. Hence, although these studies are informative when discussing with the patient about the cognitive risks of the surgery, they do not clearly depict which parts of the brain should be preserved by the surgeon to prevent their occurrence.

Basic emotion processing

There are very few studies reporting patients' performances on emotional processing following glioma surgery. Most studies relied on the well-tried Ekman's face emotion recognition (ER) test or its equivalent. This test consists in identifying which one among six basic emotions (happiness, sadness, anger, fear, surprise, disgust) is expressed on a photograph of a face. We found four studies analysing the effect of surgery on the performance of ER[32-35] (Table 2). Preoperatively, a small but significant fraction of patients (between 12% and 27%) were assessed as impaired. In the acute postoperative period, a much higher proportion of patients (between 38% and 42%) were considered as impaired, while after a few months (>3 months), the percentages were similar to their preoperative values (between 14% and 23%). Importantly, whereas some anatomical correlates could be found in the acute postoperative period,[32,36] none could be determined for the long-term outcomes (except for another study in which happiness and sadness were investigated,[37] and in which it was demonstrated that sadness recognition remained impaired at 3 months post-operation and associated with right medial orbito-frontal regions). Hence, here again, such findings corroborates the recent shift from a purely localizationist mapping of each emotion category to a (multi-)network mapping of a psychological constructionist account of emotion recognition.[38]

Of note, three groups included Ekman's ER test in their intraoperative monitoring of the cortical surface. Giussani *et al.*[39] described functional sites distributed over the right temporo-parietal junction. Papagno *et al.*[40] found eloquent sites specific to disgust recognition when stimulating the left insula. Finally, Nakajima *et al.*[37] reported sites evenly distributed over the right premotor and posterior prefrontal cortices. However, it is unclear whether all identified eloquent sites should be preserved, as in some instances, their resection would only cause a transient

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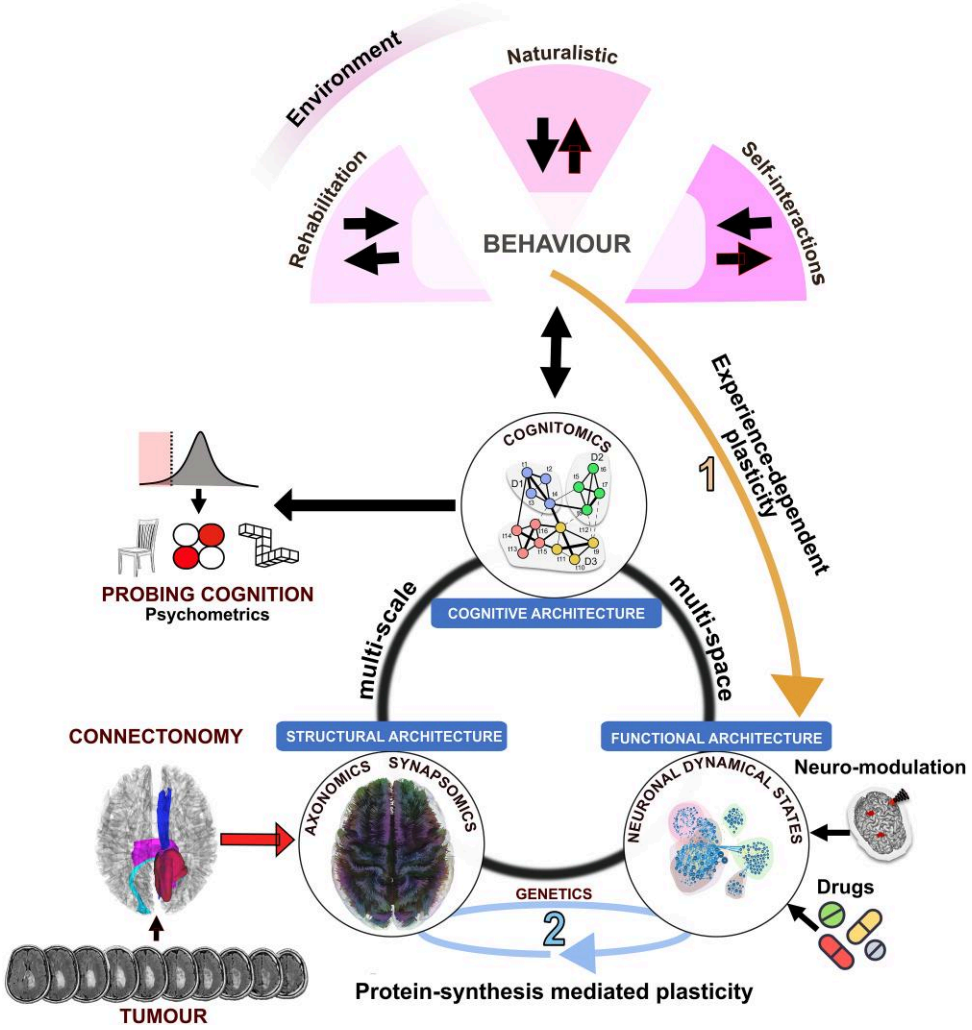


Figure 2 Integrative view of a mechanistic approach of plasticity. Behaviour results from the interaction between cognitive architecture, the environment and the self. The cognitive architecture can be probed through various psychometric measures conducted both before and after surgery. Surgery acts as a function-guided connectotomy, modifying the structural architecture of the brain and, consequently, its functional architecture (i.e. the repertoire of neuronal states dynamics). There is a complex, currently undecipherable, interplay between structural, cognitive and functional architectures. Controlling the environment, rehabilitation drives changes in behaviour, hence in functional states. This phenomenon is termed experience-dependent plasticity, akin to a behavioural-level version of the synaptic long-term potentiation and depression. In turn, experience-induced plasticity will trigger molecular events that will durably alter the micro-structure of the synapses—referred to as synthesis-mediated plasticity. Finally, non-invasive stimulation or drugs can artificially mimic experience-dependent plasticity, thereby modifying functional states.

postoperative deficit (see Schiavolin *et al.*,[7] Boele *et al.*[8] and Ng *et al.*[25] for further discussion).

Some rules of thumb

In summary, relying on the available data, the following trends are apparent, particularly for executive functions and emotion recognition: (i) postoperative acute deterioration is widespread; (ii) conventional methods of lesion-symptom mapping are inadequately suited to identify the anatomical correlates of both acute and late deficits; and (iii) only a small fraction (10%–20%) of patients will experience enduring impairments. Additionally, these observations may extend to encompass other complex cognitive functions relying on widely distributed networks, such as mentalizing and decision-making, among others. From a practical point of view, the main question to be addressed is thus as follows (Fig. 1): can we predict preoperatively, for an intended topographical resection and for each function, which patient will recover, and which one will not? As recently reviewed,[41] parameters influencing post-resection cognitive outcome are numerous and inter-dependent, spanning across multiple scales and domains. In the next sections, we will successively study the role of three major independent factors influencing long-term cognitive outcomes after a glioma resection: connectotomy, structure-function phenotype and plasticity.

From resection topography to connectotomy

Since the brain is primarily a connectome, any resection defined topographically in the Cartesian 3D-space can be represented by a unique disconnection fingerprint in the structural connectivity space (see also Gleichgerrcht *et al.*[42] for a general introduction to connectome-based lesion-symptom mapping). The structural

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Table 1 Review of the literature on set-shifting performances after glioma surgery

	Test	Tumour location	Impaired baseline, *n* (%)	Impaired postoperatively, *n* (%)	Impaired follow-up, *n* (%)	Postoperative decline, *n* (%)	Late decline, *n* (%)	Anatomical correlates of decline or impairment	
								L/R	VLSM/MLSM
Hendriks *et al.*[28]	TMT + fluencies	All	4/59 (7%)	–	–	–	4/59 (7%)	Right	Frontal
Rijnen *et al.*[29]	Shifting attention	All	–	–	–	–	11/77 (14%)	None	–
Hartung *et al.*[30]	TMT B/A	Right parietal	1/19 (5%)	–	3/19 (16%)	–	5/19 (26%)	–	Right PTS/SLF III
Lemaitre *et al.*[20]	TMT B-A	All	7/157 (4.5%)	–	15/157 (9.5%)	–	20/157 (12%)	–	–
Cochereau *et al.*[22]	TMT B-A	All	–	–	27/270 10%	–	–	Left	Left SLF II
Barberis *et al.*[19]	TMT B-A	Right frontal	1/20 (5%)	9/15 (60%)	4/19 (21%)	11/15 (73%)	2/19 (11%)	–	–
Mrah *et al.*[31]	TMT B-A	All	–	–	–	–	21/102 (21%)	None	CC12 of Yeo

L = left; R = right; MLSM = multivariate lesion-symptom mapping; PTS = posterior transverse system; SLFR = superior longitudinal fasciculus; TMT = trail making test; VSLM = voxel-based lesion-symptom mapping.

connectome can be indeed modelled as a large $N \times N$ connectivity matrix (with N being the number of cortical parcels; Fig. 3), in which each coefficient (i, j) represents a measure of the connection strength between area i and area j (such as the number of streamlines linking the two regions). Each resection topography is thus associated with a unique disconnectome matrix, in which coefficient (i, j) is set to zero if the resection damaged all the streamlines between the two areas. We thus define the 'connectotomy' as being the impact of a resection in the connectivity space. Stated mathematically, 'connectotomics' is the science of determining the part of the variance of the cognitive outcome that can be explained by the topography of the resection only, hence by the connectotomy only (albeit conditionally to a preoperative tumour topography). This means that, considering monozygotic twin patients—thus with similar genomes, brain structure and function, tumour biology, preoperative way of life and postoperative rehabilitation programme—their cognitive outcome will be exclusively determined by the connectotomy (or topography of their resection; Fig. 4). From the neurosurgeon perspective, connectotomics is of greatest importance, as resection topography is the sole parameter that is under its control. It is at the core of the on-line decision-making process in the operative theater: pushing too far the resection would expose the patient to the risk of definitive cognitive impairments, stopping too early would reduce their chances of survival. Importantly, the link between resection topography and connectotomy is not straightforward: a few more millimeters of resection might dramatically increase the connectotomy[43,44] (hence its functional impact).

Stated differently,[45] the challenge of determining the mapping between a resection topography and its impact in the multidimensional space of cognitive scores stems from the non-linearities of the problem: whenever two small areas A and B are damaged, the resulting deficit is not given by the sum of deficit A + deficit B (neither a linear weighting of the two deficits). This is the very same reason why the classically used VLSM methodology is intrinsically flawed: in this method, each voxel is considered independently from the status of any other voxel. Hence, because interactions between different voxels (or brain parcels) are neglected, VLSM bears a risk of mismapping the crucial areas (that should be spared by the resection) to non-crucial areas.[46] The only way to circumvent such limitations is to apply multivariate methods, which relies on machine learning algorithms trained on retrospectively collected datasets. However, the typical size of datasets in glioma surgery being around hundreds of patients, the dimensionality of the problem (that is the number of predictors used by the machine to produce a prediction) should be drastically reduced: instead of tens of thousands of voxels or thousands of parcels with binary values (inside or outside the resection), much of the information should be compressed in a handful of (continuous) parameters. This can be achieved through standard methods of data-driven dimensionality reduction, like a principal component analysis (see, for example, Zangrossi *et al.*[47]). However, model-based methods could be preferred, as they integrate our knowledge and understanding of the impact of the connectotomy on the brain functional and/or structural connectivity (see Yourganov *et al.*[48] for a somehow similar idea in the field of stroke patients). The most popular tools allow to quantify how the resection disconnected tractograms of healthy subjects (tract-based level) or to compute how the connectotomy changed metrics coming from graph theory applied to the global structural connectome (network-level). There are now many available toolboxes, each of a slightly different flavour, including but not limited to the Network Modification (NeMo) tool,[49] BCB-toolkit[50] and Lesion Quantification toolkit.[51] For example, application of the BCB-toolkit in the field of glioma patients allowed deterioration in set-shifting to be ascribed to damage of the left SLF II component,[22] in face-name retrieval to damage of the left inferior longitudinal fasciculus,[52] in verbal short-term memory to damage of the left arcuate fasciculus or right posterior cingulum[53] and in mentalizing to damage of the right SLF III and fronto-striatal tract.[54] On the other hand, other teams rather relied on postoperative (or changes of) functional connectivity to make correlations with cognitive outcome, the connectivity measures being obtained either from resting-state functional MRI (fMRI)[55-58] (see also Sighinolfi *et al.*[59] for a recent review) or from magnetoencephalography.[16,60] It is important to realize that none of these studies aimed to perform predictions of postoperative cognition

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Table 2 Review of the literature on emotion recognition abilities after glioma surgery

	Impaired baseline, *n* (%)	Impaired postoperatively, *n* (%)	Impaired follow-up, *n* (%)	Postoperative decline, *n* (%)	Follow-up decline, *n* (%)	Topographical correlates of deficits at follow-up	
						L/R	Lobar
Luherne-du Boullay *et al.*[33]	–	–	6/26 (23%)	–	–	None	Frontal > temporo-insular
Campanella *et al.*[34]	2/21 (9.5%)	8/19 (42%)	2/14 (14%)	11/19 (57%)	3/17 (17%)	None	–
Mattavelli *et al.*[32]	4/34 (12%)	13/34 (38%)	3/21 (14%)	–	–	None	–
Buunk *et al.*[35]	8/30 (27%)	–	5/26 (19%)	–	–	None	None

L = left; R = right.

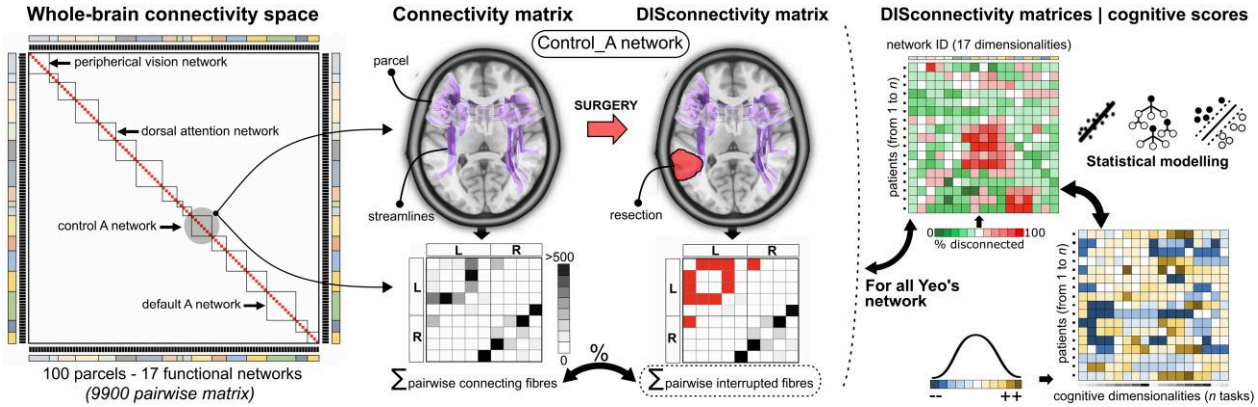


Figure 3 The DiscoNets approach. *Left*: The brain is modelled as a structural connectivity matrix of 1000 parcels × 1000 parcels. Parcels are ordered according to Yeo's brain parcellation in 17 resting-state networks. *Middle*: For each network, a within-network structural connectivity matrix is extracted, with N_{tot} the number of pairwise connecting fibres. Each resection topography has a footprint on each network, with N_{les} the number of pairwise interrupted fibres. The ratio N_{les}/N_{tot} gives a global measure of the impact of the resection on the within-network structural connectivity. *Right*: Repeating the same computation for each network, one can built an *n* lines by 17 columns disconnectivity table, with *n* being the total number of cases. Behavioural data are organized as an *n* lines by *x* columns cognitive table, with *x* being the total number of scores. Machine learning algorithms are trained to predict cognitive outcomes from the disconnectivity matrix. L = left; R = right.

from preoperative connectivity data combined with resection topography.

This motivated our group to leverage the formalism of machine learning by computing features based on both structural and functional connectivity data. To this end, we made the hypothesis that the level of structural damage to each of the (resting-state) functional connectivity networks parcellating the brain should provide the most informative features. It has indeed been demonstrated that lesion-mapping inference can be better modelled by considering networks (in the sense of functional connectivity) rather than parcels.[61,62] We thus developed a tool (DiscoNets) to compute how a set of brain networks (for example, the 17th-parcellation of Yeo's resting-state networks[63]) are damaged by a connectotomy. For each network, a first set of N_{tot} streamlines is defined by selecting in a healthy tractogram only those connecting any two nodes of the network. Then, among this set, a subset of N_{lesion} streamlines is defined by selecting only those passing through the lesion. The ratio N_{lesion}/N_{tot} gives a measure of the network damage (Fig. 3). This method successfully demonstrated the value of the damage to cognitive control B network (12th of Yeo) for predicting the long-term abilities in cognitive flexibility,[31] thus reconciling in the unitary concept of a network the diverging results reported above in the first part. Importantly, the same approach yielded similar results in the context of stroke patients.[64] It should also be mentioned that graph theory should provide more relevant measures of network damage: each network can be characterized by different metrics (see Mandal *et al.*,[65] Maas and Douw,[66] Hart *et al.*,[67] Samuel *et al.*[68] and Lang[69] for the application of graph theory to the network neuroscience of glioma), and the resection-induced change in these metrics could provide better predictors.

Finally, it should be acknowledged that the accuracy of the prediction is not yet high enough to be clinically reliable. In fact, we are not aware of any predictive tool of long-lasting cognitive deficits that is accurate enough to be of clinical interest. One solution would be certainly to increase as much as possible the number of cases in the training dataset. This will be further discussed later in this review. However, at some point, it is anticipated that the accuracy of the prediction should reach an asymptote, whatever the increase in the size of the training dataset. Indeed, the connectotomy is not the sole determinant of late cognitive outcome and two other sources of interindividual variability should be considered: structure-function phenotype and plasticity.

Preoperative structure-function phenotype

The cognitive and behavioural impact of the same resection topography may vary among patients due to inherent differences in the structural-functional connectome organization. In healthy

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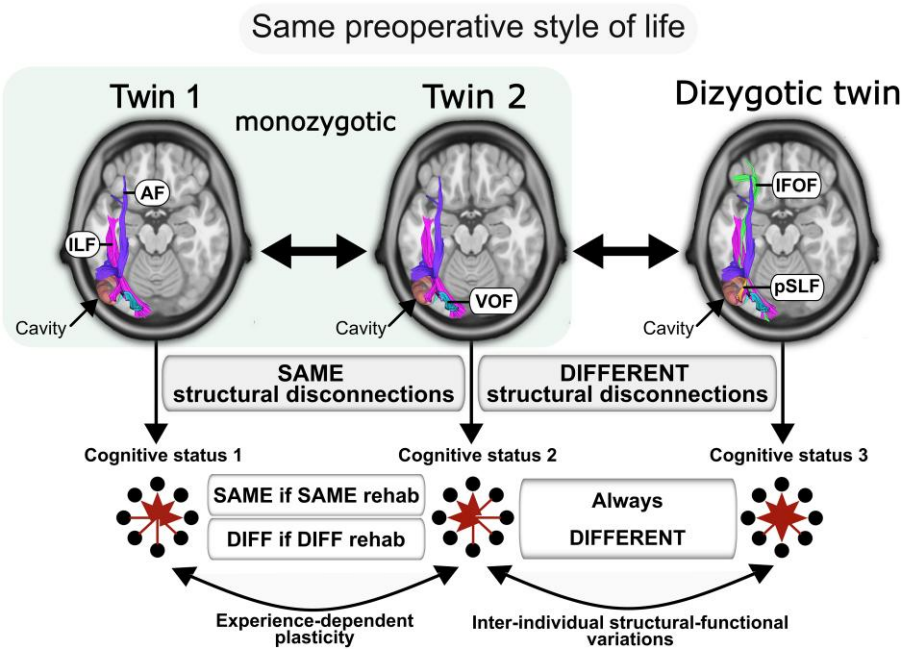


Figure 4 The three sources of variability in cognitive outcomes. In perfectly identical twins, with similar lifestyles and experiences before and after surgery, outcomes would be determined exclusively by the lesion topography. In perfect twins, with similar connectotomies and similar preoperative lifestyles, but undergoing different rehabilitation programmes, variability in outcomes would stem from experience-induced plasticity (*left*). In dizygotic twins, with similar lives before and after surgery, variability in outcomes would result from interindividual variations in structure-function phenotype (*right*). AF = arcuate fasciculus; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; rehab = rehabilitation; pSLF = posterior superior longitudinal fasciculus; VOF = vertical occipital fasciculus.

populations, it is indeed established that there is considerable variation in the structural brain architecture among individuals, and specific local features of this architecture have consistently been associated with between-individual variability in various cognitive abilities and personality traits, such as for example working memory, executive functions, intellectual abilities and impulsivity (see Kanai and Rees[70] and Genon *et al.*[71] for reviews). It is also increasingly believed that the more complex the function, the highest variability across individuals, and consequently, the greater the variability in the structures upon which it depends.[72] This structural-functional variability, which is heightened in glioma patients due to neuroplastic reshaping,[73] explains why dizygotic twins with the very same topography of resection (and preoperative tumour) would nonetheless show distinct connectotomies (Fig. 4), and consequently divergent patterns of deficits 'immediately after surgery', that is at a time the outcome cannot yet be influenced by a variation in neuromalleabilities (which would otherwise act as a confounding factor).

A well-known instance of structural-functional variability, particularly pertinent in the context of glioma surgery, is the well-established lateralization of verbal processing to the left hemisphere and visuo-spatial processing to the right hemisphere (as observed in 99% and 90% of, respectively, right-handed and left-handed individuals). It has been indeed reported that, in case of reversed lateralization (as observed in 1% and 10% of, respectively, right-handed and left-handed individuals), operating in the left hemisphere might induce long-lasting spatial neglect rather than the usually observed language deficits.[74] Similarly, resections in the right hemisphere may cause difficulties in retrieving common names and proper names,[52] such a deficit being typically observed following resection in the left hemisphere. While this left-right lateralization of verbal functions exemplifies an extreme case of interindividual variability in brain structural and functional architecture, such anatomical variability has also been extensively reported in stimulation mapping studies. It is observed not only for left-lateralized perisylvian language areas[75-77] but also for right cortical areas involved in mentalizing.[78] The introduction of intraoperative mapping of cognitive functions in awake surgery has been specifically designed to address the issue of between-patients variability in the neural implementation of functions. This surgical approach enables personalized mapping-based resection, thereby minimizing the risk of postoperative deficits.[79,80]

More directly related to the current topic, the issue of the variability in network topography of complex cognitive functions has been overlooked for a long time. While task-based fMRI has been widely used to preoperatively identify motor or language areas, it has been almost never applied to study higher-order cognitive networks, such as those involved in cognitive control network.[81,82] Therefore, its clinical utility in predicting a postoperative cognitive deficit when resecting an area showing blood-oxygen level dependent-activation during a complex cognitive task remains unknown, necessitating further investigations.

The development of automated pipelines for processing resting-state fMRI and the ease of acquiring this imaging modality in the standard care of patients with glioma have spurred its use for performing structural-functional associations. For example, working memory, as indexed by n-back performances, has been demonstrated to inversely correlate with the connectivity between the dorsolateral prefrontal cortex and the default mode network in the right hemisphere.[83] However, studies using resting-state neuroimaging in general has relied on population-based functional parcellations to derive resting-state functional networks and investigate structure-function relationships. This is a critical issue, as the topographical organization of networks differs from an

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interindividual standpoint, especially in glioma patients where tumours induce important network remodelling.[73]

It is thus only very recently that new methodological advances has allowed to determine networks parcellations at the individual level,[84-87] thus enabling the quantification of the interindividual variability in shape, size, and topography of such networks. Unfortunately, applying such advances to glioma patients is not straightforward due to the presence of the tumour. This is why, in glioma patients, individual functional connectivity matrices are usually derived from resting state sequences by mapping a pre-existing brain parcellation atlas onto patients' space. Moreover, the presence of a tumour (or surgical cavity) requires *ad hoc* methods to circumvent the fact that voxels within these regions do not behave like the rest of the brain.[88] Hopefully, current research[89] aiming to generalize to pathological brains the hierarchical Bayesian framework of Kong *et al.*[84] should enable to obtain in glioma patients individualized brain parcellation in resting state networks. These achievements are expected to have wide applications for the question at hand.

First, it will be interesting to compare such individualized parcellations with those in healthy subjects. How the gradual growth of the tumour already reshaped preoperatively brain networks should provide insights into the large-scale patterns of plasticity.

Second, the methodology of network disconnection mentioned above could be improved by relying no more on atlas-based knowledge of brain architecture (i.e. structural and functional connectivity from Human Connectome Project subjects) but rather on own patients' networks and tractograms. It must be indeed acknowledged that estimates of tract disconnection relying on population-based atlases are inherently limited when applied to glioma patients, due to the recognized potential for tracts to be displaced by a growing mass.[90] Relatedly, Silvestri *et al.*[91] highlighted disparities between atlas-derived and individual-based structural connectomes in glioma patients. The extent to which these individual adjustments might enhance prediction accuracy is yet to be determined.

Plasticity

Plasticity is the property of the brain by which neural states change their dynamics properties over multiple temporo-spatial scales in response to an ever-changing environment (physiological plasticity) or to an insult of its own integrity (post-lesional plasticity). Currently, the free energy theory[92] stands as the sole proposal in this field to explain these neuroplasticity properties, with the understanding that the governing laws are still to be discovered. There is ample evidence, coming from different kinds of pathologies (stroke,[93,94] epilepsy,[95] glioma,[73] etc.), that the cognitive changes observed over the course of these diseases correlate with changes in the brain dynamics across multiple scales, from synapse to structural and functional connectome. It is not our purpose to review here extensively what we know about plasticity in glioma surgery. We refer the reader to an excellent review that was recently published.[96] Our goal is rather to recycle recent advances in neuroscience for addressing the following challenge: can we determine preoperatively the extent of brain plasticity in a given patient? We propose to term 'neuromalleability' this measure of how much an individual brain is plastic. Neuromalleability could be incorporated as a predictor, where higher neuromalleability values are expected to correspond to better cognitive outcomes. The resulting improvement in prediction accuracy would allow to estimate the portion of the variance in cognitive outcomes that could be imputed to variance in neuromalleabilities. Importantly, it might be the case that, in addition to between-patient variability, within-patient variability should be considered, as neuromalleability may significantly differ from one network (e.g. motor) to another (e.g. cognitive control).

Following in the same spirit as Krishna *et al.*[97] (but who focused on language functions), we will thus attempt to provide a brief overview of the biological processes underpinning plasticity and from there, propose new avenues to estimate preoperatively the individual neuromalleabilities of glioma patients.

Experience-induced plasticity

Experience-induced plasticity has been extensively studied, particularly through the lens of synaptic Hebbian plasticity, and investigated using electrophysiological measures, especially in the model of hippocampal circuitry in rats.[98] This set-up has allowed to explore long-term potentiation (LTP): the greater the synchronization of firing between pre- and postsynaptic neurons, the more easily the presynaptic neuron can initiate activity in the postsynaptic neuron—the effect lasting up to 1 h.[98] At the macroscopic level, experience-induced plasticity would be defined as the brain's ability—after short but repeated interactions with the environment—to instantaneously alter synaptic strength in certain neural populations. This, in turn, induces changes in neural state dynamics, measurable through any method probing the functional connectome (Fig. 2). Importantly, these changes will last no more than 1 h: longer lasting effects would require activating the cell machinery, synthetizing new proteins and permanently reshaping the microstructure of the synapses (protein-synthesis mediated plasticity).

From a behavioural standpoint, experience-induced plasticity in the context of neurosurgery is initiated by rehabilitation programmes and other interactions with the environment: assuming two homozygote twins with similar preoperative lives and comparable connectotomies, any variability in their late outcomes, following different exposures to the environment in the postoperative period, can be solely attributed to experience-induced plasticity (Fig. 4). Indeed, the protein-synthesis mediated plasticity should be the same in two individuals sharing the very same DNA.

In general, irrespective of differences in their rehabilitation programmes and experiences, patients exhibit different varying potentials in experience-induced plasticity. This raises the question of how to estimate a patient's experience-induced neuromalleability at the time of surgery? In a recent study,[99] experience-induced plasticity was directly generated by a paired-pulsed transcranial magnetic stimulation protocol[100] (15 min, 0.1 Hz, 8 ms inter-pulse interval) over the ventral premotor cortex (vPMC) and the primary motor cortex (M1). This set-up has been well characterized for inducing LTP between vPMC and M1 during a grasping task, measured by the amplitude of motor evoked-potentials. The authors also demonstrated that this LTP is reflected in a change in fMRI of the functional connectivity between vPMC and M1 during the grasping task (see also Stampanoni Bassi *et al.*[101] for a recent review about the network-level impact of synaptic changes). Generalizing this protocol to well-chosen brains areas outside the motor system could provide a means for determining preoperatively experience-dependent neuromalleability of cognitive networks. This could be achieved by measuring the change in functional connectivity between two nodes of the network using fMRI in response to their paired-pulsed stimulation.

Protein-synthesis mediated plasticity

While a comprehensive mechanistic explanation of the underlying processes is still out of reach, there is no doubt that the transient

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changes in neuronal dynamics resulting from experience-induced plasticity will feedback to the genes, modifying their expression levels, hence reconfiguring the brain microstructure of the synapses and axons, consolidating such changes in the long term and ultimately modifying the macro-scale brain structural and functional connectivity. This process is called protein-synthesis mediated plasticity (Fig. 2). While we currently have no means of assessing this process on-line at the molecular and cellular levels in humans, we can observe their associated macroscopic changes, several weeks after the surgery. Proxies like the cortical grey matter volume (GMV) from a T1 MRI (voxel-based morphometry) permits to explore such changes. Preoperatively, increased GMV in glioma patients compared to neurotypical participants has been repeatedly observed contralaterally to the tumour. This phenomenon has been observed for various regions, including for the insula,[102,103] the temporal lobe,[104] the medial temporal lobe[105] and the frontal lobe.[106] As a rule, contralateral homotopic areas are thus supposed to play a key role. It is noteworthy however that the cellular and molecular underpinnings of GMV changes identified in studies employing morphometric analyses remain not fully understood. Hypotheses suggest the involvement of various factors, encompassing increased cell size or spine density, as well as the genesis of neural or glial cells. In a pathological context, such as gliomas, these changes could be mediated by a complex and multifaceted process. This process involves rapidly adjusting neuronal systems, such as synaptic changes, in combination with slow-evolving mechanisms like myelination, axonal remodelling or angiogenesis.[70,102,107] New recent advanced processing of diffusion-weighted sequences that estimates some features of brain microstructure[108] like axonal or dendritic density could provide a better means of quantifying the implementation of microstructural plasticity in glioma patients. In a near future, it would be essential to correlate these MRI microstructural changes with the new PET UCB-J imaging modality, allowing the probing of the synaptic density.[109,110]

This contralateral remodelling can also be assessed by longitudinal follow-up of task-based and resting-state fMRI. For example, supplementary motor area (SMA) syndrome (a transient akinesia after resection of the SMA) offers a unique opportunity to unveil such reorganization of functional connectivity. It has been repeatedly demonstrated by task-based fMRI that the contralateral SMA is taking over the missing activity of the resected SMA when moving limbs contralateral to the resection[111-113]. Resting-state fMRI allows better understanding of the changes in the sensorimotor (SM) network after right SMA resection,[114] with a strong increase in the interhemispheric connectivity between the right precentral and postcentral gyrus and the left SMA (and interestingly, a strong decrease of the functional connectivity between the right and left postcentral gyrus).[115]

However, it remains unclear which structural connections support these interhemispheric changes: heterotopic cortico-cortical fibres and crossed cortico-striatal fibres, all passing through the corpus callosum, were supposed to be the best candidate,[116-118] but a recent study observed a similar reorganization even in a patient with an agenesis of the corpus callosum.[119] Thus, the rebalance could be mediated by other inter-hemispheric tracts (like anterior and posterior commissure), connecting nodes outside of the SM networks, followed by an intra-hemispheric reweighting between non-SM and SM nodes.

In summary, protein-synthesis mediated plasticity is the support of long-lasting modifications of the synapse microstructure, hence of its function. Unfortunately, as for experience-induced plasticity, we cannot currently measure preoperatively the efficiency of these complex mechanisms in a patient-specific manner. However, recent works in brain glucose metabolism have opened up a new avenue for the study of protein-synthesis mediated plasticity. More specifically, this line of research, followed by Marcus Raichle's group, has provided strong evidence for the idea that aerobic glycolysis (AG) is a good proxy measure of protein-synthesis mediated synaptic plasticity. This group indeed demonstrated by PET imaging of cerebral glucose metabolism that AG is heterogenous in the brain and predominates in the default mode and cognitive control networks,[120] that its contribution to total glucose metabolism strongly decreases with age,[121] and even more in males,[122] and that long lasting increase of AG in Broca's area was observed after a motor adaptation learning task.[123] Hence, we posit that the intensity of cerebral AG, both at rest and during/after a task, might be an important predictor of cognitive recovery after a glioma resection.

The future

In this final section, we envision which paths could be followed to improve the precision of prediction.

Big data: an illusion?

It has become common place to say that big data and artificial intelligence hold the promise to reach, in the near future, unprecedented accuracy in medical diagnosis and prognosis. Nonetheless, such a dream will remain an empty promise if data cannot be collected on a large scale. In the case of low-grade glioma, given their rarity, an international multicentric initiative should be launched, following the example of the ongoing revolution of brain imaging genomics in psychiatry.[124] First, long-term cognitive outcomes should be measured systematically by implementing tasks on a digital tablet, to facilitate the fusion of datasets. The complexity of this fusion arises from the variations in tasks used for evaluations across centres, even within those with expertise in awake surgery of glioma.[125] While not a strict requirement due to the emerging concept of cognitive dimensions (see later), it is ideal for the battery of tasks to be standardized across different centres. Second, apart from the information stored in the pre- and postoperative MRI regarding the topography of the tumour and its resection, predictors should include parameters evaluating individual structure-function phenotype and plasticity. For the former, resting-state and task-based fMRI combined with tractography currently constitute state-of-the-art investigations. Regarding plasticity, as it cannot easily be measured directly, only proxies can be used, including but not limited to age, baseline performances, socio-professional status, socio-cultural levels and genomics.[126] Tumour characteristics, like volume and kinetics, should also be considered, as plasticity is supposed to decrease with increasing tumour growth rates. The feasibility of such an ambitious project is not warranted and would require a significant amount of fundings, but some initiatives have already started to flourish.[127]

Deciphering plasticity at the mechanistic level

We can assume that plasticity, together with lesion topography, are the greatest suppliers of variability in the outcome. Hence, an alternative philosophy, opposite but complementary to the big data approach, would be to leverage multimodal data from different types of MRI sequences obtained in a single patient to build an individualized mechanistic model of plasticity. Indeed, whilst an increasing

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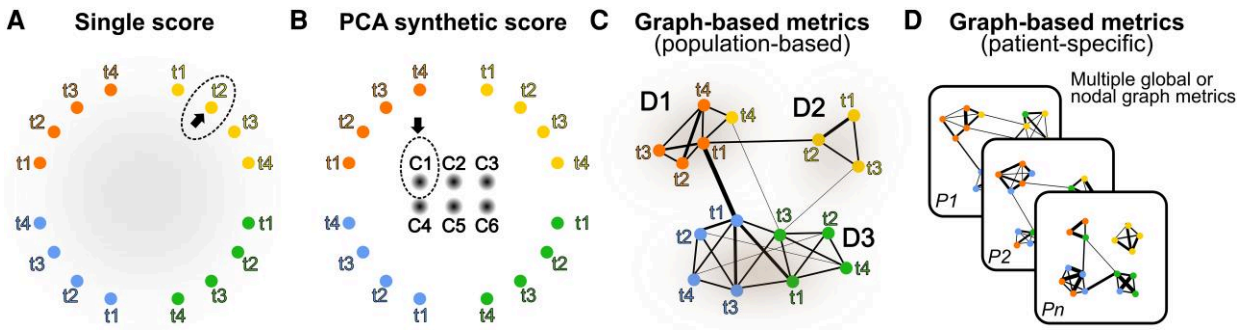


Figure 5 Graph-based approach of cognitive scores. (**A**) All scores can be used separately from each other. Colours represent different cognitive domains. However, a typical cognitive evaluation comprises numerous scores, and each score alone may be noisy and not a pure measure of a single function. (**B**) Principal component analysis (PCA) can reduce the number of variables, with each component (synthetic score) providing a more robust measure of a function. (**C**) Population-based graph-based psychometrics. From a large set of scores, a population-level graph can be built where each edge represents the between-task correlation. Graph metrics allows the description of both segregative and integrative aspects of cognition. (**D**) Subject-specific graph-based psychometrics. In this approach, the construction of the graph is tailored to individual subjects. For each subject, edges within the graph are calculated based on the performance similarity between pairs of cognitive tasks. This means that the graph's edges represent the degree of similarity in how a subject performs across different cognitive tasks. Once the subject-specific graph is constructed, various topological graph metrics can be applied to perform structure-functions associations or make predictions. These metrics provide quantitative measures of the network's topological properties.

number of studies have attempted to clarify, at the population level, the neuroplasticity strategies deployed by the brain to compensate for the tumour, the mechanistic principles governing these compensatory modulations remain unknown. Current knowledge remains very descriptive, and insufficient efforts have been made to propose macroscale, neurocomputational models of the triple interaction brain-tumour/resection-cognition.

From this perspective, we could take advantage of the recent efforts made to model the effect of a connectotomy on the functional connectivity of a virtual brain.[128] We posit that implementing a synaptic plasticity of variable strength in the model should allow a better fit between the simulations and the observed data. This strength of synaptic plasticity could be tuned according to individual neuromalleabilities, as estimated through the proxy of AG measured by PET imaging.

Are single neuropsychological scores sufficient to predict cognitive outcomes with a good level of accuracy?

Most often, patient performances obtained on a single task are used as a proxy measure of a given function. For example, the behavioural index derived from the Trail Making Test is commonly assumed to reflect set-shifting abilities and, in clinical studies, no other tasks are generally employed to competitively assess the same process. This approach is questionable, given that behavioural tasks are generally multifaceted and may engage other cognitive processes than that under scrutiny. For instance, a simple picture naming task engages processes involved in object recognition beyond lexical retrieval—the function thought to be targeted by the task. This becomes particularly problematic when the goal is to predict functional outcomes after surgery. As clinicians, our objective is to evaluate the recovery of a specific function, not merely the improvement on performance in a particular task. This problem is further complicated by the fact that many tasks commonly used in standard neuropsychological practice are based on outdated theoretical frameworks, stemming from a time when our understanding of structure-function relationships was much less developed, thereby introducing challenges in theoretical validity. Moreover, the majority of these tasks involve 'pen and paper,' leading to potentially noisy measures due to operator-dependent testing conditions. Lastly, it is important to acknowledge that tasks assessing complex cognitions and behaviours generally lack ecological validity. All of these limitations are likely to hinder the reliability, validity and robustness of anatomo-clinical predictions.

To address this methodological challenge and enhance the predictive accuracy of postoperative cognitive outcomes, one potential strategy is to use factorial designs, in particular principal component analysis, which is a variance-based data-driven approach allowing the multidimensional features within a behavioural dataset to be revealed.[129] Using this approach, orthogonal behavioural principal components are extracted from a large set of cognitive performances and serve as measurements of interest (one component is thought to approximate one function) for brain-function correlations. This approach likely yields more reliable anatomo-functional correlations, especially when the targeted processes are assessed by different tasks, and indeed considerably diminishes cognitive dimensionalities. For example, six cognitive factors may be extracted from 16 behavioural tasks (Fig. 5), facilitating interpretations.

Other interesting approaches are currently being developed in the field of network psychometrics. In both cases described above, the focus is only given to one aspect of cognitive architecture, i.e. its segregative/specialized nature (in that each function/task/component is considered independently). In other words, the interrelationships that may exist between cognitive processes are completely ignored (i.e. the integrative feature of cognition). Here the key idea is to model task performances in the form of a network by relying on the mathematical theory of graphs.[130,131] This is the same approach as that used to infer properties of neural networks in fundamental neuroscience and which is increasingly applied in several subfields of psychology (e.g. social psychology, psychometrics, neuropsychology). Graph theory algorithms make available a range of network metrics that represent different topographical properties of the graph, i.e. the network (e.g. degree, distance or connectivity measures among others). In the context of glioma patients, to the best of our knowledge, network psychometrics has been uniquely employed to explore the interrelationships of symptoms. Specifically, psychological networks based on questionnaires have recently been used to model the connections

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among depression, subjective cognitive complaints, brain-tumour related symptoms and quality of life.[132] Given the widespread application of graph theory algorithms to analyse structural and functional neural data,[133] and their increasing use in the field of cognition,[131] there are opportunities to construct graph-based multilayer networks.[134] These can be derived from various modality inputs, including fMRI, diffusion MRI and comprehensive measures of cognition. Beyond leading to a superior validity of structure-function relationships in general, such multilayer models may provide better insights into how gliomas affect the structural, functional and cognitive architecture in an interrelated manner.

However, important challenges persist in defining cognitive features as particular graph metrics. The construction of psychological/cognitive networks typically relies on population-based covariance in performances, where network edges are established through between-task correlations. This modelling approach thus remains rather descriptive and inoperable at the individual level. Innovative methods are needed to construct individual, graph-based cognitive networks, enabling the extraction of individual metrics for personalized prediction. To the best of our knowledge, only one attempt in this direction has recently been made in healthy participants, where between-task performance interrelationships (i.e. edges) were estimated based on performance similarity.[135] However, the accuracy of such modelling is inherently constrained by the accuracy of task normalization, which is a prevalent issue in neuropsychology.

In summary, using a non-reductionist approach to model cognition (i.e. task performances) at the individual level may assist in extracting valuable measurements of cognitive functioning, ultimately improving the prediction of postoperative outcomes in the context of glioma surgery. The accuracy of such modelling is likely to involve relying on a highly standardized and comprehensive battery of tasks that partially overlap in terms of the processes they assess (across-task validation). Additionally, it should extend beyond standard clinical tasks to incorporate more complex processes such as multi-tasking and decision-making, among others. These novel tasks should be designed to enhance ecological validity, better capturing patients' difficulties in daily life and contributing to a more comprehensive assessment of their overall quality of life. Lastly, it would be important to incorporate questionnaire-based subjective measures in these cognitive networks to assess the impact of factors such as fatigue or mood on cognitive functioning.

Conclusion

Surgery for glioma offers a unique opportunity to further elucidate the respective roles of connectotomy, structure-function phenotype and plasticity in the prediction of cognitive outcomes. The general framework is to combine data- and model-based methods of dimensionality reduction to feed machine learning algorithms with large datasets,[45] and the hope is to reach prediction accuracies high enough to help the neurosurgeon in their surgical planning. It should also be kept in mind that functional aspects beyond cognitive performances should not be overlooked: the structure-function reshaping comes with a price to pay in terms of reaction time and fatigability. While patients usually do not complain about their reduced cognitive speed, fatigability hampers their quality of life[136] and more efforts should be devoted to better measure fatigability[137-139] and understand its neural basis in order to find new therapeutic avenues.

More generally, mapping a brain lesion to a pattern of cognitive deficits is, among many applications of modern neuroscience to clinical practice, one of the most important and challenging. Most concepts that have been discussed here could be also transposed to other pathological domains with focal lesions such as stroke injuries. However, it should be kept in mind that each pathology has its own specificities and that the pathological process in itself is an irreducible predictor (see, for example, the difference between slow-growing gliomas and acute strokes[140] and computational modelling of it[141]). This being said, machine learning methods could offer new avenues, like transfer learning, to explore how predictions could be further refined through trans-nosological studies.

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Competing interests

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