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What do we know about intratumoral functional activity: a scoping review of imaging and intra-surgery results

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A B S T R A C T

Intratumoral functional tissue represent a challenge in neurosurgery, as its resection may induce a permanent postoperative deficit. Only little is said in literature about this pattern. Currently this issue is receiving increased attention and in the last few years, the number of reports on intratumor functionality has increased. Aim of the current review was to provide a comprehensive overview of intratumoral area functionality patterns and of how much frequently this pattern is reported. PRISMA guidelines were followed. We identified 107 papers, but only 24 articles on 1220 patients were included for having reported intratumoral activation data. Within this framework, we aimed to shed light on some issues, including whether i) it is expressed only as fMRI activation within the mass, or whether it impacts on distant areas via functional connectivity, ii) it is found in slow growing tumors such as low grade glioma or also for fast infiltrative processes such as for high grade glioma, and iii) inhomogeneity of the tumor structure and morphological appearance or the tumor histology are key factors determining intratumoral area functionality. Key methods suitable for detecting intratumour function included MEG (in 7 studies), resting-state fMRI and task-active fMRI (in 8 studies) and intra-surgery direct cortical stimulation (in 8 studies). The type of patients were patients with astrocytoma (321 cases) and oligodendroglioma (255 cases) with tumor grade II (252 cases) and isocitrate dehydrogenase (IDH) mutation. Their mean tumor volume was 53.11 ± 19.23, and the affected hemisphere was mainly the left one (895 cases); lesion site most frequently involved the frontal cortex (435 cases). We discussed the clinical implications of these aspects, as a functional intratumoral area has a high impact on both planning and outcome, and we addressed the role of intra-surgery cognitive monitoring that should encompass a wide variety of functions.

1. Background and definitions

A brain glioma, the most common primary brain tumors, invades cortical areas and the white matter underneath and can lead to cognitive and behavioural deficits involving cognitive abilities such as language and memory (Yuan et al., 2019). For these patients, surgical intervention is necessary to avoid disease progression and/or mitigate the potential for morbidity. The primary goal in the case of surgery for tumor removal is to obtain the maximum possible resection (Sanai & Berger, 2008; Duffau, 2012) while preserving the functionality of the neural networks (Young et al., 2020; Ius et al., 2012). To achieve this goal, surgical planning can be accompanied by presurgery fMRI. fMRI allows obtaining a functional map of the brain tissue involved in the tumor and the surrounding areas. Intratumor function is defined as residual functional activity that can sometimes persist within the tumour. It can manifest itself in several ways such as an fMRI activation detected within the pathological brain tissue, or as a cluster of voxels activating in a synchronized way with other clusters localized in distant areas, and more general it is defined as motor, sensory, or language functioning related tissue located within a grossly obvious tumor or the surrounding infiltrated brain.

In detail, fMRI maps output type can be threefold (conditions are not exclusive, a combination of them is possible): i) if the brain functional tissue is damaged and the patient has cognitive deficit, fMRI maps may show a poorly activated fMRI network, especially in the area involved by the lesion; ii) if the cognitive functions related to the tumor area are preserved despite a damage in the functional area, local and remote functional adaptive reorganization can be triggered allowing compensatory mechanisms. fMRI shows activations migrated in perilesional or contralateral area with respect to the glioma. In this case, different plasticity patterns according to whether Low Grade Glioma (LGG) or High Grade Glioma (HGG) occur (Yuan et al., 2019; van Dellen et al., 2012; Cargnelutti et al., 2020). iii) The third pattern consists of residual functional activity can sometimes persist within the tumour (Fig. 1).

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This effect has been reported in some preoperative functional imaging (e.g., Ganslandt et al., 2004; Schiffbauer et al., 2001) and intrasurgical electrical stimulation mapping (e.g., Ojemann et al., 1996) studies. In this case, the cognitive functions may be spared too, because are still supported by the functional area within the lesion. This pattern challenges the traditional view of a tumoral area completely silent from a cognitive point of view. For example, Ojemann et al. (1996) demonstrated that brain regions invaded by tumours can retain functional capacities, thus contradicting the traditional belief that tumour-infiltrated brain tissue is non-functional. Ojemann et al. (1996) found "essential cortex" within abnormal-appearing brain, arguing that removal of intrinsic brain tumors may cause functional injury. Similarly, Skirboll et al. (1996) using intraoperative Direct electrical stimulation (DES) of motor-, sensory-, language-related cortical and subcortical areas found functional tissue within infiltrative glioma in 28 patients. Rivera-Rivera et al. (2017) found that 5 patients had a glioma involving eloquent areas within the tumor as identified by DES. LeRoux et al. (1991) reported that removal of tumors involving the nondominant face motor cortex may be achieved using DES; concerning the dominant hemisphere, the removal of the face motor cortex is not recommended. Lastly, Black and Ronner (1987) showed that DES-induced naming difficulties occurred when stimulation was applied within the tumor margins so that the resection avoided this region.

More recent evidence of functional tumour-infiltrated brain tissue come from functional connectivity studies. Cui et al. (2022) demonstrated that a significant portion of tumor mass (33.2%) can be functionally active, especially for low grade glioma. The authors also highlighted the presence of functional connectivity between these tumor portions and other non-cancerous areas. The demonstration that intratumoral area is still functional does not exclusively apply to low grade glioma. Daniel et al. (2021) using resting State-fMRI identified functionally connected voxels within the tumor mass, thus modifying the idea that high grade glioma imply a fully functional silent tissue. Confirmation is found in Schiffbauer et al. (2001)'s reporting functional connectivity between the tumour areas and surrounding areas irrespective of tumour grade (in 18% Grade II, 17% in Grade III and 8% Grade III tumors). Interestingly, Schiffbauer et al. (2001) showed that while low grade glioma show functional connectivity within the tumor mass, high grade glioma show intratumour functional connectivity at the margins of the mass. Bartolomei et al. (2006) using magnetoencephalography found an alteration (not an absence) of functional connectivity in patients (compared to control subjects) within the tumor mass. Demonstration that intratumour area can still retain a functional role may come from preoperative diffusion tensor imaging data. For

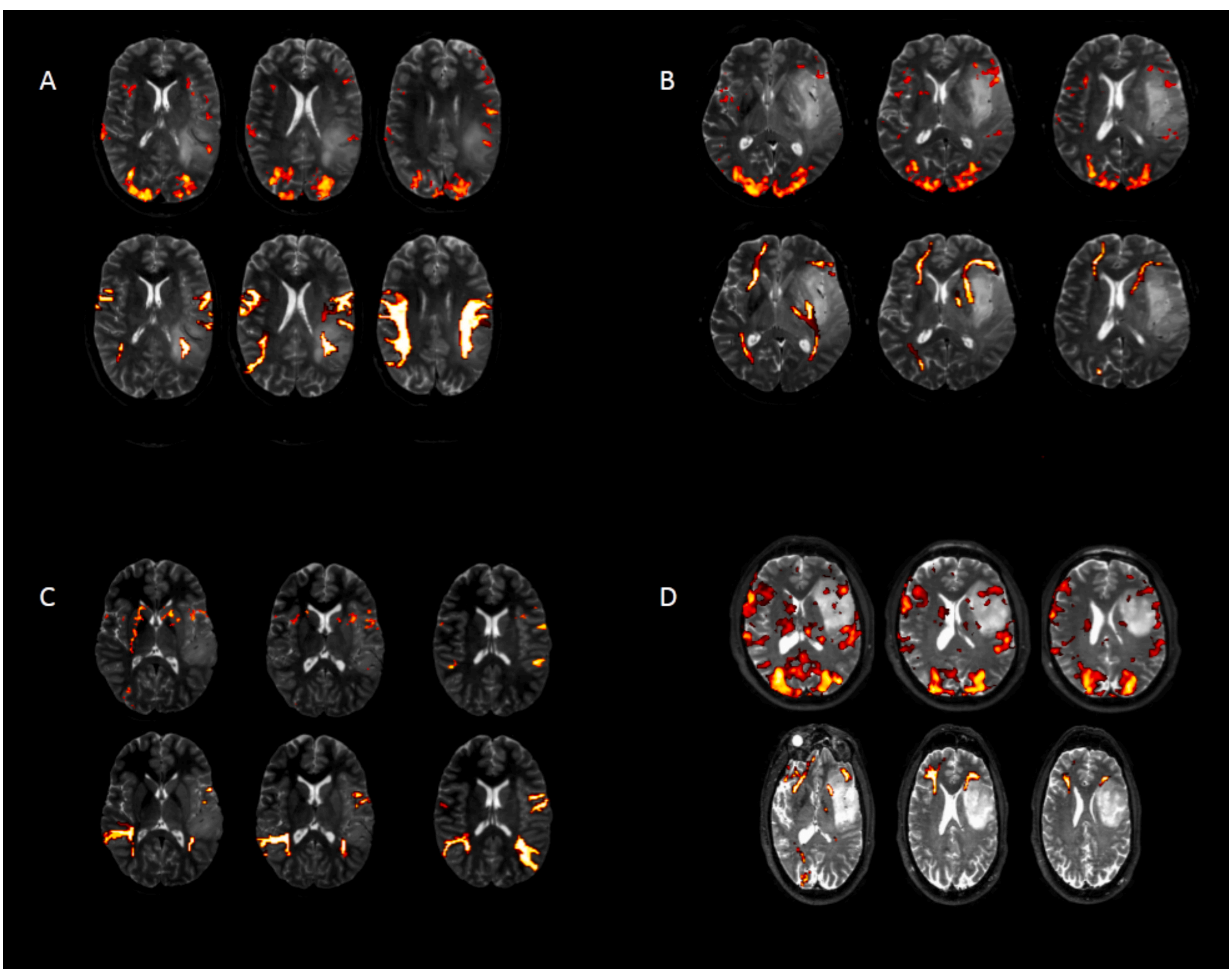

Fig. 1. Functional imaging examination showing residual functional activity persisting within the tumour in four patients with LGG in different areas (A in the left inferior parietal cortex; B in the premotor/inferior frontal gyrus; C in the fronto parietal cortex; D in the inferior frontal gyrus) from the Neurosurgery Unit, Head-Neck and NeuroSciences Department University Hospital of Udine case series. In each of the cases, the fMRI activation is superimposed on axial slices of the patient's T2-weighted MRI image (first row of A–D) and for completeness and confirmation of the activation sites, the arcuate fasciculus is superimposed on axial slices of the patient's T2-weighted MRI image (second row of A–D).

example, Mato et al. (2021) using preoperative Diffuse tensor imaging (DTI), tracked functional motor- and language-related tracts within the tumor mass. Bello et al. (2008) reported that in low-grade gliomas, fibers were frequently located inside the tumor mass.

To sum up, intratumor function is a rare pattern; we aimed at reviewing the literature and reporting on the studies who addressed this issue.

2. Relevant research questions regarding intratumour activity

The data reported above are clinically interesting; however, how much frequently this pattern occur is not reported. Furthermore, some studies warned on the interpretation of findings from fMRI studies, highlighting that in some areas a lack of fMRI signal in the tumour surroundings cannot exclude residual activity in these areas, which could be masked by tumor-induced neurovascular uncoupling (e.g., Cho et al., 2018; Murata et al., 2004; Ulmer et al., 2003, 2004). Neurovascular uncoupling indeed can show up as an altered or absent BOLD signal in the area in and around the tumor, or it can result in an activation showing up in an area where in fact this is not, and this happens because abnormal blood flow patterns influence fMRI signal (Ulmer et al., 2003, 2004). Another alternative issue is fMRI false positives, meaning that an activation is detected where this is not actually happening. This is a problem because it can induce incorrect surgical planning or surgery strategies. In these cases only the intra-operative confirmation or disconfirmation may help the surgeon to set the extent of resection and the resection margins. More studies are needed in order to understand neurovascular uncoupling and to control false fMRI positives in the context of brain tumors. To this end, we performed a literature revision, reporting how many publications / number of patients describing a within the tumour function are found. We then summarized the operational definitions of intratumor function emerged in the selected studies.

A second issue involves the local-vs-global effect of intratumor function. It is not clear whether a functional infiltrated tissue is expressed only within the mass, or whether the functional infiltrated tissue impacts on distant areas via functional connectivity. We addressed which are the techniques and methodological approached used for detecting intratumor function, as well as the cognitive aspects represented in the functional intratumor area. This issue has some implication also from a neuropsychological point of view, as the latter condition would suggest that the test used to monitor the patients' cognitive functions intra-surgery should encompass a wide variety of functions.

Third, from the data above reported it emerged that intratumour function is found in slow growing tumours such as low-grade glioma or it can sometimes be found also for fast infiltrative processes such as for high grade glioma. We summarized the most frequently reported tumor type and grade as well as location and hemisphere for which an intratumor function emerged.

A further question involves the neurophysiological mechanisms behind this pattern, namely whether it is related to the inhomogeneity of the structure and morphological appearance or to the tumour histology, and what do the studies argue about this issue.

Furthermore, we aim at summarizing the clinical implications of knowing that the tumour-infiltrated brain tissue is functional. Indeed knowing whether the intratumoral area is still functional has a high impact on surgical strategy and on the functional outcome. We addressed how finding that the tumor area is functional, impacts the extent of resection and the overall survival. On one end it is reported that intratumoral functional connectivity varies among patients and it can have a prognostic factor, becoming an important measure for neurosurgeons, oncologists and the patient himself. Thus, connective tissue metrics indicating a good prognosis may lead to a more invasive surgical choice to avoid a recurrence (Daniel et al., 2021). On the other hand, an intratumoral functional activity wold imply a lower extent of resection for obvious reasons. Based on these research clinical questions the aim of this paper is to compile the works published to date on intratumour functionality.

3. Methods

3.1. Criteria for paper selection

We carried out a literature search to select papers addressing functional activation, functional connectivity, functional mapping and intratumoral function associated with tumor growth and/or tumor surgery in patients with glioma. Preferred Reporting Items for Systematic Reviews and Metanalyses (PRISMA) guidelines were followed for the systematic review (Moher et al., 2009; Page et al., 2021). A systematic search of the PubMed electronic database was conducted by cross-matching the following keywords: Intratumoral function* AND (Magnetic Resonance Imaging OR Image Enhancement OR Image Processing, Computer-Assisted OR Magnetic Resonance Imaging OR Magnetoencephalography OR Preoperative Care Brain Mapping OR Mental Processes OR Functional Neuroimaging) AND (pathology OR Brain Neoplasms / pathology OR Glioblastoma / pathology OR Glioma / pathology OR Neoplasm Invasiveness / pathology OR Brain Neoplasms). We selected studies based on the following inclusion criteria: i) assessment of adult patients (age $>$ 18 yrs); ii) assessment of patients with a diagnosis of brain tumor; iii) assessment of intratumoral activity through neuroimaging (magnetic resonance imaging – MRI – and associated techniques) electrophysiological (magnetoencephalography – MEG, electroencephalography – EEG), or brain stimulation techniques (direct electrical stimulation with intraoperative mapping – DCS); iv) publication date before and inclusive of June 15, 2024. We excluded studies that included paediatric patients. After duplicate removal, two researchers (BT and IG) independently reviewed titles and abstracts to identify articles of interest. Disagreement was resolved with a discussion that involved a third researcher (MM).

The PRISMA flow-chart represents our paper selection (Moher et al., 2009, see Fig. 2). of the selected papers we calculated: i) the total number of patients included; ii) the site and lateralization of the lesions; iii) the histology and tumor grade and size; iv) the technique used; v) the task assessed; vi) the extent of resection and overall survival.

3.2. Quality assessment

Study quality was assessed through the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Whiting et al., 2011). Key considerations included patient selection, testing, standard reference and time sequence and completeness of the diagnostic assessment. For each a judgments on risk of bias was done by two reviewers (B.T. and I.G. who independently conducted assessments) and discrepancies were solved through discussion with third reviewer (T.I.).

Risk-of-bias plot was generated by using robvis app (McGuinness and Higgins, 2020).

4. Results

4.1. Quality assessment

Fig. 3 shows quality assessment performed by using QUADAS-2 for the selected studies.

According to the QUADAS-2, the overall risk of bias was high in 1 study and low (or some concerns) in the remaining.

In the patient selection domain, 5/24 studies had a low risk of bias and 18/24 had some concerns, while 1/24 had a high risk of bias due to the inclusion of only two cases with an undefined and unrepresentative selection. The main problem in studies labelled with "some concerns" was

Not clearly consecutive selection or selection criteria not clearly described.

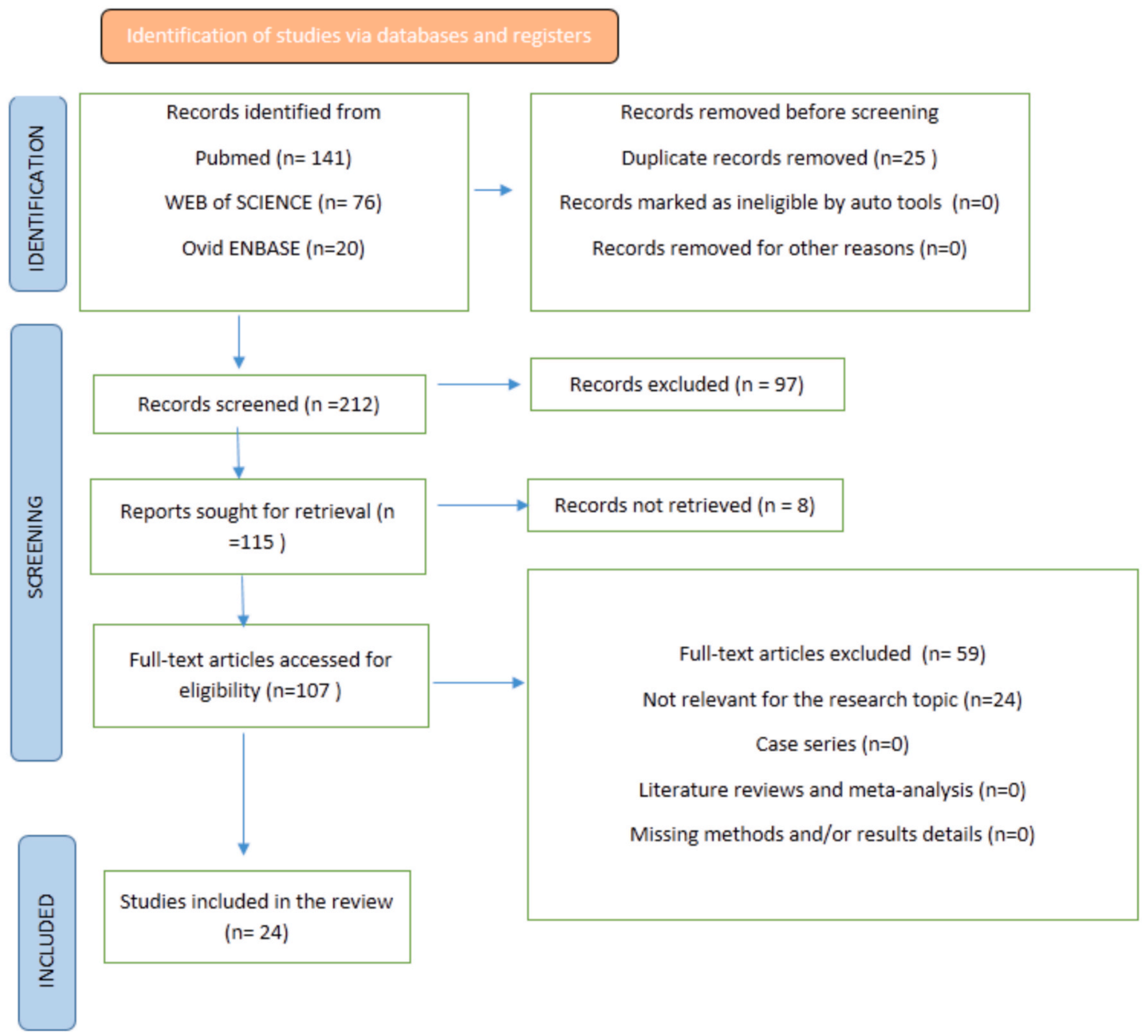

Fig. 2. PRISMA flow diagram of the systematic review (Page et al., 2021).

In the index test domain, 14/24 studies had a low risk of bias and 9/24 had some concerns, mainly due to lack of details on blinding and standardization.

In the reference standard domain, 4/24 studies had a low risk of bias, 5/24 had some concerns, mainly due to the use of established but not uniformly detailed methods or to the lack of a single, uniform gold standard. 15/24 resulted not applicable, mainly due group-control comparisons without gold standard.

In the flow and timing domain, no concerns about the risk of bias were noted in 19/24 studies. The remaining had some concerns, mainly due to a lack of details on exclusions and timing.

Regarding applicability, one study scored a limited applicability in the patient selection domain due to having included two cases only; the remaining had a high applicability.

In the index test domain, all studies had a high applicability.

In the reference standard domain, 13/24 studies had some concern regarding applicability, respectively due to the lack of a single, uniform gold standard.

In the flow and timing domain, all studies had a high applicability.

4.2. Evidence of the intratumoural activity

The intratumoral activity is reported in 24 of the scrutinized publication, confirming thus that is a rarely reported phenomenon (see Supplementary Table S1 for details). The main results of the selected studies are summarized in Table 1. In total, the 24 studies reviewed included 1220 patients, both newly diagnosed and relapsed patients. We found that intratumoral activity can be expressed in the following different operational definitions (for details see Table 1): i) as a degree of functional connectivity, which is altered, but still present in tumor-affected brain region (Bartolomei et al., 2006) or even within tumor boundaries (Daniel et al., 2021); ii) as a significant Blood Oxygenation Level Dependent (BOLD) synchronization between tumor and distant brain regions (Sprugnoli et al., 2022); iii) as a functional activity within or at the margins of brain tumors (Schiffbauer et al., 2001) or in the tumoral mass (Cui et al., 2022); the fMRI tumor signal intensity is different compared with the surrounding brain regions (Feldman et al., 2009); nonetheless the signal indicates preserved neural circuits within the infiltrating tumor (Mandal et al., 2024); iv) as a functional interaction between different microstructural tumour sub-regions and healthy brain networks (Aznarez-Sanado et al., 2024).; v) as functional sites, found positive at Direct cortical stimulation (Skirboll et al., 1996), suggesting that even though the brain tissue may appear altered, it can still remain functional (Ojemann et al., 1996); the identification of positive sites within the tumor correlate with the identification of intratumoral language and motor white matter tracts (Mato et al., 2021) and this result caused a reduced EOR. The positive cortical and subcortical direct cortical stimulation sites may retain functional

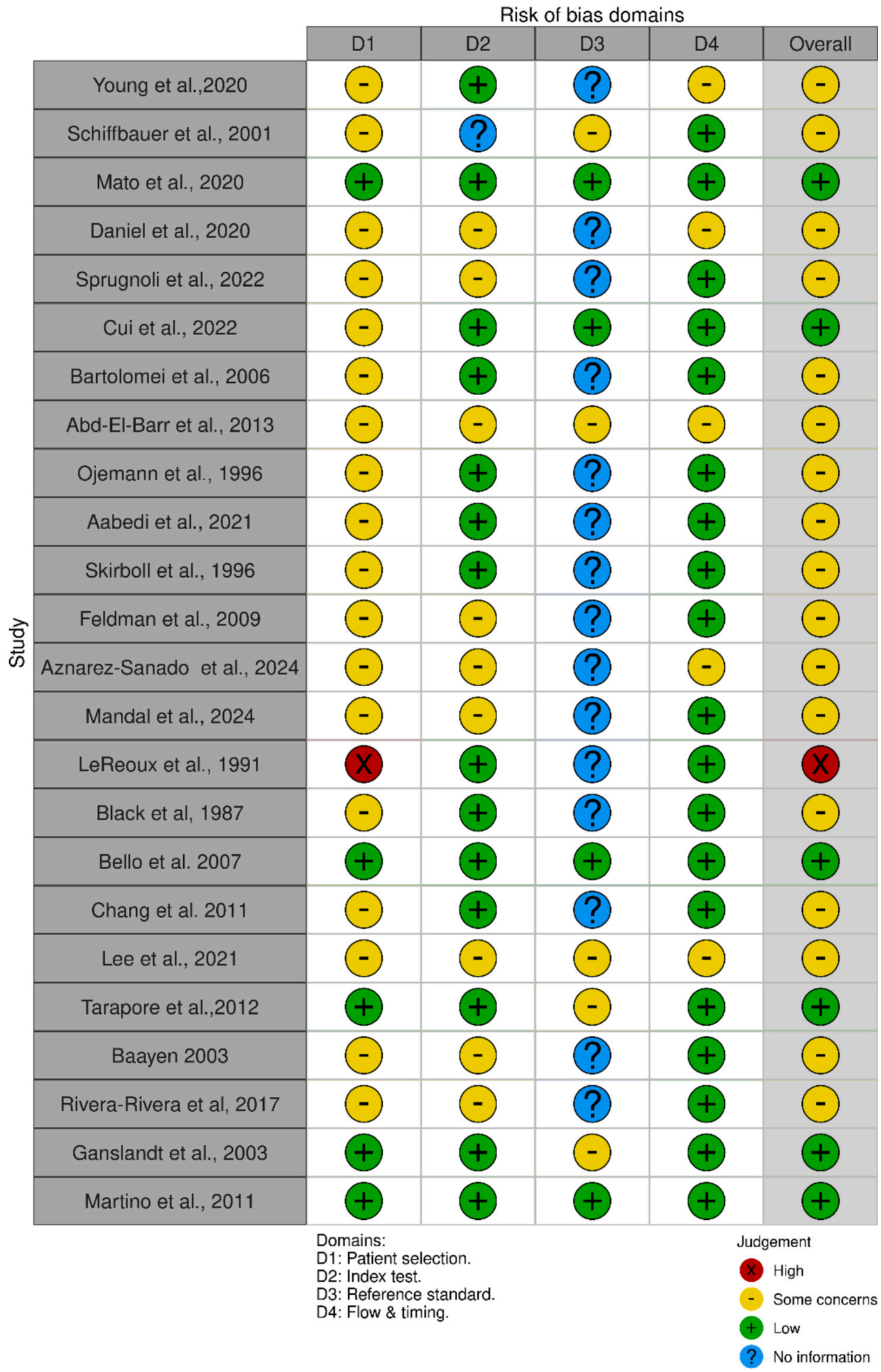

Fig. 3. Quality assessment of individual studies according to QUADAS-2.

connectivity to several brain areas (Young et al., 2020). Overall, it emerges that this variability in defining intratumoural function depends on the methodological technique. We next summarize the methods used by the different studies to detect intratumoural functional activity.

4.3. *Techniques used for measuring intratumoural functionality*

Techniques belong to pre-surgery methods and intra-surgery methods. In detail, key methods suitable for detecting intratumoural function include MEG (in 7 studies), resting-state fMRI and task-active fMRI (in 8 studies) and intra-surgery direct cortical stimulation (in 8 studies), DTI (in 2 studies) and subdural electrocorticography (in 3 studies) (see Fig. 4A), each offering unique insight into intratumoural functionality.

As to pre-surgery mapping methods, MEG and fMRI were the most used methods. For example, Baayen et al. (2003) reported that in eight cases low frequency magnetic activity was also localized within the tumor. Presence of this signal within the tumor might be an important warning signal for the neurosurgeon that the tumor area comprises functional brain tissue. As to fMRI, most of the studies used both fMRI

Table 1
Operational definition of intratumoural activation of the selected studies.

Study	Definition
Young et al.,2020	Intratumoral areas in which functional networks and neoplastic cells are intermixed
Schiffbauer et al., 2001	There is functionally relevant cortex contained within the tumor itself
Mato et al., 2021	Eloquent white matter tracts within the tumor
Daniel et al., 2021	Neurovascular units responsible for functional connectivity (FC) may exist within gross tumor boundaries
Sprugnoli et al., 2022	Gliomas demonstrate synchronized neurovascular activity with the rest of the brain
Cui et al., 2022	Brain function may be preserved within brain tumors.
Bartolomei et al., 2006	Functional neuronal tissue can sometimes be demonstrated in the midst of tumor tissue
Abd-El-Barr et al., 2013	Persistent functionality within tumors
Ojemann et al., 1996	Brain that appears to be abnormal may remain functional, thus precluding safe tumor resection.
Aabedi et al., 2021	Glioma-infiltrated cortex can meaningfully participate in neural computations
Skirboll et al., 1996	Functioning motor, sensory, or language tissue can be located within a grossly obvious tumor or the surrounding infiltrated brain
Feldman et al., 2009	The BOLD signals can be taken from selected points within the tumor
Aznarez-Sanado et al., 2024	Tumour microstructure has a role in the functional interaction between the tumour and the rest of the brain
Mandal et al., 2024	Cortical tissue infiltrated by diffuse gliomas participates in large-scale cognitive circuits
LeRoux et al., 1991	The tumor is present within or adjacent to eloquent brain regions, such as the Rolandic and speech cortex
Black and Ronner, 1987	positive stimulation effects within the tumor margins
Bello et al., 2008	Functional brain tissue surrounding or involved by the tumor
Chang et al. 2011	Functional brain areas directly involved with tumor infiltration
Lee et al., 2020	HFC network sites within low- and high-grade gliomas.
Tarapore et al.,2012	Functional tissue surrounding tumors in *peri*-eloquent and eloquent areas.
Baayen et al., 2003	Tumor area comprises functional brain tissue
Rivera-Rivera et al, 2017	Eloquent areas within a tumor
Ganslandt et al., 2004	Tumour invasion to functional cortex
Martino et al., 2011	Functional topography in and around the tumor

with the patient being asked to perform a certain task (task-related fMRI) or by resting-state imaging approach. In the latter, the patients is not asked to perform any type of exercise, so it is suitable when assessing brain-damaged patients, and it can be used to test connectivity within networks (Abd-El-Barr et al., 2013). For instance in Abd-El-Barr et al. (2013) fMRI revealed BOLD activation withinthe lesion.

Summarizing whether task-active fMRI vs. resting-state fMRI have been used allows addressing the issue whether the effect intratumoural functionality is confined within the tumor boundaries (task-active fMRI, 18.75 % of the studies) or, whether it impacts also on distant areas via functional connectivity (resting-state fMRI, 25 % of the studies). Resting state networks denote regions that show a strong temporally correlated BOLD signal at rest and reflect the synchronous co-activation of spatially distinct areas. In task-related fMRI, intratumoural function has been detected as significant fMRI activation within the tumor mass; in resting–state imaging, functional connectivity patterns between intratumoural areas and other areas of the brain are detected. For example, Daniel et al. (2021) measured resting–state fMRI of 57 patients undergoing surgery for resection of glioblastoma and compared them with 100 control subjects. They reported a proportion of functional connectivity voxels in contrast-enhanced and necrotic areas, with a significantly higher proportion of functional connectivity in the contrast-enhanced regions than in the necrotic ones. The result suggested that a loss of functional connectivity could be considered as a sign of a more infiltrative and aggressive tumour; indeed in the study a loss of functional connectivity correlated with a lower survival rate. Sprugnoli et al. (2022) used resting state fMRI on 54 patients with glioma with different histology. They showed an active functional connectivity between the glioma area and bilateral frontal regions (areas overlap with ventral attention, visual and fronto parietal control networks). The functional connectivity changed according to histology. The study proposed the possibility that the degree of synchronization in the BOLD signal could indicate different functional connectivity patterns between gliomas of varying histology and the brain.

Intra-surgery methods were used to test intratumoural functionality. Direct cortical stimulation is an intra-surgery stimulation method used to test whether a given area is involved in functional processing. It is used to stimulate (as it happens during motor or sensory mapping) or to inhibit (as it happens during language mapping) a given function (Abd-El-Barr et al., 2013). By using direct cortical stimulation, Young et al. (2020) identified intratumoral function in 19.3 % of patients with WHO 2016 grade II, III and IV tumors. Interestingly, on a further analysis authors identified a greater presence of intratumoral function in IDH-mutated than IDH wild type tumors (Young et al., 2020). As a last intra-surgery example, subdural electrocorticography during awake language mapping can give insights into neural activity and information-encoding capacity in both normal and infiltrated cortex (Aabedi et al., 2021). The authors recorded the cortical activity of 12 patients with LGG and HGG undergoing surgery during naming task and compared the activity of normal and infiltrated areas. They show that the infiltrated cortex retains the ability to activate in coordinated responses during language planning and production. Authors argued that the glioma-infiltrated cortex has spatial and temporal patterns of

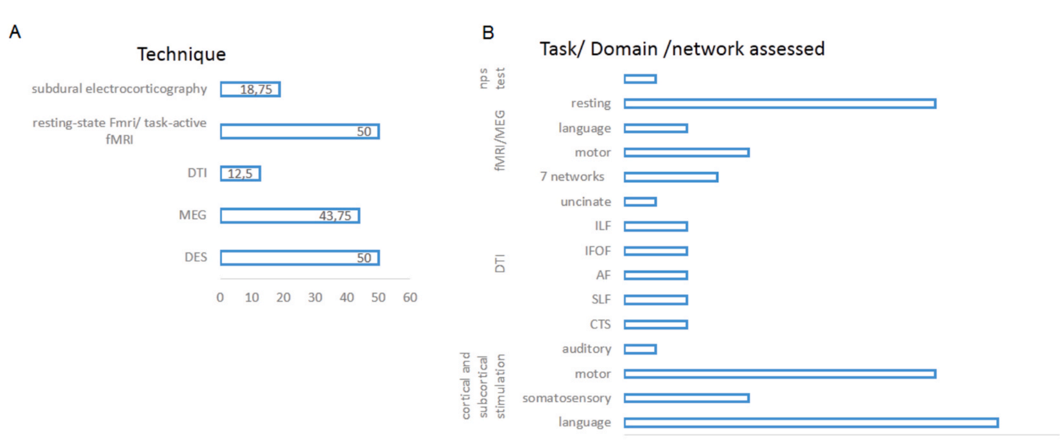

Fig. 4. Techniques used in the selected studies for addressing intratumoural functional activity (A) and the task/domains assesses (B).

activity that is similar to normal-appearing cortex but it recruits a diffuse spatial network (Aabedi et al., 2021).

4.4. Cognitive domains

We calculated the number of studies assessing a given cognitive domains (see Table 2). We found that intratumoural activity in studies using DES was related mainly to language functions (e.g., picture naming, counting, sentence completion, and repetition tasks during cortical and subcortical stimulation, Young et al., 2020). In MRI studies using resting state approach it was related to networks activity (see Fig. 4B).

4.5. Pre-surgical functional mapping correlation with intraoperative findings

Of the 24 studies we included, 5/24 used direct cortical stimulation mapping alone, thus reporting enough evidence for a functional site in the tumor area. 11/24 studies used both pre-surgical and intra-surgical mapping, and in these studies concordance between mappings was always obtained and it was high as reported by each study. Lastly, 8/24 studies used pre-surgical functional mapping alone. For example in Cui et al. (2022) it was reported that the hand motor networks mapped by rsfMRI corresponded to the hand sensorimotor region localized by intraoperative direct cortical stimulation in 100 % of patients (15/15). In Abd-El-Barr et al. (2013) it was reported that intraoperative electrocortical stimulation revealed activation of the left face where fMRI revealed activation within the lesion for lip pursing. As a further example, Martino et al. (2011) reported that functional maps showing increased functional connectivity within the tumor area had a positive predictive value of 64 % for finding language, motor or sensory cortical sites during intraoperative electrical stimulation mapping.

4.6. Patients and pathology, tumor grade and molecular genetics

Works examined patients with different aetiology (for details see Supplementary Table S1). Some, however, do not take into account the specific tumour characteristics of the patients' sample. Overall, the analysis of such clinical characteristics (see Fig. 5A) provided by the authors, show that intratumoural function has been addressed mainly in patients with astrocytoma (321 cases) and oligodendroglioma (255 cases). Followed glioblastoma (209 cases), oligoastocytoma (129 cases). The most frequently reported tumor grade were grade II (252 cases) and grade IV (188 cases, see Fig. 5B); finally, the patients described most frequently had IDH mutation (173 cases; IDH wild-type 109 cases; see Fig. 5C).

In general, it is known that HGG tend to form more compact mass (Rong et al., 2006; Abd-El-Barr et al., 2013), while LGG tend to be integrated into brain's functional white matter pathways (Cui et al., 2022; Seck et al., 2022). In this regard, a relationship has been reported between the results of the pre-surgery diffusion tensor imaging examination, and the identification of an intratumoural function as found by intra-surgery DES (Young et al., 2020). In detail, when pre-surgery DTI show HGG or LGG integrated in the corticospinal tract, the identification of intratumoural function occurs in 75 % of the cases; by contrast, in patients with HGG or LGG displace the corticospinal tract, a positive sites within the tumour is found in 15.4 %; lastly, in patients with LGG or HGG not in direct proximity to the corticospinal tract, a positive sites within the tumour is found in 7.7 % (Young et al., 2020). The interesting result is that despite a DTI examination revealing that the tract is preserved, positive sites within the tumour can still be reported in 31.8 % of the cases. The authors found the same patterns of results for the arcuate fasciculus and for the superior longitudinal fasciculus (Young et al., 2020).

As to tumor grade, it has been shown that intratumoural function can be reported for grade II to grade IV tumors. For example, in Schiffbauer et al. (2001), positive functional sites have been detected, through DES, in eloquent areas both within and around the tumor in patients with Grade II-II and IV tumors. Less functionality was seen in patients with grade IV where, due to the rapid tumor growth, where functional activity is localized more at the margins than within the tumor tissue itself.

Lastly, as to genetic mutations, some studies investigated the relationship between tumor characteristics / genetic mutations and intratumoral connectivity, leading to the observation of some patterns. Factors such as tumor aggressiveness and speed of growth play a role in the extent of intratumoral connectivity (Motomura et al., 2022). For example, Young et al. (2020) identified IDH-mutation and 1p/19q codeletion as key tumor factors that lead to an increased intratumoural functional connectivity. Gliomas with this marker, in particular IDH-mutant astrocytomas and oligodendrogliomas, show a higher tendency to be integrated into existing neural pathways without disrupting their functionality. Diffusion tensor imaging data show that IDH-mutated versus wild type-mutated tumours have a different pattern, with a tendency of the former to proliferate within the white matter bundles while wild type-mutated tumours tend to proliferate by destructing the function of the invaded tissue or by displacing it. Choi et al. (2021) in their commentary work, specifically mentioned IDH mutations as key factor: tumors with this mutation are more likely to be functionally integrated within white matter pathways (the so-called "glioma-network interface" as defined by the authors themselves).

Finally, the overall heterogeneity of intratumoral Functional connectivity (FC) across patients point to individualized tumor characteristics as pivotal determinants in FC variability necessitating a personalized approach in both research and clinical interventions.

4.7. Neuroanatomical details

Factors such as tumor location play a role in the extent of intratumoral connectivity (Motomura et al., 2022). An analysis was made of the total number of lesions per hemisphere. A total of 255 right- and 895 left-hemispheric lesions were found, 6 bilateral (Fig. 5D). In addition, the analysis of the lesion site (see Fig. 5E) showed a major involvement of the frontal cortex (435 cases), followed by the temporal (209 cases) and insular (141 cases) cortex (Fig. 5E). Their mean tumor volume was 53,11 ± 19,23 (Fig. 4F). Unfortunately, not all the studies reported neuroanatomical data (information for 34,48 % of the patients were missing). In general, at cortical level, the most studied regions were the frontal and temporal lobes, the motor cortex and the somatosensory cortex (Ojemann et al., 1996; Abd-El-Barr et al., 2013; Cui et al., 2022; Young et al., 2020). At subcortical level, the most studied tracts were the inferior fronto-occipital fasciculus or the frontal aslant tract, or the corticospinal tract, the arcuate fasciculus, the inferior and superior longitudinal fasciculus, the uncinate fasciculus and the cingulum (Mato et al., 2021).

4.8. Extent of resection and overall survival

Data about extent of resection was not reported in 75 % of the studies. In the other there were three type of presenting data. Those who reported the information about the extent of resection itself, had a mean extent of resection was 79,15 ± 12,56 cc. Some studies reported instead the number of patients for which resection was partial: the mean percentage calculated across these studies was 49,52 ± 14,72 of patients with limited resection. Lastly, there were studies in which authors calculated the predictive value of intratumoural function on patients' extent of resection. For instance, Mato et al. (2021) reported that the tracking of at least one white matter fascicle within the tumor predicts a lower extent of resection (67 %) as compared with the extent of resection in the patients with a negative intratumoral tractography (extent of resection 100 %).

As to overall survival, the studies included did not report this variable. However, there were some studies in which authors calculated the

Table 2
Tasks and cognitive domains used in the selected studies.

Study	Cortical and subcortical stimulation	Diffusion tensor imaging (DTI) tractography	fMRI and MEG	Neuropsychological test
Young et al.,2020	Picture naming, counting, sentence completion, and repetition tasks	CTS (motor); SLF and AF (language)		
Schiffbauer et al., 2001			Painless tactile somatosensory stimulation of fingers, toes, and lips and auditory presentation of pure sinusoidal tones	
Mato et al., 2021	Sensorimotor and language	Pyramidal tract, the inferior fronto-occipital fasciculus, the arcuate fasciculus andthe inferior longitudinal fasciculus		
Daniel et al., 2021			Resting state: VIS: visual network; DAN: dorsal attention network; SMN: sensorimotor network; VAN: ventral attention network; LAN: language network; FPC: fronto-parietal controlnetwork; DMN: default mode network.	
Sprugnoli et al., 2022			Resting state: maps of different networks: Default Mode Network (DMN), Fronto- Parietal Control Network (FPCN), Dorsal Attention Network (DAN), Ventral Attention Network (VAN), Limbic Network (LIM), Visual network (VS), and Somato-motor network(SM).	
Cui et al., 2022	Hand sensorimotor stimulation		Resting-state scan, two hand motor task fMRI runs were acquired for each patient; one run was acquired for the left hand and one run was acquired for the right hand. 17 networkswas estimated using data of 1,000 healthy subjects	
Bartolomei et al., 2006			Resting	
Abd-El-Barr et al., 2013	Motor		Lip pursing fMRI; Arabic (red) and English (purple) antonym generation tasks fMRI; right-hand tasks	
Ojemann et al., 1996	Motor mapping and naming for language			
Aabedi et al., 2021	Picture naming task			
Skirboll et al., 1996	Sensorimotor mapping and during number counting, object naming, or reading			
Feldman et al., 2009			Bilateralsequential thumb-to-digits opposition task; resting	
Aznarez-Sanado et al., 2024				Memory (verbal and nonverbal), verbal skills, nonverbalskills, attention, and executive function.
Mandal et al., 2024	Simple counting, and switch counting		Rest, This canonical 7-network parcellation was constructed previously by employing a clustering approach to rsfMRIdata from 1000 college-aged individuals	
LeRoux et al., 1991	Motor mapping			
Black and Ronner, 1987	Motor mapping and speaking			
Bello et al., 2008	Motor mapping and speaking	Corticospinal tract (CST), superior longitudinal, inferiorfronto-occipital and uncinatus fasciculi		
Chang et al. 2011	motor mapping and naming or reading			
Lee et al., 2020	Picture naming of visual stimuli, single-word text reading, and short-phrase sentence completion.		Resting	
Tarapore et al., 2012	Count, name objects, orread words DES e motor mapping		Resting, connectivity	
Baayen et al., 2003			Resting	
Rivera-Rivera et al., 2017	Language and motor mapping			
Ganslandt et al., 2004			Visual, sensorimotor cortex and/or of the speech related	
Martino et al., 2011	Language and motor mapping		Resting	

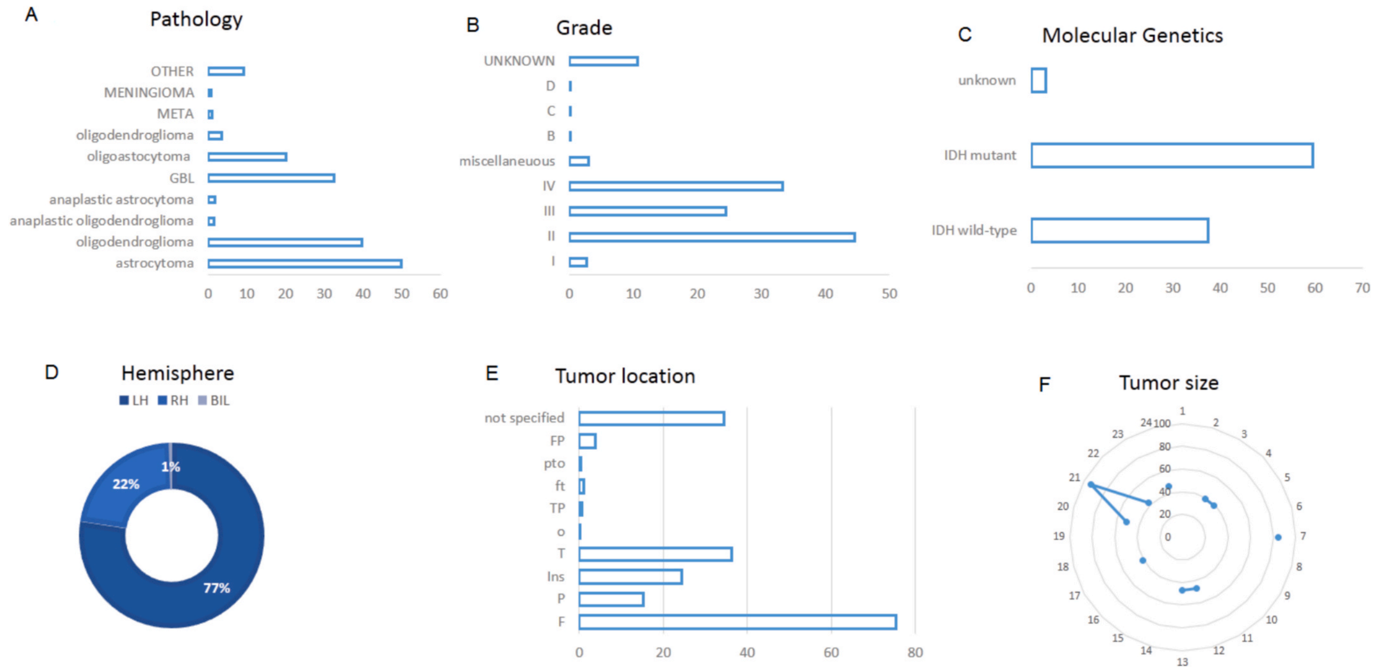

Fig. 5. Patients and pathology, tumor grade and molecular genetics, along with hemisphere (D) and lesion site (E).

predictive value of intratumoural function on patients' overall survival. For instance, Sprugnoli et al. (2022) reported a that a significant BOLD synchronization between the tumor mass and distant brain areas predicted, outperforming standard clinical, radiological and genetic predictors. In a similar vein, Daniel et al. (2021) reported that higher intranetwork connectivity strength between the glioblastoma mass and distant functional areas was associated with better overall survival even after accounting for clinical and demographic covariates. Chang et al. (2011) reported that tumor overlapping functional areas during intraoperative mapping was strongly associated with shorter survival.

5. Discussion

We summarized the results from a literature search on intratumoural function. It has been estimated that intratumoral activation occurs in about 40 % of patients with low-grade glioma (Schiffbauer et al., 2001). We quantified in this review of the literature that overall this phenomenon is rarely reported. Nonetheless, it has recently increasingly described and our literature scrutiny returned 24 studies reporting intratumoral functional activation. Techniques used for capturing the intratumoural activity are imaging techniques and intra-surgery direct cortical stimulation mapping. We found that intratumoural function is reported in a type of patients with the following characteristics: patients with astrocytoma or oligodendroglioma; mainly with a grade II tumor located often in the left frontal or temporal cortex; mainly with IDH mutation and a relatively medium mean tumor volume. Specific neurophysiological mechanisms behind the intratumoural functional activity are discussed below together with the clinical implications of finding activity within the tumor mass. A last issue concerns the importance of intra-surgery functional monitoring strategies that can help in monitoring intratumoural function status during resection.

5.1. Neurophysiological mechanisms behind this pattern

The physiological mechanisms behind activity found intratumoural mass is histological heterogeneity (Eidel et al., 2017; Pirro et al., 2017) and also heterogeneity in the different sub-regions inside brain tumor (e.g., Wang and Chung, 2022). It has been argued that finding that within the glioma there are preserved functional neural areas is related to the pathophysiological infiltrative behavior of the glioma itself (Cuddapah et al., 2014). In addition, it is known that the glioma microscopically infiltrates brain areas, thus it is not possible to clearly disentangle between tumor areas and brain (Ojemann et al., 1996). Indeed it has been shown that viable tumor cells are highly dense in the central part of LGG and decrease in the tumor periphery (Kinoshita et al., 2008).

The physiological mechanisms behind functional connectivity between the tumor mass and distant areas on the brain has been related by the authors of the included studies to the integration of glioma cells along axonal projections (Young et al., 2020). In addition, cellular mechanisms contribute to network connectivity (Young et al., 2020; Sprugnoli et al., 2022). Authors argue that the basis for the functional connectivity between the tumor mass and brain network can reside in molecular and cellular communications between gliomas and healthy neurons as shown by electrophysiological data (Venkataramani et al., 2019; Venkatesh et al., 2019; Larson et al., 2018; Osswald et al., 2015). The neuron-glioma interactions and its clinical consequences are still to be systematically investigated and are held to open new therapeutic options as it is suggested to be related also to circuit remodeling and (malignant and/or positive) plasticity potentials (Picart and Hervey-Jumper, 2024). Plasticity indeed can be involved as a mechanisms modulating intratumor function. Krishna and Hervey-Jumper (2022)'s review on brain remodeling address both plasticity occurring at long-range distant cortical sites or at peritumoral area. The latter is closely related to the topic of the present review, and, in particular, the presence of non-neoplastic astrocytes and mature neurons within gliomas interacts with neoplastic cells within the tumor are advocated as the cellular mechanisms involved in peritumoral plasticity (Krishna and Hervey-Jumper, 2022). The interaction occurs between nervous system and cancer cells making the neuron-glioma communication a key cellular mechanism underlying glioma-induced cortical neuroplasticity. Lastly, recent studies (Nejo et al., 2025) show that in the case of glioblastoma, there is a relation between intra-tumor connectivity and immunosuppression mechanisms. In particular, it has been shown that glioblastoma regions with enhanced neuronal connectivity exhibit regional immunosuppression (Nejo et al., 2025) opening new challenges for immunotherapy.

5.2. Heterogeneity of operational definition of intratumor function

There is heterogeneity in the operational definitions of intratumor function. Two major levels can be defined accordingly to whether the tumor tissue (or part of it) is found to be functional, or whether the tumor tissue (or part of it) tumor tissue actively participates in functional networks and communicates with distant brain areas. In the former case, three type of evidence may prove the functionality. fMRI signal detected within the tumor, DTI analysis detecting white matter fascicle (or part of it) passing through the tumor tissue, and DES revealing a positive functional site within the tumor mass. The implication on the postsurgical outcome are multiple. The more devastating outcome is reached if a positive DES site within the tumor mass is removed. More possibilities in terms of reorganization and compensation may be triggered in the second level, i.e., the tumor tissue (or part of it) tumor tissue actively participates in functional networks, as the tumor tissue represents a node of a network. If the first level occurs it can be hoped that peritumoral areas will assume the function; if the second level occurs it can be hoped that the other nodes of the network will take over the function.

From a technical point of view, both the first and the second level are detectable pre-surgery. However all require confirmatory evidence intra-surgery via DES to prove that the fMRI or DTI signal are true positives. DES is effective in detecting functional tissue within the tumor boundaries. Less effective can be when it has to be tested whether the functional tissue within the tumor boundaries participates in large functional network as its effect is rather local. In this case intra-surgery neuropsychological continuous monitoring (e.g., Real time neuropsychoogical testing, Skrap et al., 2016) can overcome this problem as it allows to monitor the general and function-specific patient cognitive status during all resection phase. Nonetheless detecting intratumor function already in the preoperative stage can offer important possibilities to potentiate plasticity and reorganization through neurostimulation protocols. Thus a multimodal approach that include both presurgical imaging and intra-surgery DES is recommended.

5.3. Clinical implications

We found that data about the extent of resection was not always reported in the selected studies; however, when reported, the extent of resection obviously was not 100 %. It is known that a maximal surgical resection improves long-term patients' survival (Smith et al., 2008). Given the behaviour of tumours that sometimes, as discussed above, infiltrate still functional tissue and that glioma-infiltrated cortex is capable of synchronizing its own activity, it has been suggested that it is necessary to discuss this issue and the implications of extent of resection with the patients and to plan tumour resection based on the possibility that the tumour tissue is still functional and not completely necrotic (Young et al., 2020; Aabedi et al., 2021; Cui et al.,2022). For instance Lee et al. (2020) reported that 70 % of patients in whom any tissue having functional connectivity with other areas was resected developed an early postoperative language deficit. Tarapore et al (2012) showed that patients undergoing resection of tumors with increased functional connectivity had a 60 % rate of new deficit at 1 week and a 25 % rate at 6 months post surgery. Finding functional activity within the tumor may be an inclusion criteria for conservative treatments which may be more favorable concerning quality of life in the surviving time (Ganslandt et al., 2004).

As far as overall survival is concerned, Daniel et al., 2021 stated that there is a potential relationship between functional connectivity found between the tumor mass and distant areas and overall survival. Newly GBM patients presenting with high functional connectivity had a higher overall survival (15.5 months) than patients with low functional connectivity (8.35 months) demonstrating that functional connectivity is to be considered a marker for defining the greater or lesser aggressiveness of the tumour. From what emerges from the works under analysis, however there is a critical interplay between extent of resection, functional connectivity and functional connectivity. The integration of gliomas into functional neural networks represents a significant challenge to achieve maximum extent of resection. The presence of functional connectivity within or bordering the tumor requires careful surgical planning to avoid neurological deficits, especially in LGG in which we have seen there is a greater chance that the tissue is functional. Indeed, there is a growing body of evidence that gliomas can affect the way brain regions interact as networks, causing functional and structural changes at network level (e.g., Bosma et al., 2008). In this context, network neuroscience is a challenging methodological approach (e.g., Mandal et al., 2023; Derks et al., 2021), and can improve therapeutic possibilities by analyzing networks activity patterns. It changed the view that a glioma can cause functional alteration just in the immediate tumor area by showing that patients with glioma can have widespread alterations in network organization (e.g., Alexandersen et al., 2025). Functional network changes correlate with cognitive deficits (e.g., Bosma et al., 2008), and potentially can predict patient outcomes (e.g., Daniel et al., 2021). In this perspective indeed we reviewed several studies that show that part of the tumor tissue show functional synchronization with clusters of distant areas.

Consideration of the molecular characteristics of tumor, leading to more or less functional connectivity is also an aspect to be considered in planning surgery. Sprugnoli et al., examined with a linear regression the relationship between solid tumor functional connectivity and overall survival in newly diagnosed and relapsed HGG patients and found that tumor functional connectivity with other networks significantly explained the different overall survival of patients. A relationship between functional connectivity and overall survival was also verified for LGG patients but of lesser strength ($R2 = 77.8$ % in HGG vs $R2$ across regions = 13–79 % in LGG) (Sprugnoli et al., 2022). The relation surpassed the predictive value calculated with age, genetic profile and KPS.

5.4. Intra-surgery monitoring strategies

A further implication of the described intratumoural functional patterns is the improvement of intra-surgery monitoring approach. It is reported that tumor integration into functional neural networks is the major limitation to achieving maximal extent of resection (Picart et al., 2019). Indeed, the existence of functional brain tissue "proves a caveat to the radical resection approach and would underline the requirement for individual functional mapping to guide the surgical approach" (Schiffbauer et al., 2001). Intra-resection cognitive monitoring becomes determinant for the cognitive outcome and in avoiding cognitive squeal. Indeed, monitoring of possible function within the tumour borders is therefore important to define the degree of extent of resection (EOR) (Skirboll et al., 1996). We acknowledge that direct cortical stimulation is the gold standard for mapping intraoperatively the functional tissue, but the complementary use of a continuous monitoring technique called Real Time Neuropsychological Testing (RTNT) can help the surgeon in obtaining a continuous feedback on the patients' cognitive status delivered during the resection phase (Skrap et al., 2016; Guarracino et al., 2020; Tomasino et al, 2021, 2022, 2023). Indeed, RTNT is performed continuously while resection occurs, while DES is alternated to resection phases. If the tumor mass is functional, obtaining a feedback during the whole resection phases is determinant in preventing intra-surgery cognitive decrease. In light of the results that indicate that tumor sub-areas functionally interact with other areas of the brain, it is worth including in the intra-operative protocol many tests in order to monitor as much as possible many cognitive networks.

Unfortunately, we acknowledge data limitations (e.g., missing extent-of-resection and survival data in most studies) limiting conclusions about prognostic implications. It would be of interest analysing the relation between the presence of intratumor activity and the extent of resection as well as the patients' overall survival in a more systematic analysis. We acknowledge aslo that in the present review we primarily used descriptive statistics rather than more sophisticated *meta*-analytic techniques. This is a limitation of the present study. Unfortunately, given the data limitations (e.g., missing extent-of-resection and survival data in most studies) techniques like random-effects models could not have been applied to measure effects of outcome measures across studies.

Since detecting intratumoral activity may challenge the surgical plan, operative standardized protocols and validated work flows are necessary in order to define intratumor function, to assess whether intratumor activity exists in a patient, and to establish standardized methods to analyze pre-surgical and intra-surgical data. Indeed future research focused on prospective studies assessing the relationship between intratumoral function and long-term outcomes, protocols integrating advanced imaging data acquisition with molecular and genetic profiling, and the development of predictive models for surgical planning, together with the exploration of therapeutic approaches that consider functional preservation within tumors is needed.

Due to the nature of our study, the article focuses on retrospective studies. There is no doubt that there is a need, even given the results emerging from this review, for many future prospective studies. In future studies, it would be desirable to systematically include data on postoperative outcome, extent of resection, and molecular data to verify the impact of intratumoral function on the patient's clinical status after surgery. Another aspect that deserves to be addressed in a systematic manner is neuropsychological. Little or no data on the patient's cognitive status were included in the reviewed articles. It will be interesting to test what implications it has from a cognitive standpoint to find intraoperatively that parts of the tumor are still functional. This is also from a perspective of defining whether these cases have particular plasticity.

A limitation of the imaging methods used in the reviewed studies consists of false positive or false negative that can have affected neuroimaging results. This is particularly true in the presence of a brain tumor. Indeed a brain tumor can be characterized by an abnormal tumor vasculature, in addition edema and inflammation can characterize the perilesional tissue, and also may be characterized by astrocyte dysfunction. All these pathological aspects may induce neurovascular uncoupling (e.g., Pak et al., 2017; Agarwal et al., 2021). In this context neurovascular uncoupling can confound results, especially those acquired by using resting state or task based fMRI as in the reviewed studies. Fortunately in almost all of the reviewed studies a multimodal approach, e.g. combining fMRI and DTI or imaging and DES, was used and this methodological combination can be useful to limit this can provide a more comprehensive picture and limit the effects of potential neurovascular uncoupling (e.g., Agarwal et al., 2023).

6. Conclusion

Historically, the area affected by the tumor was considered functionally silent, with attention paid mainly on the surrounding areas in order to obtain a maximal resection. Emerging research highlights a more nuanced perspective, recognizing the potential for functional activity within tumors. While functional intratumoral tissue are rarely reported, a significant presence of functional connectivity within and around tumor areas is consistently emerging from the literature. The use of different mapping techniques allows the recognition of functional activity or connectivity within tumors.

Taken together results indicate not just local effects, i.e., functional activation within tumors, but global effects, i.e., active integration into the brain's functional network.

This insight could lead to novel therapeutic and neurosurgical planning approach considering the pathological and molecular aspects of tumors, the need for maximum resection, the tumor biology and the neural functional networks.

CRediT authorship contribution statement

Ilaria Guarracino: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Marta Maieron:** Writing – review & editing, Validation, Methodology. **Serena D'Agostini:** Writing – review & editing, Validation, Methodology. **Tamara Ius:** Writing – review & editing, Validation. **Barbara Tomasino:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

B.T. designed the study; I.G. extracted the data; B.T. analyzed the data; I.G. and B.T. wrote the paper; M.M. and S.d'A. revised it critically for important intellectual content; all authors edited the paper; all authors revised the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103846.

Data availability

Data will be made available on request.

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