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Why brain radiation therapy should take account of the individual structural and functional connectivity: toward an irradiation "à la carte"

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Running title: Brain radiation and neural connectivity

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Abbreviations:

AF: Arcuate fasciculus

IFOF: Inferior fronto-occipital fasciculus

LGG: Low-grade glioma

QoL: Quality of life

RT: Radiation therapy

WM: White matter

Abstract

Although radiation therapy (RT) is a main treatment of brain tumors, delayed cerebral toxicity may lead to cognitive deteriorations with adverse effects on quality of life. Despite technological advances in RT, the concept of brain connectome has not yet been incorporated in the strategy of irradiation. Because white matter tracts represent the main limitation of neuroplasticity, tumor surgery is increasingly performed with awake cortical-subcortical mapping. Here, the purpose is to reinforce the link between cognitive neurosciences and neurooncology, which is critical for neurosurgeons but also for medical oncologists, especially brain radiation oncologists. The goal is to optimize RT planning by sparing individual critical neural networks. A redefinition of "organs at risk" should be proposed, beyond the few structures (such as brainstem, optic pathway, pituitary gland, hippocampi) which are classically preserved for brain radiation, by considering the structural and functional connectivity in order to evolve toward a RT “à la carte”.

Key words: Brain connectome; Brain tumors; Neuroplasticity; Quality of life; Radiation therapy

1. Introduction

Radiation therapy (RT) is a cornerstone of medical treatment for primary and metastatic brain tumors, which represent a major public health problem. When feasible, maximal safe surgical resection must be considered before radiation, optionally combined with chemotherapy, in order to reduce the tumoral volume and to collect tissue for integrated histomolecular diagnosis (Louis et al., 2016). Elaboration of personalized therapeutic strategies based upon the combination of surgery, RT and chemotherapy has resulted in an increase of the overall survival (OS) in various brain neoplasms, such as low-grade gliomas (LGG) (Duffau and Tallandier, 2015), glioblastomas (Stupp et al., 2005) and metastasis (Fecci et al., 2019). Due to this prolonged OS, the goal is also to preserve the quality of life (QoL), or even to improve it, especially by controlling epilepsy which represents a frequent symptom in cerebral tumors. To optimize the benefit-to-risk ratio of surgery, surgical procedures are increasingly performed under the guidance of intraoperative mapping, which allows a maximization of the extent of resection while significantly minimizing the rate of permanent severe deficits, even for surgery in so-called eloquent structures (De Witt Hamer et al., 2012). To achieve functional-based resection, i.e., to pursue the tumor removal up to critical neural networks, understanding the organization of the brain is crucial for each patient. In fact, there is a considerable interindividual variability across human brains, with an increase of these variations due to mechanisms of neuroplasticity induced by the tumor (Duffau, 2005). This is particularly true in slow-growing neoplasm such as LGG, explaining why the patients have usually no or only mild deficits at diagnosis. However, although the plastic potential is high at the cortical level, it is limited at the level of the white matter (WM) tracts (Herbet et al., 2016a). Therefore, preservation of structural and functional connectivity by means of axonal mapping in awake patient is a priority in tumor surgery. The aim is to detect and spare the cortico-subcortical networks underpinning movement, language, visuopatial processing, cognitive functions (as semantics and executive control) as well as behavior (e.g. theory of mind), in order for the patient to enjoy an active familial, social and professional life (Duffau, 2015). Such an improved knowledge of the human connectome benefited from developments in the field of neurosciences, in particular with the rise of functional neuroimaging and the proposal of new connectomal models of cerebral organization, which are helpful to better understand brain disorders (van den Heuvel and Sporns, 2019). In this spirit, a dynamic anatomo-functional architecture based upon a meta-networking theory of brain functions has recently been proposed (Herbet and Duffau, 2020). This concept is founded on a perpetual succession of equilibrium states made possible thanks to transient modifications of relationship within and between delocalized large-scale neural circuits which mediate conation, cognition and emotion: this results in long-lasting changes of circuit properties, including use-dependent brain plasticity. In other words, neural processing cannot be conceived in a segregated view, with parallel networks acting in isolation: complex cognitions at the service of adaptive, context-specific behaviors emerge from spatiotemporal dynamic interactions across the specialized functional systems. Such an integration must be generated to succeed cognitive demanding, functionally multi-determined behavior tasks (Herbet and Duffau, 2020).

2. Radiation-induced cognitive impairment

In this context of improved oncological outcomes in brain tumor patients, with a prolonged life expectancy, a reappraisal of RT is crucial. Indeed, beyond acute radiation-induced cerebral injury, which is the most often transitory, delayed brain toxicity has been evidenced following radiation, leading to cognitive deteriorations with negative consequences on QoL. These late brain damages, characterized histopathologically by vascular abnormalities, demyelination, and ultimately WM necrosis (Schultheiss and Stephens, 1992; Greene-Schloesser et al., 2013), are classically seen more than 6 months post-irradiation, and are irreversible. In fact, despite the use of fractionated RT, radiation-induced cognitive decline has been observed in up to 90% of adult brain tumor patients who survive >6 months after RT (Brown et al., 2013). For instance, in long-term survivors with LGG, although patients who did not received RT had a stable cognitive examination, those with RT exhibited a progressive impairment in attention and executive functions, even for fraction doses that are traditionally considered safe (≤2 Gy) (Douw et al., 2009). Moreover, the risk of cognitive worsening is higher after whole-brain RT: indeed, cognitive disturbances are still noted in more than half of the patients who received fractionated whole brain irradiation (Meyers and Brown, 2006; Greene-Schloesser and Robbins, 2012). This resulted in the proposal of a reduction of volume of RT, made possible thanks to technical advances, which have allowed a more precise irradiation, such as sophisticated techniques of stereotactic radiosurgery, intensity-modulated radiotherapy, volumetric-modulated arc therapy or proton therapy (Scaringi et al., 2018). The principle became to irradiate the tumor more focally, in particular in case of residue after surgical resection, instead of achieving a more diffuse RT of the brain. Such a modulation of the strategy enabled a decrease of the cognitive disturbances, as demonstrated in cerebral metastasis, with a less frequent decline in neurocognition when administering postoperative radiosurgery rather than whole-brain RT (Brown et al., 2017).

3. The pivotal role of objective neurocognitive assessment before and after RT

The first lesson gained from these observations is that an objective neuropsychological evaluation must be achieved in a more systematic way before RT in order to benefit from a baseline neuropsychological testing, then at the end RT as well as several months/years (according to the pathology) following radiation. This is particularly true for patients with a long-life expectancy (e.g. with a LGG) to evaluate the long-term consequences of RT on cognition and QoL using longitudinal detailed neurocognitive assessments, as performed before and after surgery (Mandonnet et al., 2015) - with also evaluation of the return to work following surgical resection (Mandonnet et al., 2015; Ng et al., 2020). However, in recent trials, only a Mini-Mental State Examination has been used, namely, a task which was initially designed for patients with dementia (Buckner et al., 2016). The second lesson is that these neuropsychological scores should be correlated with neuroimaging, in particular Diffusion Tensor Imaging (DTI). Indeed, it has been proposed that imaging biomarkers of WM damage, e.g. early diffusivity changes within the cingulate WM, may lead to the elaboration of new predictive models of cognitive decline following radiation (Chapman et al., 2012; Tringale et al., 2019). Such a reasoning would be in line with recent findings in glioma patients, which revealed that tumoral infiltration of WM tracts may result in specific neurological deficits before any treatment - explaining why a baseline neuropsychological testing is crucial. For example, glioma diffusion within the right arcuate fasciculus (AF) has been correlated with disturbances of social cognition (Nakajima et al., 2018), invasion of the right cingulate with high-level mentalistic deficits (Herbet et al., 2014), invasion of the left inferior fronto-occipital fasciculus (IFOF) with deteriorations of verbal semantic processing (Almairac et al., 2015), or invasion of the right superior longitudinal fasciculus with visuo-spatial deficits (Liu et al., 2020).

In the same way, anatomo-functional correlations have been established thanks to intraoperative electrostimulation achieved in awake patients to map not only the critical cortical hubs but also the subcortical tracts (Duffau, 2015), resulting in the elaboration of functional atlas of white matter bundles (Sarrubo et al., 2015; Sarrubo et al., 2020) (Figure 1). For example, stimulation of the left and right IFOF elicited verbal and non-verbal semantic disorders, respectively (Duffau et al., 2005; Moritz-Gasser et al., 2013); stimulation of the left AF generated phonemic paraphasias (Duffau et al., 2014); stimulation of the left superior longitudinal fasciculus evoked articulatory disturbances (van Geemen et al., 2015); or stimulation of the fronto-striatal tract and frontal aslant tract induced initiation disorders (Kinoshita et al., 2015). Remarkably, intraoperative mapping and preservation of the structural and functional connectome have resulted in a dramatic decrease of the rate of permanent postsurgical deficits in glioma patients (Duffau, 2018).

Finally, after glioma surgical resection, detailed neuropsychological evaluations have shown that postoperative subtle cognitive deficits were related to injury of specific WM pathways, e.g., anomic aphasia associated with lesion of the left inferior longitudinal fasciculus (Herbet et al., 2016b) or deficit of mentalizing (theory of mind) associated with lesion of the right IFOF (Yordanova et al., 2017).

To sum up, because of a considerable interindividual anatomo-functional variability in glioma patients, due to mechanisms of neuroplasticity, the way in which structural disconnection may relate to functional connectivity changes seems highly variable (Duffau, 2017). On the other hand, the recent data detailed above have evidenced that a better knowledge of the anatomo-functional connectivity, already and successfully used in awake surgery for glioma patients, may currently be applied to the radiotherapy planning in order to preserve cognition.

4. Why the strategy of brain RT should integrate the structural and functional connectivity

It is worth noting that RT has started to spare specific neural structures, especially the optic pathway and the hippocampus to preserve memory (Gondi et al., 2014; Kim et al., 2018). Nonetheless, despite these technological refinements, it must be acknowledged that the new concepts regarding the brain connectome have not yet been incorporated in the strategy of irradiation – contrary to the surgical management of brain tumor patients. In other words, RT should take account of the structural and functional connectivity, by modulating the radiotherapy treatment planning with the goal to decrease the risk to generate a disabling deficit depending on the neural networks incorporated in the radiation field. Furthermore, the neuroplastic potential should also be taken into account, by considering the lower potential of functional reorganization at the level of the subcortical WM pathways rather than at the cortical level. This might explain why a recent analysis within the EORTC 22033 clinical trial reported that the hippocampus normal tissue complication probability model did not perform as expected to predict cognitive decline based on dose to 40% of the bilateral hippocampus: indeed, WM connectivity has not been investigated in this study (Jaspers et al., 2019). This is a crucial issue because one of the major mechanisms of radiation-brain injury is WM degeneration (Greene-Schloesser and Robbins, 2012; Greene-Schloesser et al., 2013). Additionally, if a maximal surgical resection has previously been performed until functional boundaries, by definition, this means that the residual tumor which should be irradiated involves the most eloquent (non-compensable) cerebral structures. Thus, the paradox is that the risk of RT could be similar or even higher, despite technological advances enabling a smaller volume of irradiation, because radiation will be delivered on more critical networks with a less potential of recovery.

As mentioned, beyond inhibition of hippocampal neurogenesis, radiation-induced cognitive impairment is mainly related to WM tracts damages (Greene-Schloesser et al., 2013; Szerlip et al., 2011). For example, using longitudinal DTI achieved before, during and after partial brain RT for cerebral tumors, changes in radial and axial diffusivity have been observed, which correspond to demyelination and axonal degeneration, respectively (Hope et al., 2015; Chapman et al., 2016; Zhu et al., 2016). Moreover, by combining these DTI data to neurocognitive assessments, in a multivariate model, increasing radial diffusivity at the end of RT significantly predicted decline in verbal fluency 18 months following radiation (Chapman et al., 2016). In the same spirit, Ding et al. (2018) have noted that focal RT of the temporal lobe may induce loss of functional connectivity due to progressive disruption to the integrity of the WM tracts, which became significant one year after radiation. These recent findings show that despite methodological advances in RT technology, even focal irradiation can lead to brain structural and functional injury, in particular concerning the subcortical connectivity. Furthermore, regional differences in sensitivity to WM damage after brain RT have been described, especially with a higher susceptibility at the level of the corpus callosum, cingulum bundle or fornix (Connor et al., 2017). In a cognitive perspective, such results should be correlated with the recent probabilistic maps of neuroplastic limitations, mainly represented by axonal pathways (Herbet et al., 2016a; Ius et al., 2011).

5. How to apply the better understanding of brain connectome for RT

The original findings gained from intrasurgical electrostimulation mapping have permitted the elaboration of new atlases of functional anatomy of cortical areas (Tate et al., 2014) and subcortical WM tracts (Sarubbo et al., 2015) (Figure 1), especially with regard to critical neural networks (Sarubbo et al., 2020), as well as atlases of potentials and limitations of brain plasticity (Herbet et al., 2016a; Ius et al., 2011) (Figure 2). Although such data are currently correlated with the preoperative results of neuropsychological assessments and functional neuroimaging examinations for each patient with brain tumor, with the aim to tailor the surgical planning and to improve both functional and oncological outcomes (Duffau, 2018; Sanai and Berger, 2018), it is puzzling to note that this increasing knowledge of the structural and functional connectome is not yet incorporated in the RT treatment planning. In fact, technological advances in cerebral radiation will not be sufficient to preserve high-order cognitive functions without a perfect understanding of the anatomo-functional organization of brain processing at the individual level. This knowledge of the interactions between neural networks may allow to predict to what extend functional compensation is possible after RT, on the condition that critical (non-compensable) structures are spared - as it has already been performed for surgical resection. According to this prediction, RT planning could be modulated by adapting crucial parameters such as the radiation timing – in particular by deferring RT as recently proposed in subgroups of LGG according to the 1p19q status (Rudà et al., 2019; Wahl et al., 2017) or MGMT methylation score (Bady et al., 2018) – the fractionation, doses and their distribution taking account of the regional susceptibility, as well as the target volume delineation based not only on the tumor boundaries visible on imaging but also on the structural-functional connectivity and limitation of plastic potential in a given patient at this moment. Therefore, an extensive discussion with the patient and his/her family is essential to tailor the therapeutic strategy according to his/her needs, based on the lifestyle (including job, hobbies, etc) (Duffau and Taillandier, 2015). Because this principle has previously been incorporated in the surgical planning, especially with elaboration for each patient of a "mapping à la carte", it would not be logical to preserve during surgery the functional pathways critical to return to a normal life (as defined by the patient himself/herself), but to perform subsequently a postoperative RT which does not take account of the neural connectivity. On the other hand, because preservation of the functional connectome could result in less optimal oncological outcomes, the choice of the treatment attitude should be given to the patient, based on the definition of his/her own “onco-functional balance” (Mandonnet and Duffau, 2018). It is worth noting that this is already done in surgery, especially by incorporating further cognitive tasks (or not) during awake surgery

(Duffau and Mandonnet, 2013): the question is to know why such as “RT à la carte” it is not (yet) proposed to the patients in a systematic way.

6. Conclusion

To conclude, in the era of development of cognitive neurosciences, stronger links should be created between the fields of human connectomics and neurooncology, not only for neurosurgeons but also for neuro-oncologists, especially brain radiation oncologists. The ultimate goal is to optimize RT planning, not seen in isolation but integrated in a global therapeutic management, by proposing to brain tumor patients to spare individual critical neural networks (as already done for surgical resection) in order to preserve long-term QoL and then to optimize the onco-functional balance. To this end, it is time to evolve towards a redefinition of "organs at risk", beyond the few structures (as the brainstem, optic nerves and chiasm, pituitary gland and hippocampi) which are classically preserved for brain radiation in clinical routine (Scoccianti et al., 2015), that is, to consider the individual structural and functional connectome as well as its potentials and limitations of neuroplasticity. Following the example of “atlas of functional resectability” previously elaborated for glioma surgery (Ius et al., 2011), the purpose would be to build an “atlas of functional irradiation” based on the cognitive-structural correlations which should be more systematically and accurately studied in patients treated with RT.

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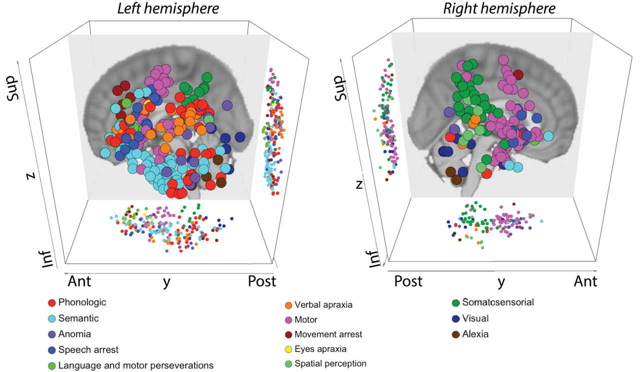
Figure Legends

Figure 1

Functional atlas of human white matter, with 3D representation of functional response errors collected during subcortical direct electrical stimulation in the left and right hemispheres. Different colors represent the different functional response errors. The small colored points represent the projections of functional response errors on the *x*–*y* and *x*–*z* planes of the Montreal Neurological Institute space (from Sarubbo et al., 2015).

Figure 2

Functional plasticity atlas of the human brain. Red indicates a low functional compensation index with a low level of confidence; purple indicates a low plasticity index with a high level of confidence; blue indicates a high functional compensation index with a high level of confidence; and black indicates a high functional compensation index with a low level of confidence (from Herbet et al., 2016a).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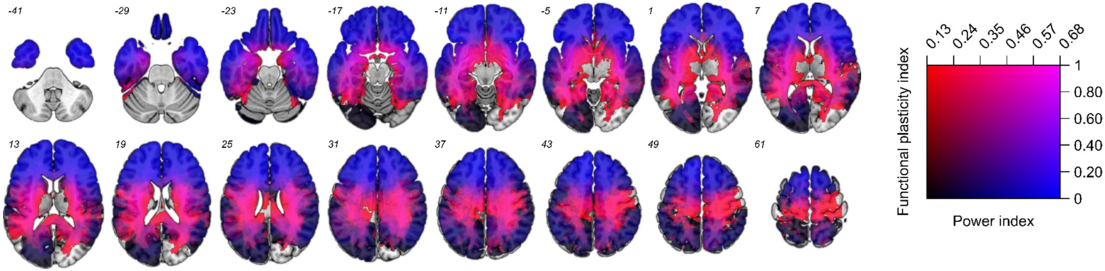
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