How much is enough—Can resting state fMRI provide a demarcation for neurosurgical resection in glioma?

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ABSTRACT

This study represents a systematic review of the insights provided by resting state functional MRI (rs-fMRI) use in the glioma population. Following PRISMA guidelines, 45 studies were included in the review and were classified in glioma-related neuronal changes (n = 28) and eloquent area localization (n = 17). Despite the heterogeneous nature of the studies, there is considerable evidence of diffuse functional reorganization occurring in the setting of gliomas with local and interhemispheric functional connectivity alterations involving different functional networks. The studies showed evidence of decreased long distance functional connectivity and increased global local efficiency occurring in the setting of gliomas. The tumour grade seems to correlate with distinct functional connectivity changes. Overall, there is a potential clinical utility of rs-fMRI for identifying the functional brain network disruptions occurring in the setting of gliomas. Further studies utilizing standardized analytical methods are required to elucidate the mechanism through which gliomas induce global changes in brain connectivity.

1. Introduction

Gliomas represent the most common primary intracranial tumour and its most aggressive form, glioblastoma, represents a lethal primary brain tumour with fewer than 5% of patients surviving at 5 years despite optimal treatment (Ostrom et al., 2014). Conversely, diffuse low-grade gliomas (DLGG) are a slow growing tumour with insidious onset that migrates along the white matter pathways, eventually undergoing malignant transformation leading ultimately to death (Duffau and Taillandier, 2015; Ghinda and Duffau, 2017). The prognosis of patients with low-grade glioma can vary from years to decades as it is determined by multiple factors, including molecular and genetic features (Obereheim Bush and Chang, 2016). Furthermore, the quality of life and the neurocognitive status are important factors in the management decision process with multiple reports providing evidence of cortical reorganization and brain plasticity occurring in the setting of gliomas raising the need of more targeted and personalized treatments (Duffau, 2013a; Fiscaro et al., 2016; Southwell et al., 2016).

Neurosurgical resection remains the standard of care for gliomas and mounting evidence suggests that more extensive surgical resection is associated with longer life expectancy for both low- and high-grade gliomas, thus representing an important prognostic marker for patient outcome (Ius et al., 2012; Sanai et al., 2011; Tarapore et al., 2011; Wen and Kesari, 2008). Although there is a lack of class I evidence, in a recent systemic review on the role of surgery in the management of DLGG, accumulating evidence supports a benefit of gross total resection when safe and feasible since it can result in increased overall survival (OS) (Aghi et al., 2015). Given this, a central question for such a surgical approach is to confirm that total resection has been achieved. Although neurosurgeons have access to a number of methods to do this,
there is reason to doubt the efficacy of these. For example, post-operative absence of contrast enhancement is interpreted as gross total tumour resection for high-grade gliomas but recent studies demonstrate that the non-enhancing peritumoural zone contains considerable amounts of “infiltrative tumour with a high cellularity which should be considered in resection planning” (Eidels et al., 2017). Furthermore, tumour recurrence typically occurs within 2–3 cm from the original lesion site (Chang et al., 2008; Ius et al., 2012). It is thus clear that making a macroscopic distinction between healthy and tumour cells remains challenging and that a maximal resection is difficult to achieve due to the infiltrative nature of brain tumours (Duffau, 2015a, 2012).

The benefits of a radical resection in prolonging survival and facilitating adjuvant therapy need to be balanced against the risk of altering the quality of life of the patients by inflicting an irreversible neurological deficit through an aggressive resection. The importance of preserving critical functional cortical areas and subcortical fiber tracts has been emphasized in multiple studies (Duffau, 2012; Keles and Berger, 2004; Southwell et al., 2016; Yordanova et al., 2011) and thus neurosurgeons use awake craniotomy and cortical stimulation mapping (CSM) as a gold standard for intra-operative mapping in attempts to identify and preserve eloquent cortex (De Witt Hamer et al., 2012; Trinh et al., 2013). Moreover, gliomas induce changes in functional localization, with some advocating that this should equally inform the surgical approach (Duffau, 2015a, 2012; Duffau and Taillandier, 2015; Robles et al., 2008). For example, DLGG infiltrating classical ‘Broca’ and ‘Wernicke’ areas in the dominant left hemisphere can be resected with no functional consequences because language network reorganization occurs in the setting of a slowly growing tumour (Sarubbo et al., 2012; Benzagmout et al., 2007; Duffau et al., 2005; Duffau, 2012; Robles et al., 2008). Thus, accurate localization of critical functional areas is crucial, not only because it may demonstrate unexpected organization patterns that may affect the neurosurgical approach to the lesion (Fisicaro et al., 2016), but also to elucidate the potential compensatory pathways that might become recruited to compensate the removal of infiltrated tissue. Combining such techniques with an aggressive cytoreduction could thus allow not only to improve the survival but also the quality of life of the patients (Meyer et al., 2001). It is in this setting that adjuncts such as functional MRI are most valuable for allowing a comprehensive pre-operative planning and thus an improved informed consent process.

Task-based fMRI (tb-fMRI) has been a useful tool for the identification of functional areas to guide surgery. However, requiring a patient to carry out an active task in the scanner has a number of drawbacks, and so over the last decade resting state functional MRI (rs-fMRI) has emerged as a simple and quick (scan time in the order of minutes) alternative technique. The concept of resting state refers to the neural activity that is generated within the brain in the absence of any specific stimuli or tasks and represents a measure of the brain’s intrinsic activity (De Luca et al., 2006; Lee et al., 2014; Xue et al., 2014). A common application of this form of data is to use it to estimate the degree of communication between brain areas and thereby describe brain networks (Hart et al., 2016a; Martino et al., 2011).

Several functional connectivity networks have been defined using rs-fMRI including the sensorimotor, language, visual, auditory, default mode, executive, attention and salience network (Hart et al., 2016a). Although these networks are obtained from intrinsic activity fluctuations obtained while the individual is not engaged in any particular task, they match up well with the networks of brain regions that appear to underlie specific cognitive functions (Smith et al., 2009). This includes “low-level” functions in the case of, for example, the sensorimotor or visual networks, which correspond to the brain regions involved in the basic processing of the relevant stimulus types (Smith et al., 2009). Other networks relate to “higher-order” functions, with the language network, for example, covering those brain regions involved in the production and comprehension of language (Tomasi and Volkow, 2012), or the default mode network (DMN) which is thought to be involved in the integration of cognitive and emotional processing (Greicius et al., 2003), self-reference (Qin and Northoff, 2011) and mind-wandering (Mason et al., 2007; van den Heuvel and Hulshoff Pol, 2010).

While it is also possible to portray structural networks delineating anatomical connectivity with deterministic tractography-derived fiber tracts (Golby et al., 2011; Javadi et al., 2017), ‘functional networks’ are derived from statistical relations between the rs-fMRI time series from different brain regions, allowing the investigation of dynamic neural networks. The pattern of neural activation measured with functional MRI has a resolution “approaching 1 mm² spatially and 1 s temporally” (Buxton, 2013), thus allowing a good spatio-temporal localization. The focus on such functional networks meshes with one of the main proposed mechanisms of adult plasticity, namely the “connectome concept”, where brain processing relies on “dynamic large-scale, parallel subcircuits able to interact and to compensate themselves following cerebral injury” (Duffau, 2013a; Mandonnet and Duffau, 2014; Vassal et al., 2017).

In this network perspective, our current approaches to delineate precisely the extent of resection in the setting of a glioma needs further refinements. We currently know that a more extensive resection ensures better outcomes given the infiltrated nature of glial tumours (Duffau, 2016; Duffau, 2012; Sanai and Berger, 2009), and we avoid injuring the areas that we map as critical for functioning. Nonetheless, this approach does not unfortunately take into account the ongoing plasticity and functional reorganization occurring in the setting of brain tumours and does not necessarily protect brain areas that are required for higher-order cognitive functions that are not routinely mapped. This raises the question of how far should we actually push the limit of our resection in order to offer the precise individualised surgery we advocate for as neurosurgeons.

2. Objectives

Given the emergent application of a network approach in the context of neurooncology, the incentive for this review is to evaluate the application of rs-fMRI in patients harboring a glioma and to provide a precise description of the current findings in a systematic way. As discussed throughout the paper, multiple studies outline the potential benefits of rs-fMRI use for the glioma patients in terms of delineating the network changes (Esposito et al., 2012; Ghumman et al., 2016; Harris et al., 2014; Hu et al., 2013; Maesawa et al., 2015; Mallela et al., 2016; Niu et al., 2014; Otten et al., 2012; Park et al., 2016; Vassal et al., 2017; Wang et al., 2016; Zhang et al., 2016), the functional areas (Böttger et al., 2011; Branco et al., 2016; Cochereau et al., 2016; Kokkonen et al., 2009; Liu et al., 2009; Roder et al., 2016; Rosazza et al., 2014; Shimony et al., 2009) and the tumour infiltration zones occurring in the setting of glial tumours (Agarwal et al., 2016a,b; Chow et al., 2016; Feldman et al., 2009). Despite the increased use of this technique for glioma patients, a systematic review of those various studies has, to our knowledge, not yet been performed. For the purpose of the current review, the studies pertaining to the use of rs-fMRI in glioma will be discussed according to their main objective, as divided into two categories: neuronal changes occurring in the setting of glioma and eloquent area mapping.

By comparing the interpretations of the different rs-fMRI approaches published so far, we also aim to explore the insights provided by this technique to our understanding of glioma pathophysiology and determine if there is consensus in terms of glioma effects on local and large-scale brain networks. Moreover, through this study we aim to give insights in terms of the optimal extent of resection that should be considered in the case of glial tumours. As such, the three main aims of this paper are (i) to review the clinical usefulness of rs-fMRI, (ii) to determine what this technique can reveal about glioma’s pathology, and (iii) to highlight some potential confounds that should be considered for best practices. The included rs-fMRI studies are rather
heterogeneous in terms of the regions and networks targeted as well as in the different type of analysis methods used. For that reason, a quantitative meta-analysis is impossible; henceforth we focus on a critical description of the studies included according to each study objective. The limitations and future directions of rs-fMRI in the management of gliomas patients are also discussed.

3. Methods

The literature search strategy used the medical subject headings (MeSH) and text words related to resting state MRI and gliomas. The databases utilized included MEDLINE (OVID interface, 1994 onwards), EMBASE (OVID interface, 1994 onwards), and Cochrane Central Register of Controlled Trials. The specific search strategies were created with the help of a Health Sciences Librarian with expertise in systematic review searching. To be included in the review, studies were required to: 1) investigate patients harboring a glioma, 2) investigate resting-state brain activity via rs-fMRI. Studies using tasks (e.g. motor, sensory, visual, language, breath-holding, etc.) during the MR scanning sessions were excluded. Nonetheless, the underlying rs-fMRI spontaneous activity can still be analyzed from tb-fMRI experiments by removing the effect of task-related activation on the underlying intrinsic fluctuations (Fox et al., 2006; Harris et al., 2014). This is generally done by fitting the task model and then using the residual data as pseudo-resting (Harris et al., 2014). As this approach is an established method for studying intrinsic activity studies employing pseudo-resting data were included. In addition, as previous studies portrayed similar correlation patterns between continuous resting state data and interleaved resting data taken from a block-design task (Fair et al., 2007; Zhu et al., 2017), studies using functional connectivity (FC) estimation from concatenated rest blocks of tb-fMRI were also included. There were no restrictions by study design, number of participants, outcome and language.

Screening of the titles and abstracts generated by the literature search against the inclusion criteria was performed and the complete papers that met the inclusion criteria were obtained. The full text papers were then assessed independently by the authors to decide whether these texts met the inclusion criteria. Data extracted from each study include: clinical findings related to the study population (cohort size and demographics, glioma type, tumour grade/volume and location, post-surgical/clinical status etc.), the study design, the rs-fMRI analysis approaches used and the main study findings. Given the sparsity of the studies available, we extracted composite and individual outcomes in all data forms (e.g. dichotomous, continuous) as reported in the included studies and we refined the outcome definitions based on definitions used in the reviewed papers (ex. functional connectivity, DMN alterations, neurocognitive changes, etc.).

4. Results

From the 579 articles generated by the search criteria, forty-five resting-state fMRI studies of patients with glioma were included in the review (PRISMA flow diagram). The results from the studies are summarized in the following sections according to the overall aim of the papers categorized in glioma-related neuronal changes and eloquent area localization.

4.1. Gliomas-related regional and network changes

4.1.1. Decreased long distance functional connectivity and altered global efficiency

4.1.1.1. Changes in the functional organization of the sensorimotor cortex. In terms of the network changes occurring in the setting of a glioma, four studies used a seed based approach to demonstrate diffuse alterations in FC (Niu et al., 2014; Otten et al., 2012; Vassal et al., 2017; Quigley et al., 2001). Such an approach takes a specific brain region and calculates the correlation between its activity over time and the activity in the rest of the brain or a set of other specific regions. Two studies attempted to link the connectivity measures with the motor strength and one study showed a significant correlation between the motor weakness and the decrease in FC (Niu et al., 2014; Otten et al., 2012).

Otten and colleagues were the first group to report a correlation between motor deficits and decreased connectivity within motor functional networks. This was driven primarily by decreased inter-hemispheric connectivity between the primary motor cortices along with changes in the activity correlation between the primary motor cortex and premotor areas. Notably, they observed this effect in patients with tumours outwith the primary motor structures. The authors concluded that “motor networks become weaker as the subjects become weaker, and may become strong again during motor recovery” (Otten et al., 2012). However, the authors found that motor networks were similar between asymptomatic patients with brain tumours (no weakness) and the controls.

The correlation between motor deficits and motor network connectivity was further analyzed by Vassal and colleagues, who used independent component analysis (ICA) to assess the influence of surgical treatment on the large scale reorganization of the sensorimotor network. In contrast to a seed-based approach, this technique estimates networks in a data-driven manner without the need to set a specific target region. The team demonstrated that the interhemispheric connectivity between the lesion side motor area and the contralateral supplementary motor area was “decreased during the immediate post-operative period and had returned to preoperative values at 3 months after surgery” (Vassal et al., 2017).

Conversely, by comparing 15 asymptomatic patients with brain tumours located in eloquent region with a matched control group, Niu et al. found significantly reduced inter-hemispheric functional connectivity between the left and right PMC in glioma patients compared with controls (Niu et al., 2014). This difference might be accounted for by the different patient populations and analysis methods of the two studies (see discussion section). Furthermore, Niu et al. observed decreased power spectral density (PSD) in patients compared to controls, in three frequency bands (low: 0.01–0.02 Hz; middle: 0.02–0.06 Hz; and high: 0.06–0.1 Hz) at three key motor regions. Although the authors concluded that the “power spectral analysis is more sensitive than functional connectivity analysis” (Niu et al., 2014) for identifying motor function plasticity, further prospective studies are required to confirm these findings.

Nonetheless, a study published in 2001 reported different results stating that “patterns of functional connectivity remain intact in patients with focal cerebral lesions and (...) disruption of major neuronal networks, such as agenesis of the corpus callosum, may diminish the normal functional connectivity patterns” (Quigley et al., 2001). However, it must be stressed that this study included multiple different pathologies with only three glioma patients. Besides the heterogeneity of the pathologies included in the study group, the authors used a cross-correlation analysis method and no subgroup analysis was performed. These features could thus account for the different results obtained compared to the other studies mentioned above and further studies are required to accurately delineate the glioma-related changes occurring in the functional organization of the sensorimotor network and their correlation with the clinical symptoms.

4.1.1.2. Changes in the functional organization of the language network. The changes in the functional organization of the language network occurring in the setting of tumours has been assessed in several studies (Branco et al., 2016; Briganti et al., 2012; Sair et al., 2016). Briganti and colleagues analyzed the functional connectivity reorganization of the language network (LN) in 39 right-handed patients with a left hemisphere brain glioma and compared the results with 13 healthy controls. The inclusion criteria for this study
Contrasting with the tumour patients, suggesting a possible compensatory mechanism entailed absence of aphasia although no objective test for language deficit was employed. Also, the choice of the first region of interest (ROI) corresponded to the region with maximum blood oxygen level-dependent (BOLD) response that was closest to a reference Talairach coordinate (the pars opercularis of the inferior frontal gyrus (IFG): Broca area, 44/45). The subsequent five ROIs were selected by using the region with maximum Pearson correlation coefficients closest to the reference Talairach coordinates obtained in previous studies. The authors showed that the functional connectivity was significantly reduced within seed regions of the LN, especially in the left temporoparietal junction (TPJ) node (Briganti et al., 2012). Nonetheless, it is important to note that this study used the active regions identified with a verb-generation task, such as left IFG, as seeds to create whole-brain background connectivity maps and to identify the LN following regression of task-evoked activity. Although the results obtained by the authors are intriguing, tumours not only distort the normal brain anatomy but are also associated with network plasticity and reorganization that might confound the results obtained. Also important to note is the fact that the FC analysis was performed on the residual dataset obtained by removing the deterministic task evoked components of the BOLD signal and so potential effects related to effort might still be a confound for the analysis.

Zhang et al. used different ROIs, respectively posterior cingulate cortex (PCC) and TPJ, and observed that the intra-hemispheric FC strength values between the two ROIs were decreased bilaterally in tumour patients (Zhang et al., 2016). Although the correlation analysis between WHO grades and the functional connectivity pairs was significant in the dominant hemisphere, no significant correlation was present in the entire dataset. Interestingly, the authors equally found that the correlation coefficients between the FC pairs in the patients were increased compared with the corresponding controls (Zhang et al., 2016).

In summary, multiple studies provide evidence of decreased functional connectivity occurring in the setting of gliomas and suggest possible clinical functional correlations. Nonetheless, further studies are required to elucidate the mechanism through which gliomas induce those changes in brain connectivity.

4.1.2. Distinct changes in low-grade versus high-grade gliomas
A few studies have attempted to delineate the alterations occurring in the setting of different glioma grades. Compared with LGG, HGG have a more complex anatomical morphology and BOLD-fMRI features in the tumour region (Wu et al., 2015) and are associated with the largest reduction in DMN functional connectivity (Harris et al., 2014; Mallela et al., 2016). Furthermore, functional connectivity loss was associated with motor deficits in LGG but not in HGG despite the fact that tumour volume and distance to ipsilateral motor cortex demonstrated no association with the functional connectivity loss (Mallela et al., 2016). The presumed decreased sensitivity of rs-fMRI in HGG patients was postulated to be due to the presence of neurovascular uncoupling.

Using a data driven method, Esposito and colleagues explored the DMN modifications occurring in patients with left hemisphere gliomas. While the DMN is not typically lateralized in normal subjects, the researchers found a significant DMN lateralization to the hemisphere contralateral to tumour in the low-grade, but not in the high-grade tumour patients, suggesting a possible compensatory mechanism occurring in the setting of low-grade tumours (Esposito et al., 2012). Contrasting with the findings mentioned above, Zhang et al. found no significant differences in functional connectivity across different WHO (World Heath Organization) grades when they performed correlation analysis for the total patient data. Nonetheless, when the subgroups were analyzed based on the location of the glioma, they found a significant correlation between the left intra-hemispheric FC and the tumour grade (Zhang et al., 2016).

In summary, although research is in the preliminary stage, tumour grade seems to be associated with distinctive functional connectivity changes. Nonetheless, the few studies available included patients with different tumour grades and various locations raising the need to validate those results with larger populations.

4.1.3. Regional alterations for tumour infiltration assessment
In addition to the standard correlation-based methods, multiple neurodegenerative and neuropsychiatric studies use voxel-wise approaches that assess the spontaneous time series (Martino et al., 2016; Zang et al., 2007). Those approaches include regional homogeneity (ReHo), the amplitude of low-frequency fluctuations (ALFF), and fractional ALFF (fALFF). Recent studies also attempted to use those approaches for brain tumours so a short description of those approaches is presented (Boyer et al., 2016; Niu et al., 2014; Wu et al., 2015). ALFF calculates the voxel-wise power of low-frequency (generally those between 0.01 and 0.08 Hz) oscillations (Zuo et al., 2010) while fALFF is the ratio of these low frequency oscillations to the power over the entire frequency range of the signal (Boyer et al., 2016). ReHo assesses the similarity of a voxel’s timecourse to those of its immediate neighbours and can be seen as a correlate of the degree of synchronization within a specific local brain area (Zang et al., 2004).

Several studies concentrated on the regional alterations occurring in the setting of tumours. Boyer and colleagues assessed the longitudinal changes occurring in the cerebellar and thalamic spontaneous neuronal activity in 14 patients with diffuse low-grade gliomas undergoing awake surgery (Boyer et al., 2016). The authors focused on the properties of brain activity over time within local regions (as opposed to the FC between different regions), exploring ReHo, ALFF and fALFF, identifying a temporary drop of ALFF and fALFF scores 24 h after surgery that recovered within 3 months. Nonetheless, as stated by the authors, the aim of this study was predominantly to delineate remote consequences of the tumour resection during wide-awake brain surgery.

Other studies attempted to localize the extent of tumour infiltration with rs-fMRI using the seed based analysis (Chow et al., 2016). For instance, Chow et al. used BOLD fMRI to assess the disruption in vascular regulation induced by a glioblastoma. The authors found that “the spatial distribution of these disruptions is localized to the immediate vicinity of the tumour and peritumoral edema” (Chow et al., 2016).

Furthermore, Agarwal and colleagues demonstrated evidence of neurovascular uncoupling (NVU) occurring in regions ipsilateral to gliomas comprising primary motor and somatosensory cortices (Agarwal et al., 2016a,b). They also demonstrated evidence of NVU on resting-state ultrahigh field 7T rs-fMRI similar to the one observed on 3T motor tb-fMRI (Agarwal et al., 2016a).

In summary, the discussed studies provide convincing evidence of localized alterations occurring in the setting of glioma. As glioma invasion is often ill defined on standard clinical MR imaging techniques, rs-fMRI measures may provide additional insight into the degree of tumour infiltration and could become an additional tool in the clinician’s tools for brain tumour delineation.

4.1.4. Network hubs and intratumoural connectivity as a prognostic factor
Several studies attempted to correlate the results obtained through rs-fMRI images with prognostic factors. Touvinen et al. (2016) assessed the connectivity changes occurring in the setting of adjuvant radiotherapy administered for glioma patients. They observed that although the tumour predominantly affects connections in close vicinity, “when the lesion relates to a functional hub, these changes involve long-range connections leading to diverse connectivity profiles pre- and post-radiotherapy” (Tuovinen et al., 2016). The authors used both a seed based method and an ICA approach to delineate the network hubs involved and the results were in general consistent between the two methods. As such, distinct alterations seem to occur depending if a central or a non-central functional hub is involved.

The authors advocate the importance of tumour location in comparison to network hubs given the observed “global but temporary
improvement in the post-radiotherapy connectivity obtained when treating a lesion close to a network hub, such as the PCC” (Tuovinen et al., 2016). Interestingly, Derks and colleagues reported in a recent abstract that de novo glioma patients show increased functional connectivity between hub and non-hub regions and that “patients with higher hub-to-non-hub connectivity have a shorter OS, indicating the prognostic potential of this imaging phenotype” (Derks et al., 2017). As only the study abstract is available currently, one cannot comment on the specific approach and arguments used by the authors to reach this conclusion. Nonetheless, it would be very interesting to further assess the theoretical framework proposed by the authors that portray their findings as “a hypothetical first phase of hub overload, which is thought to eventually lead to cascading failure of the entire global network” (Derks et al., 2017).

Similarly, Park and colleagues assessed the long-distance connectivity and network topology in 36 patients with supratentorial brain gliomas and 12 healthy subjects (Park et al., 2016). When comparing between patients and healthy controls, the patients showed decreased long-distance, inter-hemispheric connectivity with an increased local efficiency while there was preservation of other network topology parameters such as clustering coefficient, global efficiency, and small-world property.

These findings are consistent with the results found by Huang et al. where glioma patients were found to have preserved small-world properties (Huang et al., 2014). In the attempt to retain the small-world character while enabling a dynamic measure of brain network, Wang and colleagues applied an exponential truncated power-law function to fit the node degree distribution (Wang et al., 2016). This method showed “major discrepancies on glioma patient brain network in different brain regions and dynamic evolution on regional hub network, compared to those of normal subjects” (Wang et al., 2016).

Interestingly, while the previous articles concentrated on the connectome alterations occurring in the brain secondary to glioma, Whitlow et al. portrayed a distinct type of connectivity: the intratumoural connectivity. The researchers assessed the clustering coefficient and characteristic path length and they computed a Pearson correlation coefficient between all pairs of node time series within the brain and the tumour area. The authors found that “higher histologic grade astrocytoma demonstrated greater small-worldness than the lower grade gliomas, suggesting a less random and more organized pattern of intratumoural connectivity” (Whitlow and Maldjian, 2012).

Although the study used a small number of participants (four patients), the results are in keeping with recent findings assessing intratumoural connectivity at the cellular level (Oswald et al., 2016, 2015). However, this work is also available only in the form of an abstract, so no detailed assessment of the method employed can be performed.

Other studies attempted to correlate basic measures of connectome analysis with neuro-cognitive measures. The preliminary work suggests that in patients with low-grade frontal gliomas, the small worldness and efficiency are related to cognitive deficits and intelligence (Huang et al., 2014; Xu et al., 2013). Xu and colleagues compared patients harboring a LGG with controls and demonstrated that LGG patients display disturbed small-world network hubs and decreased global efficiency compared to the control group (Xu et al., 2013). Furthermore, the global efficiency was found to be positively correlated with the IQ test scores in LGG patients, therefore proposing a network mechanism for the intellectual decline observed in LGG patients.

In order to characterize overall network topology and individual patterns of connectivity alterations, Hart and colleagues applied different graph-theory based analysis in five patients with glioblastoma and demonstrated distinctive patterns of alterations in both local and long-range connectivity patterns (Hart et al., 2016b). The authors concluded that “lesions produced both local and distant effects in terms of reduced connectivity, network fragmentation, as well as alterations to the topological core structure of hubs and robustness” (Hart et al., 2016b).

In summary, although the connectivity results obtained through different analysis methods could be a helpful adjunct in the pre-operative planning by delineating regions essential to brain network function, further work is required to delineate the functional relevance of those measures and the specific clinical correlates. As it is acknowledged in the neurooncological literature, the functional relevance of those measures needs to be carefully balanced against the oncological benefits of an extensive tumour resection as ultimately both will impact the quality of life and overall survival of the patient. Thus, although in its beginning, the graph analysis approach portrays different local and distant changes in the network hubs and global efficiency that could potentially correlate with some neuro-cognitive symptoms displayed by patients with glioma. This approach offers a unique perspective of the network alterations occurring in the setting of glioma and offers a potential modality to get a deeper insight of gliomas’ pathophysiology from a network perspective.

4.2. Eloquent area mapping

4.2.1. Current validity of rs-fMRI in sensorimotor and language mapping

4.2.1.1. Sensorimotor network. Three studies used a priori seed selection in order to assess the use of rs-fMRI for localization of the motor cortex in the pre-operative stage. Liu and colleagues was the first group to use the seed based approach based on the spontaneous activity correlations to localize motor regions and found that the results were “similar to the regions defined by actual movement tasks and cortical stimulation” (Liu et al., 2009). Qiu and colleagues assessed specifically the capacity of hand motor area localization using resting state and tb-fMRI (Qiu et al., 2014). The rs-fMRI sensitivity and specificity were found to be 90.9 and 89.4%, and in 15 patients who successfully underwent both rs-fMRI and tb-fMRI there was no statistical difference in sensitivity or specificity between the two methods. Dorfer and colleagues reported the potential clinical benefit of such approach by demonstrating the use of rs-fMRI for intraoperative neuronavigation in children unable to perform task-related fMRI (Dorfer et al., 2014). The study is however only present in an abstract form and details about the rs-fMRI processing and comparison methods used are not yet available.

Other studies used a data driven approach in the attempt to localize sensorimotor and language networks in patients with glioma (Kokkonen et al., 2009; Roder et al., 2016; Schneider et al., 2016). In terms of the sensorimotor-region of interest mapping there was a good concordance between resting-state and task-related maps in all three studies. Similarly, the motor cortex was successfully and consistently identified with rs-fMRI and the results correlated with the tb-fMRI results.

Besides the previously discussed papers, seven additional manuscripts performed both approaches in terms of the rs-fMRI analysis. In three of the studies, rs-fMRI was used to successfully localize the sensorimotor cortex both with seed-based and ICA analyses (Cochezrea et al., 2016; Rosazza et al., 2014; Sair et al., 2016; Zhang et al., 2009). Zhang and colleagues was the first research team that used both approaches in the attempt to localize sensorimotor areas in glioma patients. The authors found that rs-fMRI based results were consistent with cortical stimulation mapping and “performed as well or better than task-based fMRI” (Zhang et al., 2009).

Rozanna and colleagues localized successfully the hand, foot and mouth motor subregions with seed-based analyses. The rs-fMRI results were, however, not entirely in line with those of tb-fMRI and tended to identify more extensive areas than CSM (Rosazza et al., 2014). A similar good but imperfect match was found in an additional study where the correlation between CSM-positive sites and rs-fMRI results for motor network was 0.80 (Mitchell et al., 2013), as well as between rs-fMRI and tb-fMRI (Mangalore et al., 2013; Shimony et al., 2009). Finally, an abstract describes using a connectivity-based technique based on rs-fMRI to parcellate and localize the SMA, confirming the accuracy of the
technique with CSM (Zhu et al., 2016). Thus, the current studies show encouraging results in terms of using resting-state as an adjunct for the sensorimotor mapping.

4.2.1.2. Language network. The relevance of resting-state approaches for the mapping of the language network has been assessed in several studies (Branco et al., 2016; Briganti et al., 2012; Cochereau et al., 2016; Sair et al., 2016). Briganti and colleagues analyzed the functional connectivity reorganization of the language network in 39 right-handed patients with a left hemisphere brain glioma and compared the results with 13 healthy controls. The inclusion criteria for this study entailed absence of aphasia however no objective test for language deficit was employed. Also, the choice of the first ROI corresponded to the region with maximum BOLD response that was closest to a reference Talairach coordinate (the pars opercularis of the IFG: Broca area, 44/45). The subsequent five ROIs were selected by using the region with maximum Pearson correlation coefficients closest to the reference Talairach coordinates obtained in previous studies. The authors showed that the functional connectivity was significantly reduced within seed regions in the LN, especially in the left TPJ node (Briganti et al., 2012). Nonetheless, it is important to note that this study used the active regions identified with a verb-generation task, such as left IFG, as seeds to create whole-brain background connectivity maps and to identify the LN following regression of task-evoked activity. Although the results obtained by the authors are intriguing, tumours not only distort the normal brain anatomy but also are associated with network plasticity and reorganization that might confound the results obtained. Also important to note is the fact that the FC analysis was performed on the residual dataset obtained by removing the deterministic task evoked components of the BOLD signal and so effects related to effort might still be a confound for the analysis.

Also looking at the concordance of different measures, Sair and colleagues used ICA analysis to directly compare task and rs-fMRI results for language mapping in 49 patients and found a moderate concordance between the two techniques but with considerable subject-level variability (Sair et al., 2016). Similarly, Branco and colleagues suggested that there is a concordance between the language mapping results obtained via task-based and rs-fMRI. Of the 15 patients included in the study, 9 patients had a glioma and the authors performed a semi-automated template-matching procedure to identify each subject’s language resting-state component. Nonetheless, the Dice coefficients obtained in the whole brain analysis were quite low (0.248 for tb-fMRI) questioning the use of “resting-state as a stand-alone alternative to task-fMRI for clinical purposes” (Branco et al., 2016). Another study using artificial neural network analysis found that the correlation between CSM-positive sites and rs-fMRI results for language mapping was 0.64 (Mitchell et al., 2013).

Recently, a comprehensive study attempted to validate the functional relevance of resting-state networks (RSNs) by comparing the overlap between the intraoperative functional mapping results with different modalities of resting state connectivity (RSC) calculation. The authors calculated the language RSN using language seeds elicited by direct cortical stimulation versus RSC between random regions and evaluated the accuracy of rs-fMRI by assessing the overlap between RSNs and intraoperative functional mapping results. ICA partly succeeded to distinguish the eloquent language areas and there was a significantly higher RSC between language seeds than between random seeds (Cochereau et al., 2016).

Nonetheless, it is important to acknowledge that there is no established protocol for using tb-fMRI for localization of all relevant language areas, and that there is variation in experimental design across institutions which in turn influences the fMRI results (Binder, 2011). Given that the different tasks will localize different areas, a panel of tasks would likely provide a more reliable model for language mapping via fMRI (Gaillard et al., 2004). For instance, Benjamin and colleagues delineated six clinically relevant language areas that can be mapped with fMRI which could be used as a model to reflect the current knowledge of the language system (Benjamin et al., 2017; Tremblay and Dick, 2016).

In summary, there is increasing evidence that delineating the language RSN with rs-fMRI could potentially serve as an additional tool to assess the language network plasticity occurring in the setting of gliomas. Studies that assessed directly the functional role of the extracted language network by comparing them with the gold-standard DCS provided favorable results. Future similar studies could provide more evidence of the clinical significance of the language RSN.

4.2.2. Default-mode network

Several studies specifically looked at DMN changes occurring in the setting of a glioma. Esposito and colleagues demonstrated reduced DMN connectivity in tumour patients with respect to controls. The modifications observed in the DMN area were related to tumour grading and DMN lateralized to the hemisphere with tumour in the low-grade, but not in the high-grade tumour patients (Esposito et al., 2012). Similarly, Harris and colleagues showed that in the dominant hemisphere, the “parietal lobe tumors showed a more impaired DMN compared with tumors located in the frontal lobe, while tumors within and outside the network nodes did not differ significantly” (Harris et al., 2014).

Moreover, besides previous surgery and adjuvant treatment, a higher tumour grade had the highest impact on DMN functional connectivity, supporting the widespread infiltration inherent to higher grade tumours. The authors found no statistical association between DMN connectivity and tumour size on T2-weighted images and suggested that the “large T2 lesions may not necessarily disrupt the DMN if they do not have histopathological features of malignancy, but rather may displace neural connections between functional regions” (Harris et al., 2014). It may be noted though that this study used pseudo-resting state fMRI signal generated from tb-fMRI data, possibly raising concerns about task-evoked contamination of the signal analyzed.

Using a seed-based approach to evaluate the DMN, Zhang and colleagues equally observed that the intra-hemispheric FC strength values between the two ROI’s were decreased bilaterally in tumour patients comparing to controls (Zhang et al., 2016). Although the correlation analysis between WHO grades and the functional connectivity pairs was significant in the dominant hemisphere, no significant correlation was present in the entire dataset. Interestingly, the authors equally found that the correlation coefficients between the FC pairs in the patients were increased compared with the corresponding controls (Zhang et al., 2016).

The integrity of the DMN in children with different tumours (including gliomas) was investigated in two studies. Bush and Murakami was the first study to identify DMN in a single patient population by assessing both the areas of deactivation during a semantic word generation task and by performing a RSN analysis using ICA technique on a concatenated dataset from the task-based exams. They found that the DMN identified through those two techniques were spatially similar (Bush and Murakami, 2015). Nonetheless, a distinction between the two approaches was that the medial prefrontal cortex (mPFC) was identified in the ICA-derived DMN but not in the one derived from the task-induced deactivation. Although no quantitative or group comparisons were performed in this study, the authors suggested that the task-based DMN alterations could be linked to the presence of seizures in the study group (all besides one patient had seizures). In the same line, Poliakov and colleagues described that for both the motor and DMN networks, functional connectivity was displaced but preserved in the patients without epilepsy while it was decreased or absent in the patients with epilepsy (Poliakov et al., 2012). Nonetheless, the small size of the patient population in both studies (only 2 patients had a glioma) precludes any conclusions in terms of glioma-related findings.

Additionally, two other studies used a data-driven approach to investigate the effect of brain tumours on DMN connectivity and
Table 1
A glioma-related network changes.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Pathology (# of patients), healthy control (HC) (# of subjects)</th>
<th>Brain regions and/or networks analyzed</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyer et al. (2016)</td>
<td>DLGG (14)</td>
<td>Thalamus and cerebellum</td>
<td>Variations of spontaneous neuronal activity were particularly significant within the cerebellum which showed altered ReHo and neuronal activity intensity in different subregions. These variations were observed in the immediate postoperative period and recovered after 3 months.</td>
</tr>
<tr>
<td>Derks et al. (2017)</td>
<td>Glioma (71-grade NS), HC (22)</td>
<td>DMN, FPN</td>
<td>De novo glioma patients show increased FC between hub and non-hub regions. Furthermore, patients with higher hub-to-non-hub connectivity have a shorter OS. DMN connectivity in the left side of the brain may be more fragile to insults by tumours. Tumours in the left hemisphere had the largest effect on DMN connectivity regardless of their size and type, while this effect was not observed for right hemispheric tumours. Tumours in the cerebellum also altered the DMN connectivity.</td>
</tr>
<tr>
<td>Ghumman et al. (2016)</td>
<td>Glial lesions (40, grade NS), other (27)*, HC (23)</td>
<td>DMN</td>
<td>Tumours produced both local and distant effects in terms of reduced connectivity, network fragmentation, as well as alterations to the topological core structure of hubs and robustness. An exponentially truncated power-law fit to the degree distribution predicted findings of general network robustness and a core of highly connected and integrated hubs with disproportionate vulnerability.</td>
</tr>
<tr>
<td>Hart et al. (2016a,b)</td>
<td>GBM (5)</td>
<td>Brain parcellation into 116 regions</td>
<td>Tumours produced both local and distant effects in terms of reduced connectivity, network fragmentation, as well as alterations to the topological core structure of hubs and robustness. An exponentially truncated power-law fit to the degree distribution predicted findings of general network robustness and a core of highly connected and integrated hubs with disproportionate vulnerability.</td>
</tr>
<tr>
<td>Mallela et al. (2016)</td>
<td>GBM (9), AA (4), diffuse astrocytoma (4), oligogl (3), mixed HGG (1), mixed LGG (1), gliosarcoma (1), HC (12)</td>
<td>Motor network</td>
<td>Decreased PSD in all 3 frequency bands at 3 key motor regions and reduced inter-hemispheric FC between the left and right PMC in patients compared with controls. The tumour affects connections in close vicinity, but when the lesion relates to a functional hub, these changes involve long-range connections leading to diverse connectivity profiles pre- and post-radiotherapy. A global but temporary improvement in the post-radiotheraphy connectivity was obtained when the lesion was located close to a network hub, such as the PCC.</td>
</tr>
<tr>
<td>Niu et al. (2014)</td>
<td>Diffuse astrocytoma (6), AA (5), oligogl (4), HC (15)</td>
<td>Motor network</td>
<td>Global network activation and interhemispheric connectivity were reduced in gliomas; HGG had lower FC than LGG. The loss is associated with motor deficits in LGG, but not in HGG. Tumour volume and distance to ipsilateral motor cortex demonstrated no association with FC loss.</td>
</tr>
<tr>
<td>Touvinen et al. (2016)</td>
<td>GBM (3)</td>
<td>DMN, DAN &amp; SMN</td>
<td>Tumours produced both local and distant effects in terms of reduced connectivity, network fragmentation, as well as alterations to the topological core structure of hubs and robustness. An exponentially truncated power-law fit to the degree distribution predicted findings of general network robustness and a core of highly connected and integrated hubs with disproportionate vulnerability.</td>
</tr>
<tr>
<td>Vassal et al. (2017)</td>
<td>DLGG (6)</td>
<td>Sensorimotor network</td>
<td>Interhemispheric connectivity was decreased in the postoperative period, and increased again during the recovery process. Connectivity between the lesion side motor area and the contralateral SMA rose to higher values than in the preoperative period.</td>
</tr>
<tr>
<td>Wang et al. (2016)</td>
<td>Glioma (12-grade NS), HC (10)</td>
<td>Voxel level network</td>
<td>Compared with controls, there were major discrepancies in glioma patient brain network and in the dynamic evolution on regional hub network. In glioma patients, more hub nodes have high degree value at tumour edge.</td>
</tr>
<tr>
<td>Zhang et al. (2016)</td>
<td>Astrocytoma (8), oligogl (3), AA (2), anaplastic oligogl (2), glioma (1), GBM (4), HC (20)</td>
<td>DMN</td>
<td>Intra-hemisphere FC strength was decreased while the correlation coefficients were increased in patients compared with controls. FC in the dominant hemisphere was more vulnerable and its decrease correlated with the WHO grade of gliomas.</td>
</tr>
<tr>
<td>Chamberland et al. (2015)</td>
<td>AA (1), HC (10)</td>
<td>DMN, motor, visual, SN, LFC, auditory</td>
<td>Tractography-driven resting-state connectivity showed PC changes induced by the mass effect of the tumor. This technique could reduce the bias introduced by seed size, shape and position.</td>
</tr>
<tr>
<td>Maesawa et al. (2015)</td>
<td>WHO grade II glioma (7), WHO grade III glioma (3), WHO grade IV gliomas (2), HC (12)</td>
<td>DMN, ECN and SN</td>
<td>Decrease in the contralateral FC of the DMN and ECN in patients with tumours compared with controls. Changes correlated with some aspects of cognitive function indicating that patients with gliomas may undergo cognitive changes even before the onset of major symptoms.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Pathology ( # of patients), healthy control (HC) ( # of subjects)</td>
<td>Brain regions and/or networks analyzed</td>
<td>Main findings</td>
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</tr>
<tr>
<td>Park et al. (2016)</td>
<td>LGG (8), HGG (28), HC (12)</td>
<td>32 cortical seeds</td>
<td>Patients with supratentorial brain gliomas showed decreased long-distance connectivity with increased local efficiency and preserved small-world topology.</td>
</tr>
<tr>
<td>Harris et al. (2014)</td>
<td>WHO grade II gliomas (21), WHO grade III gliomas (14), WHO grade IV gliomas (33), HC (12)</td>
<td>DMN</td>
<td>Tumour location has an impact on connectivity: left parietal lobe tumours showed a more impaired DMN compared with tumours in the frontal lobe. Higher tumour grade along with prior surgery and/or treatment cause the largest reduction in DMN functional connectivity in patients with primary gliomas.</td>
</tr>
<tr>
<td>Huang et al. (2014)</td>
<td>LGG (12), HC (12)</td>
<td>Brain parcellation into 90 regions</td>
<td>Disturbed small-world networks in LGG patients might be responsible for the neurocognitive dysfunction of those patients.</td>
</tr>
<tr>
<td>Xu et al. (2013)</td>
<td>LGG (21), HC (20)</td>
<td>Brain parcellation into 90 regions</td>
<td>Compared with controls, LGG patients display disturbed small-world manner and decreased global efficiency. Global efficiency is positively correlated with IQ test scores in LGG patients. The right insula was identified as a major hub only in control group, while the right thalamus has emerged as a crucial potential hub in LGG group, implying that insula is one of the most vulnerable focal areas in LGG group.</td>
</tr>
<tr>
<td>Briganti et al. (2012)</td>
<td>Glioma (39 – grade NS), HC (12)</td>
<td>Language network</td>
<td>Global FC of the LN was significantly reduced in patients with tumour compared with controls. Specifically, FC was significantly reduced within seed regions of the affected hemisphere and between the TPJ of the 2 hemispheres. In patients, the left TPJ node showed the greatest decrease of FC within the LN.</td>
</tr>
<tr>
<td>Esposito et al. (2012)</td>
<td>WHO grade II (14) &amp; WHO grade IV (10) gliomas, HC (14)</td>
<td>DMN</td>
<td>Reduced DMN connectivity was detected in tumour patients comparing to controls and the modifications were closely related to tumour grading. DMN lateralized to the hemisphere contralateral to LGG but not to HGG.</td>
</tr>
<tr>
<td>Otten et al. (2012)</td>
<td>Diffuse astrocytoma (1), AA (3), GBM (9), astroglia (1), other (9)*, HC (22)</td>
<td>Motor network</td>
<td>Decrease interhemispheric connectivity between the primary motor cortices, as well as between the left PMC and the right premotor area. Reduced connectivity was observed in subjects with motor weakness versus subjects with normal strength.</td>
</tr>
<tr>
<td>Poláškov et al. (2012)</td>
<td>AA (1), GBM (2), other (11)*</td>
<td>DMN &amp; motor network</td>
<td>FC was often displaced but relatively preserved in patients without epilepsy. It was disrupted or absent in patients with epilepsy. Higher histologic grade astrocytomas demonstrated greater small worldliness than the lower grade gliomas, suggesting a less random and more organized pattern of intra-tumoural connectivity.</td>
</tr>
<tr>
<td>Whitlow and Maldjian (2012)</td>
<td>GBM (1), WHO grade II astrocytoma (1), oligo (2)</td>
<td>Correlation matrix between brain and tumour</td>
<td>Showed intra- and interhemispheric reorganization induced by LGG. There was a decrease in the intrahemispheric ipsilateral integration, while the infrahemispheric contralateral integration was preserved to a certain extent.</td>
</tr>
<tr>
<td>Marrelec et al. (2008)</td>
<td>LGG (6)</td>
<td>SMA, SMC, PMC</td>
<td>Patterns of FC remain intact in patients with focal cerebral lesions. Disruption of major neuronal networks, such as agensis of the corpus callosum, may diminish the normal FC patterns.</td>
</tr>
<tr>
<td>Quigley et al. (2001)</td>
<td>Oligo (1), other (11)*</td>
<td>Auditory, sensorimotor, and language networks</td>
<td></td>
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B. Tumour infiltration

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Pathology ( # of patients)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow et al. (2016)</td>
<td>GBM (14)</td>
<td>Disruption in vascular regulation induced by a GBM can be detected with BOLD fMRI; the spatial distribution of these disruptions is localized to the immediate vicinity of the tumour and peritumoural edema.</td>
</tr>
<tr>
<td>Agarwal et al. (2016a,b)</td>
<td>Oligo (1) and oligo (1)</td>
<td>Authors demonstrated evidence of NVU on ultra-high field 7T rs-fMRI comparable with the findings on standard 3T motor task-based fMRI. NVU can result in false negative BOLD signal changes on rs-fMRI comparable to previously published findings on standard motor tb-fMRI.</td>
</tr>
<tr>
<td>Agarwal et al. (2016a,b)</td>
<td>GBM (2), oligo (3), oligo (1), AA (1)</td>
<td>Compared with LGG, HGG had more complex anatomical morphology and BOLD-fMRI features in the tumour region. An SVM tumour grading classification model, using SK, fALFF and ReHo as features, has an sensitivity and specificity greater than 80.</td>
</tr>
<tr>
<td>Wu et al. (2015)</td>
<td>LGG (18), HGG (17)</td>
<td></td>
</tr>
</tbody>
</table>
**C. Functional Network Localization**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Pathology (of patients/healthy control (HC) (of subjects)</th>
<th>Networks analyzed</th>
<th>Motor and language</th>
<th>Post-operative outcome</th>
<th>Validated via</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatia et al. (2016)</td>
<td>HGG (1)</td>
<td>rs-fMRI</td>
<td>Motor and language</td>
<td>Post-operative outcome</td>
<td>rs-fMRI integrated with intraoperative neuronavigation software can provide an alternative option for functional cortical mapping in the setting of an aborted awake craniotomy.</td>
<td></td>
</tr>
<tr>
<td>Bush and Murakami (2015)</td>
<td>LGG (2), other (6)*</td>
<td>Language</td>
<td></td>
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</tr>
<tr>
<td>Cochraneau et al. (2016)</td>
<td>LGG (98)</td>
<td>ECS</td>
<td>Sensorimotor and language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorfer et al. (2014)</td>
<td>Low grade tumour (2-grade NS)</td>
<td>Primary motor area</td>
<td>ECS</td>
<td>rs-fMRI can be used for intraoperative neuronavigation in children showing a good correlation with ECS mapping.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foo et al. (2016)</td>
<td>Diffuse glioma (5), other (2)*</td>
<td>ECS</td>
<td></td>
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<tr>
<td>Kusumoto et al. (2014)</td>
<td>GBM (3), WHO grade III astrocytomas (3), WHO grade II astrocytomas (4), other (2)*</td>
<td>DMN</td>
<td></td>
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</tr>
<tr>
<td>Liu et al. (2009)</td>
<td>Oligodendroglioma (1), other (5)*</td>
<td>Motor cortex</td>
<td></td>
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</tr>
<tr>
<td>Mitchell et al. (2013)</td>
<td>Low-grade astrocytoma (3), astrocytoma (2), GBM (1), other (7)*</td>
<td>DMN, VAN, PPN</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Shapira et al. (2019)</td>
<td>Low-grade glioma (1), other (10)</td>
<td>DMN</td>
<td></td>
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</tr>
<tr>
<td>Zhu et al. (2016)</td>
<td>Glioma (8-grade NS), HC (243)</td>
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</table>

described distinct changes. Ghumman et al. found that tumours in the left hemisphere had a larger effect on “DMN connectivity regardless of their size and type, while this effect was not observed for right hemispheric tumors [...] suggesting that DMN connectivity in the left side of the brain may be more fragile to insults by lesions” (Ghumman et al., 2016). Maesawa et al. assessed the connectivity changes occurring in tumours localized in the left side of the brain, and observed connectivity changes also occurring in the contralateral side. Moreover, these changes correlated with different cognitive functions associated with DMN and executive control network such as attention, IQ, spatial and working memory indicating that “patients with gliomas may undergo cognitive changes even in the absence of or before the onset of major symptoms” (Maesawa et al., 2015). As such, different changes have been described to occur in the DMN in the setting of glioma that serve as routes for brain invasion, proliferation, and communication (Maesawa et al., 2015). As such, different changes have been described to occur in the DMN in the setting of glioma that serve as routes for brain invasion, proliferation, and communication (Maesawa et al., 2015). 

In summary, given the encouraging results obtained by the ICA decomposition of the resting-state networks and the good concordance between resting-state and task-based language and sensorimotor mapping, further research could propel the use of rs-fMRI as a complementary tool for presurgical mapping. Although the mapping of DMN seems to be quite reliable, further correlations with clinical symptoms and intra-operative testing would be necessary to demonstrate the clinical use of this approach. Additional large, prospective studies are required to delineate the optimal analysis method and the ability to replicate the results obtained through the gold standard intra-operative stimulation mapping.

5. Discussion

The current article provides a comprehensive review on the current rs-fMRI research performed for patients with gliomas (Table 1). As a dynamic hodotopical model of the network alterations occurring in the setting of gliomas can influence the management approach used for these patients, resting state brain network delineation and its correlation with structural anatomy and electrophysiology is one of the current priorities in neuro-oncology. Incorporating the rs-fMRI network assessments into the traditional glioma mapping approaches could prove to be a versatile method for preoperative localization of distinct functional networks for patients suffering from gliomas.

5.1. Untangling glioma’s pathophysiology

5.1.1. Brain network disruptions

Resting state functional connectivity MRI analysis has emerged as a versatile and broadly applicable approach to the modeling of brain function and for localizing neurological symptoms in the setting of a wide variety of brain lesions (Boes et al., 2015; Friston, 2009; Razi and Friston, 2016). Related to this, the concept of the brain connectome aims to map the complex dynamic networks that allow the efficient computation of different neural processes at multiple spatial and temporal scales (Bassett and Bullmore, 2009; Bassett and Sporns, 2017; Duffau, 2015b; van den Heuvel and Sporns, 2013). The functional reorganization that occurs within this intricate dynamic system can give new insights in the pathology of different disorders and opens the door to new therapeutic approaches (Duffau, 2015a,b,c). For an excellent review in this area, readers are referred to an article by Castellanos and colleagues who provide a comprehensive appraisal of the evidence and challenges of using resting-state based functional connectomics as a clinically meaningful biomarker in a wide variety of neurological and psychiatric disorders (Castellanos et al., 2013). As described by Duffau et al., the “hodological” framework attempts to characterize a dysfunction through the means of altered networks where there may be an increase in connectivity, a decrease, or a mixture of both (De Benedictis and Duffau, 2011).

Capturing the characteristics of the large-scale cortico-subcortical dynamical networks forming the human connectome could thus allow us to understand the physiology and functional consequences of glioma within this framework. While the structural connectivity typically reflects the white matter fiber bundles and thus the structural integrity of the brain, FC refers to the “temporal correlations or statistical dependences between observed neurophysiologic events in spatially remote brain areas” (Wang et al., 2015). Combining the structural-functional relationship with the clinical symptomatology allows a dynamic assimilation of the physical topological constraints with the functional network patterns across both local and global scales (Wang et al., 2015). A theoretical model for the diffuse network changes observed in the setting of gliomas is illustrated in Fig. 1.

The results of the studies described here provide preliminary evidence for the feasibility of such an approach but also demonstrate that much work remains to be done. In the setting of network alteration occurring in asymptomatic patients, Niu and all described a significant reduction in inter-hemispheric functional connectivity confirming the vulnerability of long-distance connections, especially the interhemispheric networks. As delineated in previous work related to network plasticity occurring in the setting of low-grade gliomas (Duffau, 2013a), intrinsic reorganization of brain networks may occur to allow functional compensation. As such the altered inter-hemispheric FC portrayed in different studies could either reflect tumour infiltration or “recruitment of compensating areas from the brain regions surrounding the slow-growing gliomas” (Niu et al., 2014). Conversely, Otten and colleagues obtained different results portraying a similar intrinsic architecture with strong interhemispheric functional connections between asymptomatic patients and control subjects as well as a higher mean connectivity in the tumour patients (Otten et al., 2012). The differences in results may stem from differences in methodology. Otten et al. included heterogeneous pathologies (gliomas, astrogliosis, ependymoma, lymphoma, metastatic tumours) whereas Niu had a more homogenous study population including only glioma cases. Furthermore, while all tumours included in the study of Niu et al. involved or were near the premotor cortex (PMC), no lesions in the dataset analyzed by Otten et al. directly affected the PMCs. The finding of greater mean connectivity in patients with brain tumours could also reflect the functional reorganization across networks with an initial increase in the brain connectivity as the brain adapts to the lesion growth. This would fit with a view of the brain as a dynamic collection of parallel sub-modules that can interact with each other, allowing them to compensate for loss in a particular area by shifting work to others (Duffau, 2014).

Identifying the functional and structural brain network disruptions occurring in the setting of gliomas represents a critical step allowing us to understand the glioma pathophysiology. The systematic review of the different approaches used in previous studies could incentivize the development of further standardization (e.g. eyes closed/open, awake/asleep) and optimization of rs-fMRI’s methodology. Furthermore, performing longitudinal studies outlining the network changes occurring over time throughout surgical and radiation therapies could also allow development of more personalized treatments.

5.1.2. Molecular mechanisms

In terms of the insights provided by rs-fMRI in glioma’s pathology, some researchers discussed here report an increase in the connectivity within the tumoural tissue (Whitlow and Maldjian, 2012) consistent with the hypothesis that the tumour creates an independent functional network of its own. This is further supported by recent studies performing in vivo imaging of glioma cell’s membrane tube development over time revealed that microtubule-connected tumour cells containing circulating mitochondria create a multicellular anatomical network that serves as routes for brain invasion, proliferation, and communication over long distances (Caino et al., 2016; Hoitzing et al., 2015; Osswald...
Regarding glioma infiltration demarcation, the studies assessing the BOLD changes occurring in the setting of gliomas portrayed evidence of decreased BOLD signal occurring in the regions ipsilateral to the tumour (Agarwal et al., 2016a,b), in the peritumoural area (Chow et al., 2016) as well as a higher degree of uniformity inside the tumour (Feldman et al., 2009). Another study using tb-fMRI by Feldman and colleagues hypothesized that the distinct BOLD features they observed could represent different oxygen consumption levels in the tumoural tissue comparing to the non-infiltrated brain (Feldman et al., 2009). Despite the fact that the study did not include haemodynamic data and had a low number of patients suffering from different pathologies, it represents the first study to depict distinct BOLD features occurring in the setting of tumours which could have a diagnostic value for tumour infiltration.

The concept of neurovascular decoupling was extensively reported in the literature and its occurrence has significant implications in terms of the reliability and accuracy of the results obtained through different imaging modalities (see Liu, 2013 for a review on the role of neurovascular coupling in rs-fMRI studies (Liu, 2013). Although the exact mechanism of coupling is not well elucidated, it was recently proposed that the increased level of pro-inflammatory cytokines could represent important mediators of neurovascular coupling.

For instance, intra-atrial interleukin-1β was reported to decouple cortical neuronal activity from the related haemodynamic response (Bray et al., 2016). It is known that the neuroinflammatory response occurring in the setting of a brain injury or stroke can worsen the extent of initial injury (Lozano et al., 2015). Likewise, in the setting of glioma there is compelling evidence that microglia – immune cells within the central nervous system – are involved in establishing an immunosuppressive microenvironment that favors glioma invasion (Hussain et al., 2006; Zhai et al., 2011).
As such, the decreased hemodynamic response and decoupling observed in the peritumoural area could reflect the distinct network profile of the glioma associated microglia. Similarly, the distinct BOLD profile observed over the tumoural area comparing to the macroscopically healthy tissue could reflect the underlying histologic and metabolic alterations intrinsic to tumour processes. Further delineation and association between the structural, metabolic and electrophysiological alterations could not only allow the establishment of distinct markers of tumour infiltration but also potentially allow the design of more effective treatment options based on individualised markers.

5.2. Clinical utility of rs-fMRI

In the setting of a connectome perspective with different dynamic interconnected networks, the optimal extent of brain tissue resection is sub-optimally delineated with the current approaches. Proponents of a more aggressive treatment approach suggest supra-total resection with extension of the resection beyond the macroscopically perceived radiological boundaries (Duffau, 2016; Duffau, 2012; Sanai and Berger, 2009), as this can lead to higher overall and progression-free (i.e., without tumour recurrence) survival rates (De Witt Hamer et al., 2012; Duffau, 2016; Duffau, 2015a; Meyer et al., 2001; Yordanova et al., 2011). Since the recurrence of high-grade gliomas usually occurs at the site of the original resection (Lemée et al., 2015; Petrecca et al., 2013), both neurosurgical resection and radiotherapy target extensive tissue beyond the tumoural tissue itself, denting into peritumoural tissue where the likelihood of infiltrating tumoural cells is the highest (Eidel et al., 2017; Tarapore et al., 2011). As such, techniques such as fluorescence guided tumour surgery with 5-aminolevulinic acid (5-ALA) has been used for a more extensive intraoperative visualization of malignant gliomas and was shown to increase overall and progression-free survival (Senders et al., 2017; Zhao et al., 2013).

However, a more extensive resection may include non-infiltrated functionally-relevant areas, whose resection can potentially cause new neurological impairments affecting the patients’ life quality. To avoid additional neurological impairments, neurosurgeons use techniques such as awake craniotomy and intra-operative mapping to localize and preserve the eloquent cortical areas and subcortical fibers (De Witt Hamer et al., 2012; Duffau, 2016, 2014; Duffau, 2015a; Gupta et al., 2007; Meyer et al., 2001; Saito et al., 2015; Yordanova et al., 2011). Nevertheless, the ongoing plasticity and functional network reorganization occurring in the setting of brain tumours is not yet integrated in the management approach. As such, the exact answer for the optimal extent of resection in the case of glial tumours is yet to be defined. Although it can be foreseeable that in the future, advanced computational methods such as deep learning algorithms could allow a more accurate prediction of the ensuing outcomes (neurological and oncological) by taking into account individualised factors such as tumour kinetics and network reorganization.

Besides identifying abnormal signatures of brain connectivity in patients with gliomas, several rs-fMRI studies also attempted to correlate the network disruption to the patient’s neurological status such as neuropsychological deficits. For instance, the degree of network perturbation such as global efficiency and small-worldness changes was correlated with the neurocognitive function (Bosma et al., 2009, 2008; Huang et al., 2014). Magnetoencephalography studies showed that a specific pattern of preoperative network disruption was able to predict neurocognitive outcome and that regions showing decreased coherence could be resected without inducing new deficits (Guggisberg et al., 2008; Martino et al., 2011). Also, preoperative disorganized networks displayed a more organized state in the postoperative state. Such attempts could provide new ways of delineating resection boundaries as a function of the anticipated neurological and cognitive consequences (Hart et al., 2016a).

As outlined by research teams utilizing different analysis approaches, the network changes occurring in the setting of glioma involve distinct local and global network changes (Table 2). Although the specific spatial pattern of distinct RSNs vary in the literature, several studies described well-defined sensorimotor and language networks based on rs-fMRI (Cochezereau et al., 2016; Mitchell et al., 2013; Tie et al., 2014). Based on these, some research groups have already attempted to create tools to ease the clinical implementation of rs-fMRI for surgical planning (Böttger et al., 2011; Chamberland et al., 2015).

Resting state fMRI measures and data driven approaches may also improve the ability of clinicians to delineate more accurately the degree of tumour infiltration. For instance, Feldman and colleagues analyzed voxels from the tumour and the macroscopically normal brain and found that the BOLD signals from all of the tumours were “significantly different from those in the surrounding normal tissue” (Feldman et al., 2009). Nonetheless, it is important to note that the study population included meningiomas, metastatic tumours and gliomas (six patients). Moreover, only two patients had both rs-fMRI and tb-fMRI (motor) and no statistical difference was found in the R value (ie, the correlation value that identified closely related voxels) between the two approaches.

In an attempt to merge structural and functional connectivity,
Chamberland et al. provided a novel approach to visualize tractography-driven resting-state functional connectivity based on data obtained from ten healthy patients and one patient with a grade III astrocytoma (Chamberland et al., 2015). Another case report described the use of rs-fMRI integrated with intraoperative neuronavigation in a case of an aborted awake craniotomy, outlining the possible clinical benefit of this modality in similar settings (Batra et al., 2016). Similarly, Böttger et al., developed an interactive visualization tool in order to facilitate the visualization of functional connectivity by neurosurgeons. Although the study did not concentrate on the changes occurring in the setting of glioma and included diverse pathologies, the proposed tool seemed to have a good usability and applicability for neurosurgeons. It must be mentioned though that although the use of rs-fMRI seemed to be successful for localization of the sensorimotor cortex, the language network failed to obtain consistent results (Böttger et al., 2011).

Furthermore, multiple studies attempting to correlate rs-fMRI with other techniques such as tb-fMRI reveal the current endeavor to optimize the inherent limitations of the available pre-surgical mapping techniques. Although tb-fMRI is increasingly used in the clinical setting to delineate eloquent regions pre-operatively, this method is mainly used clinically for mapping the motor and language regions, disregarding higher cognitive processes such as executive functions. It also requires the patient’s ability to cooperate reliably for the tasks. This may not be achievable in some patient populations, such as children or patients with significant neurological deficits, making rs-fMRI an excellent alternative for those cases. It may also be noted that task-based approaches, since they primarily aim at identifying eloquent functional areas, do not attempt to investigate other issues such as precise tumour localization or alterations in functional networks. These may be additional areas where rs-fMRI represents a superior alternative.

5.3. Limitations and future directions

Performing robust research with surgical groups presents a range of challenges. For the research described here there is the issue of considerable heterogeneity in the methods employed for resting-state data acquisition and analysis across studies. This makes direct comparison between results difficult. It may also be that some studies that one would wish to compare to others use sub-optimal scan parameters or analysis approaches, meaning that what is reported in them may not genuinely add to our overall understanding of glioma or the clinical applicability of rs-fMRI in that area. Compounding this issue is the heterogeneity in the patient populations included in different studies. This can be as a result of different tumour location, tumour type, patient age, and so on. Again, this makes comparing the results from different studies unreliable and may lead to the apparently conflicting findings of some studies.

Additional challenges relate to small sample sizes and the magnitude of differences in measures between groups. For instance, several studies report a significant difference in FC between healthy patients and controls using relatively small sample sizes (Ghumman et al., 2016; Maesawa et al., 2015; Zhang et al., 2016). Although statistical significance is achieved using appropriate statistical methods, it is important to remember that this is not necessarily synonymous with a practically significant difference. In order to be applied clinically, it must be possible to determine a threshold value that adequately separates glioma patients or brain voxels into clinically significant subgroups. This is challenging in cases where there are small absolute differences between groups and overlaps in membership due to individual variance. Improvements in scan sensitivity and the analysis methods applied have the potential to give greater specificity to measurements and the development of clear thresholds for separating groups.

The question of reliability is a key one in current science and inappropriately small sample sizes have been identified as a major contributor to problems on this front. A potential (partial) solution for some of these problems is the initiation of larger, multi-site projects with standardized scanning setups, set patient inclusion criteria, and robust approaches to confound control. Using such consistent data samples with hundreds rather than tens of patients we might be able to get a clearer answer to some of the questions highlighted in this review.

Additionally, FC analysis is prone to errors inferred by artefactual connections (Smith et al., 2011) and the limited number of observations available in rs-fMRI data can influence the estimations of statistical dependency between nodes. These issues could be partially addressed by different approaches such as regularization (Ryali et al., 2012) and non-parametric methods (Castellanos et al., 2013; Cox et al., 2017).

Furthermore, although the rs-fMRI pre-processing steps and analysis methods used by the papers addressed in this review (including ICA, seed based analysis and graph theory metrics) have been validated on healthy subjects, a direct translation to patients with gliomas might be questionable, especially in the setting of group analysis. For instance, group analysis techniques such as registration to a standard atlas might not always be feasible or reliable in the case of brain tumour patients and different techniques might be more appropriate. Similarly, the selection of nodes for analysis using parcellation methods based on anatomical features might be inaccurate in the setting of tumours given the functional plasticity occurring in this setting (Duffau, 2014; Ghinda and Duffau, 2017). The need to develop new techniques validated for brain tumours is thus imperative. Additionally, future research should include clinical variables and longitudinal data-collection in order to correlate the proposed image-based biomarkers to patient outcomes and prognosis. In summary, as eloquently detailed by Castellanos and colleagues, there is a need of “emerging conceptual, analytical and cultural innovations” (Castellanos et al., 2013) as well as open science initiatives for rs-fMRI based functional connectomics to lead to a clinically meaningful biomarker.

The localizationism concept, where the tumour was regarded as a mass that needs to be debulked, has been gradually replaced by a surgical strategy tailored to the particular structural and functional anatomy. The advent of functional MRI has allowed surgeons to acquire a pre-operative understanding of the plastic reorganization of the brain and to plan their surgical strategy accordingly. As discussed by Spena et al., in order to advance the field of neurosurgery for supratentorial gliomas (Spena et al., 2015) there is a pressing need to merge microsurgical techniques with novel functional mapping concepts. While intra-operative CSM represents the gold standard in terms of localization of function (Castellanos et al., 2013; Sahjpaul, 2000), this technique is not perfect given the potential of triggering intra-operative seizures and poor patient cooperation in the setting of pre-existing neurological and cognitive deficits (Castellanos et al., 2013; Nossek et al., 2012). Although in experienced centers those issues are not found to hinder the surgical intervention (Boetto et al., 2015; Duffau, 2013b), there also remains the potential of incorrect functional localization by “activating distant areas through corticocortical connections” (Sinaı et al., 2005).

It is conceivable that in the future, advanced computational models could predict if resecting infiltrated functional epicenters will produce a neurological deficit on an individual basis and whether the surgical resection should be limited to the functional limits imposed by intra-operative stimulation (Spena et al., 2015). The possibility to predict the functional recovery potential by taking into account possible compensating networks could only be imaginable through a systematic collection of large scale longitudinal multimodal datasets including clinical, radiological and electrophysiological modalities (Spena et al., 2015). Similar to large scale genomic datasets, multicenter anatomical functional data collections could have major implications both for the neurosurgery and neuroscience fields (Sarùbbo et al., 2015). The challenge will be to translate the advances achieved in network analysis to clinical practice through realistic models factoring the dynamic growth patterns of gliomas as well as the brain’s plasticity potential (Hart et al., 2016b).
6. Conclusion

Taken together, the various findings indicate a potential clinical utility of rs-fMRI for assessing the local and diffuse alterations occurring in the setting of glioma. The use of network measures to identify glioma and surgical related changes by correlating the patterns of network disruptions could provide new ways of delineating functional resection boundaries in light of anticipated neurological consequences. However, it should be mentioned that the different study designs, the variable analysis approaches and the diverse patient populations analyzed so far preclude any clear conclusions about the current use of rs-fMRI as a clinical biomarker. Future large systematic studies utilizing standardized rs-fMRI analysis methods may provide a more direct proof for the clinical use of rs-fMRI. Moreover, more detailed insights and correlations with the pathophysiological and molecular mechanisms of glioma are needed for developing specific diagnostic and therapeutic markers. It can be envisioned that future research may allow to model the dynamic interplay between the tumour, brain network plasticity and surgical intervention in order to tailor the extent of resection according to the potential of network reorganization and anticipated functional consequences.

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Appendix A. PRISMA Flow Diagram.

References


