BRAIN
SCIENTIFIC COMMENTARY

Cancer meets neuroscience: the association between glioma occurrence and intrinsic brain features

This scientific commentary refers to 'Transcriptomic and connectomic correlates of differential spatial patterning among gliomas' by Romero-Garcia *et al*. (https://doi.org/10.1093/brain/awac378)

Gliomas are a deadly and relatively poorly understood form of brain cancer. Different subtypes of glioma are associated with distinct prognostic profiles, both in terms of survival as well as (cognitive) function, and are amenable to different treatment strategies. This renders glioma a complex disease to understand and treat. In addition, different glioma subtypes show distinct spatial profiles of occurrence: lower grade, slower growing gliomas seem to occur more frequently in frontal areas, whereas more malignant, faster growing tumours are often found in temporal-parietal areas. However, exactly what causes glial cells to become neoplastic, and why this occurs in one brain region rather than another, is unclear. In this issue of *Brain*, Romero-Garcia and colleagues[1] show that the preferential occurrence of low versus high grade glioma is associated with distinct regional transcriptomic features and brain connectomic characteristics in normative populations.

The study uses publicly available datasets to build on recent literature showing extensive communication between glioma cells and the supposedly healthy cells surrounding the tumour. Preclinical research in this new field of 'cancer neuroscience' has uncovered direct neuroglioma synapses,[2] and a host of indirect cross-talk mechanisms between peritumoural neurons and glioma cells.[3] Put simply, higher brain activity leads to faster tumour growth, and tumour presence increases brain activity, in a bidirectional manner. This insight is obviously worrisome and may have implications for our understanding of glioma symptomatology: pathological and non-pathological features of the non-invaded cortex may constitute both cause and effect in the relationship between brain and tumour. At the same time, gaining insight into the ways in which brain–tumour cross-talk impacts both tumour growth and brain function could lead to new treatment strategies, be it in terms of inhibiting tumour progression or better preserving cognitive function and quality of life.

The first steps in this direction have been taken: translational work using electrocorticography (ECoG) acquired during tumour resection has shown that brain activity around the tumour is higher than in normal-appearing brain regions.[3] Moreover, non-invasive measurement of brain activity with magnetoencephalography (MEG) has revealed that patients with greater brain activity have significantly shorter (progression-free) survival, even after adjusting for known predictors such as tumour subtype and age.[4] Importantly, the predictive value of brain activity for survival is similar between peritumoural activity and global brain activity, underlining the involvement of non-tumour-invaded cortex well beyond peritumoural cells. This 'rest of the brain' had previously been viewed as largely on the receiving end of the deleterious effects of glioma, rather than as having an active role in tumour growth. However, a large body of literature has linked glioma symptomatology to the activity and functional connectivity, operationalized as synchronized patterns of activity between different brain areas, of the non-tumour-infiltrated cortex. Glioma patients show whole-brain differences in their functional connectivity networks as compared to healthy controls, with different tumour subtypes showing distinct network profiles. Overall, lower global integration and efficiency of the functional network as well as higher local connectivity and potentially pathological clustering of connectivity relate to poorer cognitive functioning in these patients.

In light of the role that neural features play in tumour progression and, potentially, in the cognitive impact of glioma, the fundamental question of how premorbid brain features contribute to tumour development is relevant both for determining the trajectory of the disease as well as its effects on function. Regional variations in healthy brain activity, as measured with MEG, go hand-in-hand with preferential tumour occurrence: gliomas more often occur in cortical regions with higher intrinsic brain activity.[5] Moreover, variations in regional network connectivity within healthy brains associate with differences in tumour incidence: areas with greater local and integrative connectivity are more vulnerable to glioma.[6,7] Combined, these studies suggest that intrinsic, potentially premorbid regional network characteristics may contribute to the occurrence of glioma.

To better understand how intrinsic brain features influence tumour occurrence, it is important to delineate how the occurrence of distinct tumour subtypes differs according to these features. Analyses show that intrinsic brain activity is most strongly associated with occurrence of the more malignant isocitrate dehydrogenase (IDH)-mutant glioblastoma, but correlations are present for each tumour subtype, suggesting that higher brain activity is a rather non-specific correlate of tumour occurrence. Romero-Garcia and colleagues[5] now use a sophisticated method to first identify transcriptomic alterations in gliomas of different

Received January 24, 2023. Accepted January 24, 2023. Advance access publication February 3, 2023

malignancy grades. They then link these differentially expressed genes to intrinsic regional transcriptomic variations in normative healthy control data. The results show that low versus high grade glioma occurrence correlates with intrinsic variations in the expression of tumour subtype-relevant genes. Similarly, occurrence across grades differs in terms of regional network feature correlations: low-grade (and IDH-mutant) glioma occurrence relates to regional connectivity strength, whereas high-grade (and IDH-wildtype) gliomas localize more often to regions intrinsically characterized by higher integrative connectivity. These findings suggest that the vulnerability of brain regions to glioma relates more specifically to their intrinsic network features than to levels of activity. It would be interesting to learn how other molecular subtypes of glioma behave in terms of a predilection for brain regions with specific transcriptomic and connectomic regional vulnerability. This is all the more relevant since 1p/19q codeleted gliomas are characterized by much less, if any, cross-talk between neurons and glioma cells.[2,3]

An important next question in this field is: how can we determine individual tumour and patient trajectories? One way to do so is by extracting a snapshot of intrinsic brain features in the regions invaded by tumour in individual patients.[5] This approach has revealed relationships between intrinsic brain activity at individual tumour locations and both tumour subtype and Karnofsky performance status across patients, indicating that intrinsic regional features of the brain are not only relevant for group-level associations. It has also yielded more insights into functional network differences between patients: although glioma preferentially occurs in regions with high clustering, patients with a tumour in regions characterized by intrinsically low clustering show pathologically high whole-brain clustering at diagnosis.[6] So although generally less vulnerable to glioma, regions with intrinsically low clustering that harbour a tumour associate with more extensive differences in global network function versus controls. Age also seems to play a role here, since patients with pathologically high global clustering are younger than patients with normal clustering. How other factors, such as glioma subtype and transcriptomic features, relate to this complex relationship remains to be seen, particularly in light of the work by Romero-Garcia and colleagues.[1]

Patient functioning in terms of performance status and cognitive deficits may thus depend on a complex interplay between intrinsic, tumour-related, and patient-specific brain features. Indeed, lesion-network mapping, where lesions are overlaid with normative functional network data in order to better explain cognitive deficits, has so far not yielded the same promising results in glioma as in other types of lesional brain disease.[8] Here, the interplay between regional vulnerability and network plasticity may prove of importance. Moreover, intraoperative recordings have revealed that even in the context of normal task-related brain activity in terms of amplitude, the network encoding potential of the

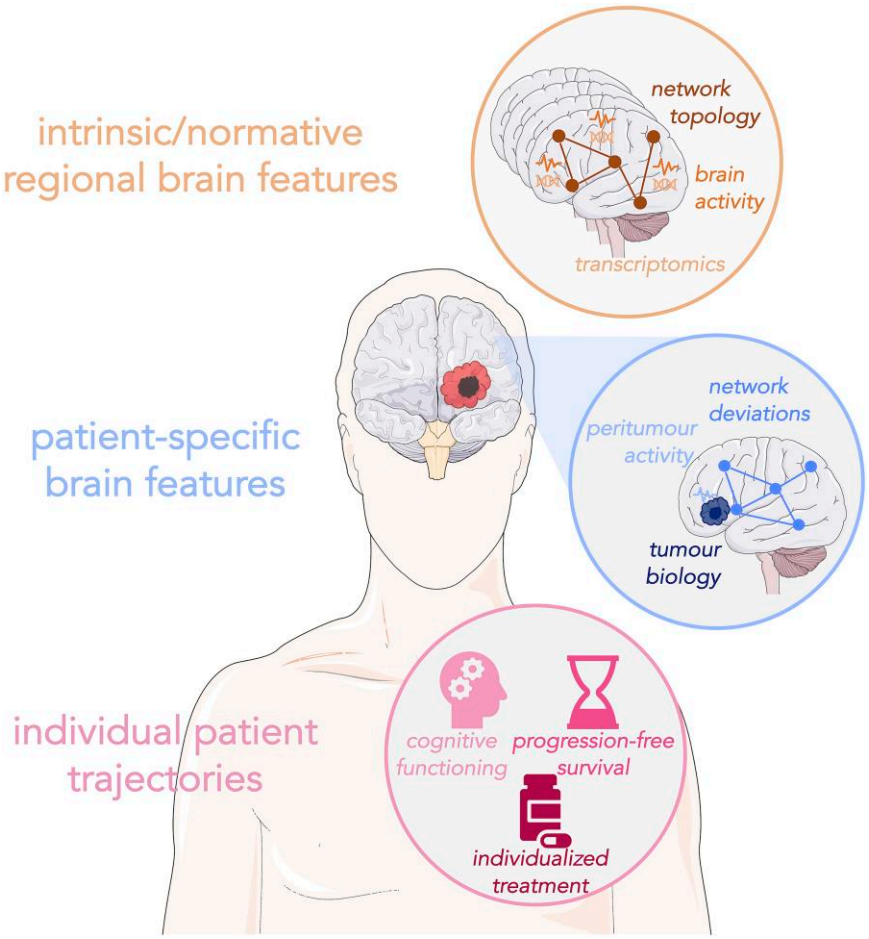

Figure 1 Integrating normative data with patient-specific brain features may provide insights into disease trajectories of glioma in individual patients. Parts of this figure were created using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

peritumoural region may be low.[9] Interestingly, recent work shows a generally positive group-level relationship between regional brain activity and both local and integrative connectivity in healthy controls and patients. However, within-subject analyses reveal that pathologically high brain activity of non-tumour-invaded regions in glioma patients correlates with very low local connectivity, while normal brain activity associates with very high local clustering.[10] These associations do not depend on the extent of pathological peritumoural activity, supporting the idea that network topology and dynamics may show differential trajectories across glioma patients.

In conclusion, combining normative data and patient-specific information may lead to better understanding of disease trajectories in terms of tumour growth and cognitive deficits (Fig. 1). Hypothetically, gliomas that occur in regions premorbidly characterized by high activity levels, by patterns of gene expression associated with more malignant tumours, and by high local and particularly integrative connectivity, may show faster growth, and the functional network may show less plasticity. Cognitive deficits in individual patients may thus be more specific to local disruptions at the tumour location and more comparable to the impact of acute lesions. Conversely, gliomas that occur in regions intrinsically marked by low activity, low grade glioma-specific gene expression, and low connectivity may show slower growth and the functional network may show greater plasticity. Cognitive functioning may either already be impaired, or may be preserved by means of plasticity or compensation. Future work using the elegant normative data approach that Romero-Garcia and colleagues describe, integrated with patient-specific data on transcriptomics, activity, connectomics and cognition, could be the next frontier within the field of cancer neuroscience.

Linda Douw, Lucas C. Breedt and Mona L. M. Zimmermann
Department of Anatomy and Neurosciences, Amsterdam Neuroscience, Cancer Center Amsterdam, Amsterdam University Medical Centers location Vrije Universiteit Amsterdam, 1081 HV Amsterdam, The Netherlands

Correspondence to: Linda Douw
E-mail: l.douw@amsterdamumc.nl

Funding

L.D. and L.C.B. are (partially) funded by the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO Vidi 198.015), M.L.M.Z. is funded by KWF Kankerbestrijding.

Competing interests

The authors report no competing interests.

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