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Central Nervous System Plasticity Influences Language and Cognitive Recovery in Adult Glioma

Gliomas exist within the framework of complex neuronal circuitry in which network dynamics influence both tumor biology and cognition. The generalized impairment of cognition or loss of language function is a common occurrence for glioma patients. The interface between intrinsic brain tumors such as gliomas and functional cognitive networks are poorly understood. The ability to communicate effectively is critically important for receiving oncological therapies and maintaining a high quality of life. Although the propensity of gliomas to infiltrate cortical and subcortical structures and disrupt key anatomic language pathways is well documented, there is new evidence offering insight into the network and cellular mechanisms underpinning glioma-related aphasia and aphasia recovery. In this review, we will outline the current understanding of the mechanisms of cognitive dysfunction and recovery, using aphasia as an illustrative model.

KEY WORDS: Language, Aphasia, Glioma, Cognition, Neurogenesis, Radiation, Plasticity

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Gliomas make up the majority of primary intrinsic brain tumors.[1,2] Molecular characterization and epidemiology studies have greatly enhanced our understanding of molecular drivers of progression with implications for overall and progression-free survival.[3-5] However, the truth remains that gliomas exist within the framework of complex neuronal circuitry in which network dynamics both influence tumor biology and impact cognition. Cognitive dysfunction, such as aphasia (or the generalized loss of language function and communication), is a widely observed occurrence for glioma patients.[6,7] Globally, the interactions between intrinsic brain tumors, such as gliomas, and functional cognitive networks are poorly understood. Aphasia, therefore, in addition to having a profound impact on an individual's health-related quality of life, also serves as an excellent model for understanding glioma-related cognitive dysfunction in a broader sense.[8]

ABBREVIATIONS: AF, arcuate fasciculus; **ApoE,** apolipoprotein E; **BDNF,** brain-derived neurotrophic factor; **CNS,** central nervous system; **COMT,** catechol-O-methyltransferase; **DA,** dopamine; **DCS,** direct cortical stimulation; **DTI,** diffusion tensor imaging; **IDH,** isocitrate dehydrogenase; **LGG,** low-grade gliomas; **MRI,** magnetic resonance imaging; **OPC,** oligodendrocyte precursor cells; **PFC,** prefrontal cortex; **SNPs,** single nucleotide polymorphisms

Classically, language processing is thought to occur through dorsal and ventral streams along the dominant hemisphere perisylvian network.[9,10] Glioma-related aphasia is thought to occur in the setting of three clinical occurrences: (1) infiltration of low- and high-grade gliomas into cortical and subcortical structures, (2) lesions created during cytoreduction surgery, or (3) through therapeutic interventions such as brain irradiation. Anatomic considerations alone do not fully account for aphasia or aphasia recovery. Interestingly, multiple studies have revealed normal language performance in patients with low- and high-grade glioma within dominant hemisphere language areas. Therefore, cortical regions presumed to contain populations of neurons responsible for motor speech initiation (Broca's area) or language comprehension (Wernicke's area) may not be static or may be variably positioned in the setting of adult glioma.[11] Absence of language impairments when gliomas invade anatomic structures subserving behavior has been attributed to glioma-induced neural network plasticity. It is believed that language homologue areas in the

contralateral hemisphere or language-eloquent networks in the peritumoral area undergo neuroplastic reorganization and take over the function of damaged components of language cortex in the affected hemisphere.[12,13]

The physiological underpinning of language processing in adults has been characterized by ablative lesions defined by vascular territories following stroke.[14] The study of cognition, particularly language in adult glioma patients, has permitted a broader understanding of language processing and recovery. The ability to communicate in an unhindered fashion remains a potent predictor of social, emotional, and psychological well-being.[15] Although the propensity of gliomas to infiltrate cortical and subcortical structures and disrupt key anatomic language pathways is well documented, there is new evidence offering insight into the network and cellular mechanisms underpinning glioma-related aphasia and aphasia recovery, which we will highlight in this review. We begin by outlining the current understanding of the mechanisms of cognitive dysfunction using aphasia as an illustrative model. We then describe potential contributing sources of cognitive recovery, describing both macroscopic level network dynamics and potential cellular mechanisms leading to clinical recovery. A working understanding of these interactions are important as neurosurgeons make critical decisions about patient selection and surgical goals at both initial diagnosis and the point of recurrence.

MECHANISMS OF APHASIA IN ADULT GLIOMA

For several decades, the field of language neurobiology was dominated by the classic model of language processing in which cortical structures, namely Broca's and Wernicke's areas and arcuate fasciculus (AF), which connects these 2 brain regions, were considered to be predominantly responsible for language production and comprehension.[16,17] However, this localizationist view of language organization was limited in explaining all phonological, syntactic, and lexical disorders.[16,18] Voxel lesion mapping and functional imaging studies in patients with aphasia uncovered numerous cortical and subcortical regions, including the anterior superior temporal lobe, middle temporal gyrus, inferior parietal lobe, insula, and basal ganglia. These data confirmed the importance of structures outside of the canonical Broca's and Wernicke's areas. Normal language processing requires a large-scale neural network spanning cortical and subcortical regions and their interconnecting pathways, including both active and latent components.[18-20] A contemporary model thereby employs dual-stream models of language processing which incorporates language-relevant cortico-subcortical structures and their interconnecting white matter fiber tracts.[9,21-23]

With a reported prevalence of 8% to 48%, aphasia is one of the most prominent neurological impairments in the setting of glioma.[24] Transient aphasias, which are commonly reported during the immediate postoperative period, range from 17% to 100%.[25] When gliomas are situated within the dominant hemisphere perisylvian language network of the frontal-parietal-temporal-insular lobes, normal language processing may be disrupted (Figure 1). Unlike stroke models of aphasia, glioma-related aphasia may change at times, mirroring the disease trajectory. The result of these distinct yet overlapping forces creates a longitudinal picture of aphasia which fluctuates, including periods of symptom-free time, alternating with phases of increased symptom burden (Figure 2).

Aphasia Resulting From Glioma Infiltration Into Cortical and Subcortical Structures

Tumor proliferation may disrupt essential pathways for language processing. Diffusion tensor imaging (DTI) has been widely used as a noninvasive imaging tool to study brain white matter microstructure and to provide valuable information regarding glioma proximity to subcortical white matter structures.[26,27] Using DTI tractography, Ormond et al[28] studied the impact of gliomas on white matter integrity and showed large-scale white matter alterations characterized by edema, degradation, and demyelination of language tract irrespective of the tumor grade. Altered white matter fiber tract density, which was characterized by a 2-fold decrease in the absolute number of AF fibers, was observed in glioma patients who developed transient aphasia.[29]

Furthermore, tumor invasion may interface with language tracts in three distinct patterns: (1) infiltration, (2) disruption, and (3) displacement of fiber tracts.[30] It is possible that a combination of all 3 processes may manifest in any individual patient. The underlying reason behind why gliomas cause varied alterations of the state of the white matter tracts remains unknown; however, as published by Witwer et al,[30] it is thought to depend on WHO grade, molecular subclassification, and location.[31-33] Depending upon the proximity of the tumor lesion to the eloquent cortex, glioma patients can exhibit aphasia as early as the time of initial diagnosis[34,35] or the point of progression.[36] Both low- and high-grade gliomas, in addition to surrounding peritumoral structures, exhibit neuronal activity during language task performance, and it remains unknown whether this physiology is due to maintained intratumoral astrocyte-neuron connections or if glioma-neuron interactions contribute to language network connectivity (Figure 1).

Aphasia Resulting From Cytoreduction Surgery

The impact of glioma proliferation on language and cognition may occur slowly over the course of months to years, depending on the glioma grade and extent of language network disruption. In contrast, glioma resection by itself can instantaneously impact outcomes. Intraoperative cortical and subcortical functional mapping remains the gold standard intraoperative technique to identify essential language sites. Importantly, direct cortical stimulation (DCS) causes a brief reversible lesion, thereby interrupting network processing during intraoperative mapping. DCS

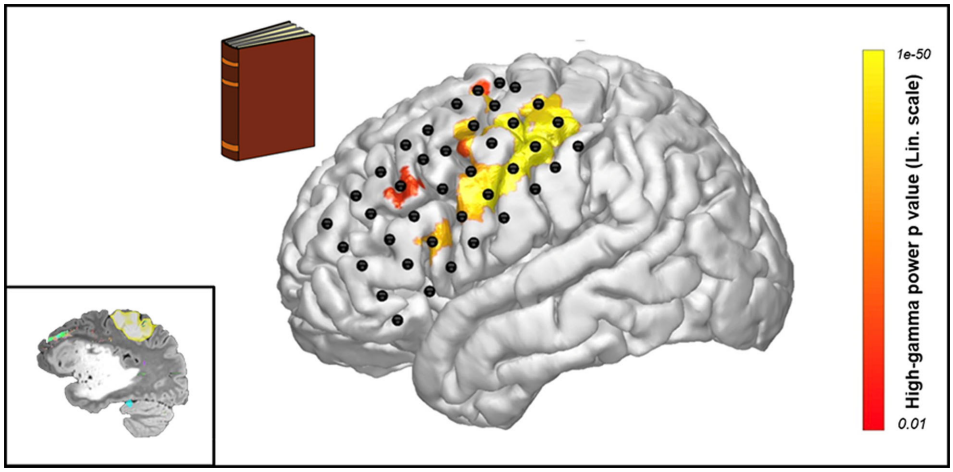

FIGURE 1. *Illustrative case of electrocorticography during picture naming for a 46-yr-old right-handed patient with isocitrate dehydrogenase (IDH)-wildtype WHO II astrocytoma reveals increased high gamma signal indicative of neuronal activity (yellow voxels) within the tumor 300 milliseconds prior to speech onset, illustrating that a subpopulation of cells within diffuse gliomas may contribute to language network processing.*

may elicit a multitude of transient language alterations, such as dysphasia, aphasia, dysarthria, and phonological paraphasias.[16] Several reports have illustrated immediate and short-term postoperative language outcomes; however, the published incidence is dependent on one's definition of aphasia.[37,38] Through these data, we now know that most patients will experience transient language impairments following surgical resection, and the long-term rate of aphasia following surgery remains low.[11,39-42]

Despite mapping, it remains possible that language sites can go undetected and removal of this tissue could result in poor outcomes.[7] This is particularly true when surgery involves subcortical white matter structures or violates accessory functional language pathways.[43] Compared to cortical structures in which neuron-glial interactions are dynamic, reorganization within white matter is likely limited.[43,44] Specifically, injury to the temporal parietal portion of the superior longitudinal fasciculus and AF results in severe language impairments.[44] The use of subcortical language mapping during glioma surgery assists in the identification of relevant dorsal and ventral language tracts.[45,46] Moreover, the identification of subcortical language sites through mapping may predict long-term language impairment in glioma patients.[44,46]

Aphasia Resulting From Brain Irradiation and Chemotherapy

Language and cognitive deficits are commonly reported as a consequence of radiation treatment administered in patients with both low- and high-grade gliomas (Figure 2).[47,48] Therapeutic radiation with a total dose of ≤60 Gray (Gy) has yielded longer survival in glioma patients.[49-51] However, the beneficial effect of radiation[49] must be balanced with a higher risk of developing late delayed cognitive and language declines.[50,52] The same may be true for patients with brain metastases, as Kerklaan et al[53] reported neurological impairments, including aphasia, in patients who underwent focal brain radiation for high-grade gliomas or with whole-brain radiation therapy for brain metastases.

The cellular mechanisms leading to postradiation cognitive decline are not completely understood. It is, however, known that decreases in fractional anisotropy (DTI-derived index of white matter integrity) are associated with cognitive impairment and are commonly identified in pediatric brain tumor survivors who received radiation treatment. Brain irradiation is thought to impact language and cognition through disruption of existing white matter tracts, as well as impairment of oligodendrocyte precursor cells (OPCs).[54-58] Although not conclusive, white matter necrosis associated with depletion of oligodendrocytes or their precursors, as well as impaired neurogenesis in the subgranular zone of dentate gyrus, accounts for the deleterious effects of radiation on cognitive outcomes.[59,60]

Similar to radiation-induced toxic effects, research from a wide range of preclinical and clinical studies has reported chemotherapy-induced white matter dysfunction and related cognitive changes and impairment.[48,61-63] Mechanistically, glial dysregulation, and defective myelination characterized by microglial and astrocyte activation, as well as incomplete differentiation and depletion of white matter OPCs, underlies the observed cognitive impairments following exposure to the common chemotherapy drug methotrexate in mouse models of cancer.[63,64]

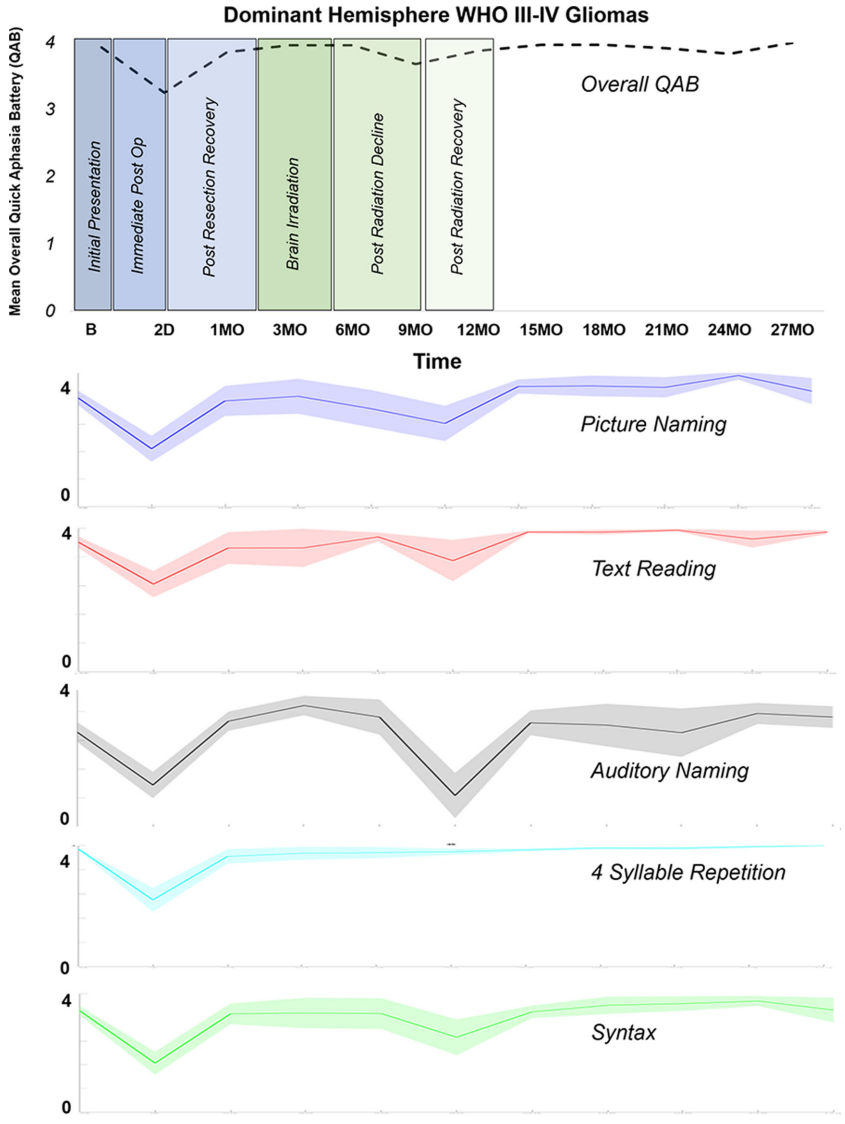

FIGURE 2. *Group level statistics for overall language task performance (QAB- Quick Aphasia Battery) for patients with newly diagnosed WHO III-IV gliomas from the point of diagnosis denoted by B (baseline) throughout first 27 mo of treatment (n = 43). Overall QAB is influenced by stage of oncological treatment including initial diagnosis, immediate postoperative period, postresection recovery, initiation of brain irradiation, and postradiation decline followed by postradiation recovery. Individual tasks include picture naming, text reading, auditory naming, 4 syllable repetition, and syntax task performance, which fluctuates throughout stages of treatment (shaded outline is standard error). Note, a score of 4 on the QAB assessment is a correct answer; a score of 3 is an answer that is correct but is delayed >3 s or self-corrected; a score of 2 equals an answer in which at least half of the phonemes are correct; a score of 1 equals an answer that is incorrect but somewhat related to target; and a score of 0 is an unrelated response within 6 s or no answer.*

GENETIC PREDISPOSITIONS MAY INFLUENCE THE SEVERITY OF COGNITIVE DYSFUNCTION AT THE POINT OF INITIAL DIAGNOSIS AND THROUGHOUT RECOVERY

Cognitive impairment in multiple domains, including attention, working memory, executive functions, processing speed, language comprehension, and speech production is a common sequela of dominant and non-dominant hemisphere gliomas.[65] However, there may be considerable variability in the severity of cognitive decline, as well as rate of recovery, between patients. It is well established that genetic factors, particularly genes involved in neurotransmission and synaptic plasticity, play an important role in the development of cognition and intelligence in both healthy individuals and patients with chronic disease, including cancer patients.[66-69]

In an effort to understand the influence of genetic variants on cognition, as well as to address the interpatient variability in the cognitive outcomes, several groups have studied single nucleotide polymorphisms (SNPs) of various gene products implicated in network connectivity and neurocognitive processing.[65,70,71] The $\varepsilon 4$ allele of apolipoprotein E (ApoE), a glycoprotein that plays a key role in neuronal growth and repair, has been strongly associated with cognitive impairment in both central nervous system (CNS) and non-CNS cancer population.[72-75] Importantly, polymorphisms in ApoE are a risk factor for developing primary progressive aphasia, a neurodegenerative disorder characterized by gradual selective loss of language function, without significant decline in other cognitive domains.[76,77] Long-term brain tumor carriers of at least one ApoE $\varepsilon 4$ allele, who received standard chemotherapy alone or in combination with radiotherapy, display poor verbal memory and executive functions compared to non-$\varepsilon 4$ carriers.[74] Although the mechanistic significance of the ApoE $\varepsilon 4$ allele and other SNPs in the ApoE gene remains unknown, these alterations appear to increase the vulnerability of brain tumor patients to cognitive and language dysfunction following chemoradiation. Mechanistically, the adverse effect of the $\varepsilon 4$ allele is thought to occur through disruption of neuronal repair, glial activation, and excitotoxicity, thereby resulting in greater inflammation and oxidative stress affecting oligodendrocytes and myelin production.[75,78,79]

The prefrontal cortex (PFC) has been studied extensively for its neuroanatomic connections, electrophysiological properties, and imaging correlates with cognitive domains of clinical importance.[80,81] The PFC is therefore regarded as a critical region of the brain for higher-order cognitive processes such as executive function.[80,81] Dopamine (DA), catechol-O-methyltransferase (COMT), and brain-derived neurotrophic factor (BDNF) are among a multitude of gene products contributing to network connectivity in the PFC.[82] The association of DA, COMT, and BDNF SNPs with memory and cognitive function in healthy individuals, as well as in clinical populations with neurological, neurodegenerative, and psychiatric disorders, is well documented.[83-85] However, studies exploring a similar association in brain tumor patients, and, specifically, whether SNPs contribute to individual patient vulnerability to treatment-related neurotoxicity are very limited. Correa et al[71] reported lower scores in delayed recall, attention, and executive functions in a diverse population of brain tumor survivors with COMT and BDNF SNPs. Furthermore, patients carrying 2 or any minor allele of COMT (rs174696 and rs165774) and BDNF (rs10767664) gene variants showed magnetic resonance imaging (MRI) changes indicative of impaired white matter integrity. Interestingly, adult glioma patients with higher performing alleles of BDNF, dopamine receptor 2, and COMT genes exhibited minimal cognitive impairment (including semantic fluency) and greater capacity to return to work compared with patients found to have low performing alleles.[82] In addition to the above described neuroplasticity related genes, several SNPs in genes involved in inflammation, DNA repair, and metabolism pathways have been reported to influence cognition in a variety of patient populations, including cancer patients.[70] The above-mentioned studies provide evidence of the associations between SNPs and neurocognitive outcomes in adult brain tumor patients, thereby opening the possibility of identifying vulnerable patient populations at the onset of disease.

NETWORK AND CELLULAR MECHANISMS OF APHASIA RECOVERY

Although many glioma patients experience language and cognitive dysfunction, many experience clinical recovery, especially during periods of stable disease (Figure 2).[25] Across several chronic disease models, a multitude of studies have documented restoration of motor and language dysfunction following stroke, epilepsy, and glioma.[13,86-88] However, compared to stroke and epilepsy, limited data exist regarding the trajectory and mechanisms of cognitive recovery in the adult glioma patient population.

CNS imaging techniques such as positron emission tomography and functional magnetic resonance imaging have been widely used to study language and cognitive recovery in stroke patients.[89,90] Increased activation of the language networks in the peri-infarct or ipsilateral areas was shown to correlate with improved performance in language tasks in patients recovering from stroke-induced aphasia.[91] Besides the ipsilesional adaptive changes occurring during recovery in stroke patients with left hemispheric lesions, increased activation of the right hemispheric (contralateral) cortical regions that are homologous to the structures invaded has also been demonstrated to mediate aphasia recovery.[86,89,92,93] Some studies have, however, demonstrated that recruitment/activation of language networks within the contralateral hemisphere may be associated with poor language recovery and might indicate faulty recovery attempts.[94-96] In this section, we review the published literature focused on potential network and cellular level mechanisms of aphasia recovery.

Network Level Plasticity

Complex cognitive processes such as language rely on network level activation. Similar to stroke, the mechanism of aphasia recovery in adult glioma remains poorly understood. Although some have demonstrated ipsilateral functional reorganization during language recovery,[97,98] others found evidence of contralateral functional reorganization in right hemisphere regions, which are homologous to the left hemispheric regions typically employed in language processing.[99] Conflicting data also exist with regard to whether the time of onset of seizures is a critical factor that determines the recruitment of left- vs right hemispheric neural networks to aid language recovery. For example, several groups showed an association between early onset epilepsy and right hemispheric-lateralized language function that triggers intrahemispheric language reorganization.[100,101] Others have argued that language reorganization associated with aphasia recovery involves network level changes in both ipsi- and contralesional hemispheres and that the allotment of left- vs right-language processing brain regions do not depend on age or time of onset of seizures.[99,102]

The severity of symptoms for patients with low-grade gliomas (LGG) is often less severe when compared with high-grade patients.[1,103,104] Duffau et al[13] suggested that differences in disease trajectory may be due to the slow and progressive growth of the tumor itself, thereby potentially promoting large-scale functional rearrangements of peritumoral neural networks due to activation of latent functional parts of the broader neural language network.[98,100,101] Mechanistically, there are 3 levels of network reorganization: first, allotment of eloquent neural networks that are still left intact within the tumor; second, recruitment of neural networks adjacent to the tumor site; and third, recruitment of ipsilateral or pre-existing contralateral connections.[105] Consistent with stroke and epilepsy data, activation of the contralateral connections is thought by some to be less effective than ipsilateral activation in preserving language functions and, rather, indicative of an unsuccessful language recovery attempt made by the affected dominant hemisphere.[106] However, this point remains controversial, as other reports[98] demonstrate robust contralateral hemisphere language activation.

There has been some thought that network level plasticity may occur quickly, as Duffau and colleagues[107,108] demonstrated patients with a spontaneous increase in neural activity in language or motor-related regions that were functionally silent prior to tumor resection. In the longer-term, perilesional network reorganization contributes to language, as DCS-positive cortical regions identified during initial surgery no longer have functional DCS significance during second surgery. These data provide the closest direct causal evidence that surgery-induced network reorganization can lead to long-term neuroplastic changes. It is therefore increasingly common to offer a staged surgery approach in LGG, leaving behind DCS-positive regions with the hopes of returning to the operating room for greater extent of tumor resection without compromising normal neurological functions at the point of recurrence.[107,109] Despite the documented neuroplastic changes occurring during surgery, the majority of LGG patients often exhibit transient aphasia postsurgically, which could be due to the removal of functional structures that might still exist within or in the immediate vicinity of the tumor.[110] Restoration of normal language function usually occurs within 1 to 3 mo of surgery following awake language mapping in the vast majority of patients.[90,98,105,111]

Potential Cellular Contributions to Network Dynamics

Despite the inconsistencies regarding the contributions of ipsilateral and contralateral language networks to aphasia recovery, the resulting rewiring of pre-existing connections or newly formed language and/or motor networks drives functional recovery in affected patients. The precise neuronal mechanisms underlying functional recovery in humans remains largely unknown.

Most of the existing data about the pathophysiological mechanism underlying neuroplasticity stems from animal models. For example, pharmacological blockade of cortical GABAergic inhibitory circuits in a small region of the primary motor cortex in adult rats was shown to rapidly elicit new representational patterns in the motor cortex area adjacent to the affected part.[112] The authors further demonstrated that a decrease in intracortical inhibition can unveil pre-existing latent excitatory connections that are normally masked by inhibitory neurons and that the balance between excitatory and inhibitory circuits is a strong dictator of cortical reorganization. Interestingly, downregulation of GABA-mediated inhibitory networks and an associated increase in intracortical excitatory activity in regions remote from the lesion have been implicated in motor function improvement in patients with stroke.[113-115] Similarly, the short-term plastic changes observed in the primary motor cortex of glioma patients during surgery was attributed to the sudden unmasking of latent redundant motor connections.[107] Latent or redundant cortical motor neurons in primary motor and sensory regions have long been known; even within S1 primary sensory cortex, pure motor tasks elicit robust motor neuron activation illustrated by DCS mapping and electrocorticography (Figure 3).

Other potential mechanisms of neuroplasticity include modification of synaptic strength via long-term potentiation or depression, which is in turn mediated through excitatory and inhibitory neurotransmitter systems.[116] Of note, existing evidence for synaptic efficacy-mediated neuroplasticity and associated motor functional recovery stems mostly from stroke patients and animal models of ischemia[117-119]; data suggesting this mechanism in the brain tumor patient population, especially in the context of language recovery, are still largely lacking.

Other mechanisms implicated in the reorganization of neural networks following brain injury involve the formation, as well as the integration, of new neurons into the existing neuronal circuits.[120] However, this mechanism is more likely to occur in acute brain insults, such as stroke, wherein the sudden death

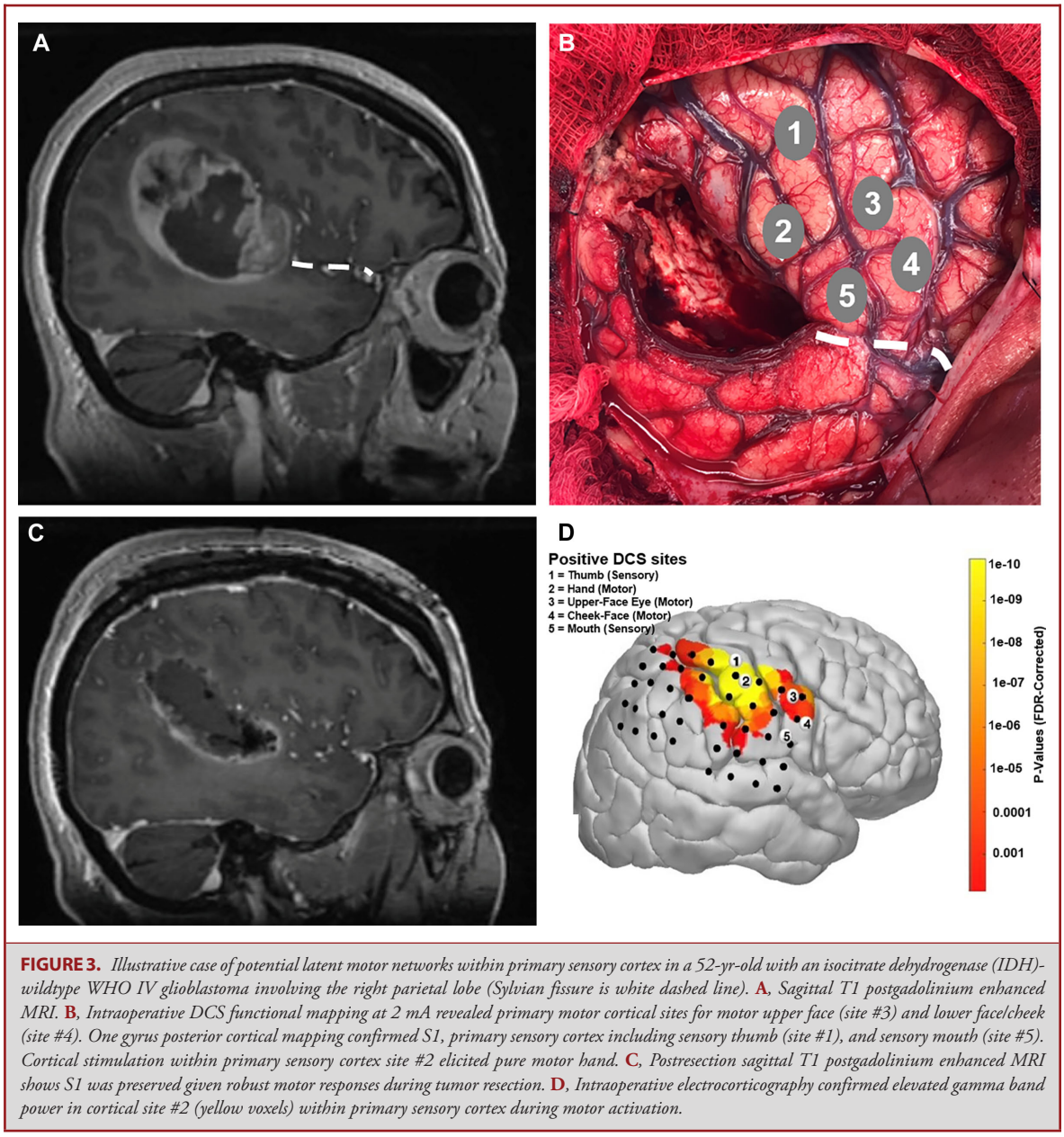

FIGURE 3. *Illustrative case of potential latent motor networks within primary sensory cortex in a 52-yr-old with an isocitrate dehydrogenase (IDH)-wildtype WHO IV glioblastoma involving the right parietal lobe (Sylvian fissure is white dashed line).* **A**, *Sagittal T1 postgadolinium enhanced MRI.* **B**, *Intraoperative DCS functional mapping at 2 mA revealed primary motor cortical sites for motor upper face (site #3) and lower face/cheek (site #4). One gyrus posterior cortical mapping confirmed S1, primary sensory cortex including sensory thumb (site #1), and sensory mouth (site #5). Cortical stimulation within primary sensory cortex site #2 elicited pure motor hand.* **C**, *Postresection sagittal T1 postgadolinium enhanced MRI shows S1 was preserved given robust motor responses during tumor resection.* **D**, *Intraoperative electrocorticography confirmed elevated gamma band power in cortical site #2 (yellow voxels) within primary sensory cortex during motor activation.*

of neurons would trigger neurogenesis to compensate for the damaged areas. It is thus not surprising that the majority of experimental and clinical studies on neurogenesis-mediated functional recovery have mainly focused on stroke research.[121-123] Intraoperative electrical stimulation before and after glioma resection has uncovered functional reorganization of cortical language sites.[104] Disruption of functional networks plus regional hyperexcitability induced by surgical lesioning itself may result in acute network remodeling in glioma patients.[13]

Importantly, it has been reported that the temporal progression of cerebral insults strongly influences neuroplasticity and that functional recovery is more efficient in chronic lesions, such as epilepsy and slow-growing tumors, than in acute lesions such as stroke.[102] Hence, it is logical to think that brain lesions, depending on their acute or chronic nature, are likely to involve different patterns of reorganization, and therefore, a broad generalization of the aforementioned stroke mechanisms to other types of brain injuries may be overly simplistic.

Further studies are warranted to specifically investigate the microscopic changes associated with the recovery of motor and language abilities in adult brain tumor patients. Although gliomas are traditionally considered an ablative process, evidence suggests

the presence of functional astrocytes and intact neuron-glial interactions within the tumor.[13] There is also strong preclinical evidence that malignant glioma cells can electrically integrate into neural circuitry through bona fide neurogliomal synapses and that excitatory neuronal activity can promote glioma growth and invasion.[124-126] Moreover, a recent study reported a specific population of cells in glioblastoma that differentially supported synaptogenesis.[127] It is therefore possible that a fourth mechanism of cognitive recovery should be added to the classical teaching in which glioma cells integrate into the broader neuronal network. Future studies aimed at investigating how gliomas maintain functional network connectivity with surrounding brain would not only increase our understanding of the neurobiology of language, but also might add to our understanding of the causal mechanisms underlying aphasia.

CONCLUSION

Many patients with low-grade glioma histology and favorable genetics will have extended disease-free survival periods during which they experience a wide range of language and neurocognitive impairments that compromise both health-related quality of life as well as survival. In this review, we outlined the current understanding of the mechanisms of cognitive dysfunction and recovery using aphasia as an illustrative model. Adult patients with gliomas experience aphasia because of tumor infiltration into cortical and subcortical structures, cytoreduction surgery, and chemoradiation. Cellular and network level processes contribute to cognitive plasticity.

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REFERENCES

1. Forst DA, Nahed BV, Loeffler JS, Batchelor TT. Low-grade gliomas. *Oncologist*. 2014;19(4):403-413.
2. Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the united states, 1977-2000. *Cancer*. 2004;101(10):2293-2299.
3. Ceccarelli M, Barthel FP, Malta TM, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. *Cell*. 2016;164(3):550-563.
4. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med*. 2016;374(14):1344-1355.
5. Louis DN, Perry A, Reifenberger G, et al. The 2016 world health organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803-820.
6. Satoer D, Visch-Brink E, Dirven C, Vincent A. Glioma surgery in eloquent areas: can we preserve cognition? *Acta Neurochir*. 2016;158(1):35-50.
7. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med*. 2008;358(1):18-27.
8. Bosma I, Reijneveld JC, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. *Neuro Oncol*. 2009;11(1):51-58.
9. Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition*. 2004;92(1-2):67-99.
10. Findlay AM, Ambrose JB, Cahn-Weiner DA, et al. Dynamics of hemispheric dominance for language assessed by magnetoencephalographic imaging. *Ann Neurol*. 2012;71(5):668-686.
11. Satoer D, De Witte E, Smits M, et al. Differential effects of awake glioma surgery in "Critical" language areas on cognition: 4 case studies. *Case Rep Neurol Med*. 2017;2017:6038641.
12. Jehna M, Becker J, Zaar K, et al. Symmetry of the arcuate fasciculus and its impact on language performance of patients with brain tumors in the language-dominant hemisphere. *J Neurosurg*. 2017;127(6):1407-1416.
13. Duffau H, Capelle L, Denvil D, et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. *J Neurol Neurosurg Psychiatry*. 2003;74(7):901-907.
14. Forkel SJ, Catani M. Lesion mapping in acute stroke aphasia and its implications for recovery. *Neuropsychologia*. 2018;115:88-100.
15. Cruice M, Worrall L, Hickson L, Murison R. Finding a focus for quality of life with aphasia: social and emotional health, and psychological well-being. *Aphasiology*. 2003;17(4):333-353.
16. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. *J Neurosurg*. 2015;122(2):250-261.
17. Duffau H, Moritz-Gasser S, Mandonnet E. A re-examination of neural basis of language processing: proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. *Brain Lang*. 2014;131:1-10.
18. Poeppel D, Hickok G. Towards a new functional anatomy of language. *Cognition*. 2004;92(1-2):1-12.
19. Turken AU, Dronkers NF. The neural architecture of the language comprehension network: converging evidence from lesion and connectivity analyses. *Front Syst Neurosci*. 2011;5:1.
20. Tremblay P, Dick AS. Broca and wernicke are dead, or moving past the classic model of language neurobiology. *Brain Lang*. 2016;162:60-71.
21. Rauschecker JP, Scott SK. Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. *Nat Neurosci*. 2009;12(6):718-724.
22. Griffiths JD, Marslen-Wilson WD, Stamatakis EA, Tyler LK. Functional organization of the neural language system: dorsal and ventral pathways are critical for syntax. *Cereb Cortex*. 2013;23(1):139-147.
23. Gow DW Jr. The cortical organization of lexical knowledge: a dual lexicon model of spoken language processing. *Brain Lang*. 2012;121(3):273-288.
24. IJzerman-Korevaar M, Snijders TJ, de Graeff A, Teunissen S, de Vos FYF. Prevalence of symptoms in glioma patients throughout the disease trajectory: a systematic review. *J Neurooncol*. 2018;140(3):485-496.
25. Wilson SM, Lam D, Babiak MC, et al. Transient aphasias after left hemisphere resective surgery. *J Neurosurg*. 2015;123(3):581-593.
26. Stadlbauer A, Nimsky C, Buslei R, et al. Diffusion tensor imaging and optimized fiber tracking in glioma patients: histopathologic evaluation of tumor-invaded white matter structures. *Neuroimage*. 2007;34(3):949-956.
27. Dick AS, Tremblay P. Beyond the arcuate fasciculus: consensus and controversy in the connectional anatomy of language. *Brain*. 2012;135(12):3529-3550.
28. Ormond DR, D'Souza S, Thompson JA. Global and targeted pathway impact of gliomas on white matter integrity based on lobar localization. *Cureus*. 2017;9(9):e1660.
29. Negwer C, Beurskens E, Sollmann N, et al. Loss of subcortical language pathways correlates with surgery-related aphasia in patients with brain tumor: an investigation via repetitive navigated transcranial magnetic stimulation-based diffusion tensor imaging fiber tracking. *World Neurosurg*. 2018;111:e806-e818.
30. Witwer BP, Moftakhar R, Hasan KM, et al. Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. *J Neurosurg*. 2002;97(3):568-575.
31. Campanella M, Ius T, Skrap M, Fadiga L. Alterations in fiber pathways reveal brain tumor typology: a diffusion tractography study. *PeerJ*. 2014;2:e497.
32. Liu F, Scantlebury N, Tabori U, et al. White matter compromise predicts poor intellectual outcome in survivors of pediatric low-grade glioma. *Neuro-Oncol*. 2015;17(4):604-613.

33. Schonberg T, Pianka P, Hendler T, Pasternak O, Assaf Y. Characterization of displaced white matter by brain tumors using combined DTI and fMRI. *Neuroimage*. 2006;30(4):1100-1111.
34. Wood JM, Kundu B, Utter A, et al. Impact of brain tumor location on morbidity and mortality: a retrospective functional MR imaging study. *AJNR Am J Neuroradiol*. 2011;32(8):1420-1425.
35. Banerjee P, Leu K, Harris RJ, et al. Association between lesion location and language function in adult glioma using voxel-based lesion-symptom mapping. *NeuroImage: Clinical*. 2015;9:617-624.
36. Meyers CA, Hess KR, Yung WK, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. *J Clin Oncol*. 2000;18(3):646-646.
37. Hervey-Jumper SL, Li J, Lau D, et al. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. *J Neurosurg*. 2015;123(2):325-339.
38. De Witte E, Satoer D, Colle H, Robert E, Visch-Brink E, Marien P. Subcortical language and non-language mapping in awake brain surgery: the use of multimodal tests. *Acta Neurochir*. 2015;157(4):577-588.
39. Jackson C, Westphal M, Quinones-Hinojosa A. Complications of glioma surgery. *Handb Clin Neurol*. 2016;134:201-218.
40. Peraud A, Meschede M, Eisner W, Ilmberger J, Reulen HJ. Surgical resection of grade II astrocytomas in the superior frontal gyrus. *Neurosurgery*. 2002;50(5):966-975; discussion 975-967.
41. Russell SM, Kelly PJ. Incidence and clinical evolution of postoperative deficits after volumetric stereotactic resection of glial neoplasms involving the supplementary motor area. *Neurosurgery*. 2003;52(3):506-516; discussiom 515-506.
42. Garrett MC, Pouratian N, Liau LM. Use of language mapping to aid in resection of gliomas in eloquent brain regions. *Neurosurg Clin N Am.* 2012;23(3):497-506.
43. Smits A, Zetterling M, Lundin M, et al. Neurological impairment linked with cortico-subcortical infiltration of diffuse low-grade gliomas at initial diagnosis supports early brain plasticity. *Front Neurol*. 2015;6:137.
44. Caverzasi E, Hervey-Jumper SL, Jordan KM, et al. Identifying preoperative language tracts and predicting postoperative functional recovery using HARDI q-ball fiber tractography in patients with gliomas. *J Neurosurg*. 2016;125(1):33-45.
45. Duffau H, Peggy Gatignol S, Mandonnet E, Capelle L, Taillandier L. Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with grade II glioma in the left dominant hemisphere. *J Neurosurg*. 2008;109(3):461-471.
46. Duffau H, Capelle L, Sichez N, et al. Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain*. 2002;125(Pt 1):199-214.
47. Butler JM, Rapp SR, Shaw EG. Managing the cognitive effects of brain tumor radiation therapy. *Curr Treat Options Oncol*. 2006;7(6):517-523.
48. Pendergrass JC, Targum SD, Harrison JE. Cognitive impairment associated with cancer: a brief review. *Innov Clin Neurosci*. 2018;15(1-2):36-44.
49. Stege EM, Kros JM, de Bruin HG, et al. Successful treatment of low-grade oligodendroglial tumors with a chemotherapy regimen of procarbazine, lomustine, and vincristine. *Cancer*. 2005;103(4):802-809.
50. Villa S, Balana C, Comas S. Radiation and concomitant chemotherapy for patients with glioblastoma multiforme. *Chin J Cancer*. 2014;33(1):25-31.
51. Brown PD, Buckner JC, Uhm JH, Shaw EG. The neurocognitive effects of radiation in adult low-grade glioma patients. *Neuro Oncol*. 2003;5(3):161-167.
52. Mann J, Ramakrishna R, Magge R, Wernicke AG. Advances in radiotherapy for glioblastoma. *Front Neurol*. 2017;8:748.
53. Kerklaan JP, Lycklama a Nijeholt GJ, Wiggenraad RG, Berghuis B, Postma TJ, Taphoorn MJ. SMART syndrome: a late reversible complication after radiation therapy for brain tumours. *J Neurol*. 2011;258(6):1098-1104.
54. King TZ, Wang L, Mao H. Disruption of white matter integrity in adult survivors of childhood brain tumors: correlates with long-term intellectual outcomes. *PLoS One*. 2015;10(7):e0131744.
55. Khong PL, Leung LH, Fung AS, et al. White matter anisotropy in post-treatment childhood cancer survivors: preliminary evidence of association with neurocognitive function. *J Clin Oncol*. 2006;24(6):884-890.
56. Prabhu RS, Won M, Shaw EG, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J Clin Oncol*. 2014;32(6):535-541.
57. Marsh JC, Gielda BT, Herskovic AM, Abrams RA. Cognitive sparing during the administration of whole brain radiotherapy and prophylactic cranial irradiation: current concepts and approaches. *J Oncol*. 2010;2010:1-16.
58. Dhandapani M, Gupta S, Mohanty M, Gupta SK, Dhandapani S. Trends in cognitive dysfunction following surgery for intracranial tumors. *Surg Neurol Int*. 2016;7(8):S190-S195.
59. Kim JH, Brown SL, Jenrow KA, Ryu S. Mechanisms of radiation-induced brain toxicity and implications for future clinical trials. *J Neurooncol*. 2008;87(3):279-286.
60. Raber J, Rola R, LeFevour A, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res*. 2004;162(1):39-47.
61. Briones TL, Woods J. Dysregulation in myelination mediated by persistent neuroinflammation: possible mechanisms in chemotherapy-related cognitive impairment. *Brain Behav Immun*. 2014;35:23-32.
62. Moore HC. An overview of chemotherapy-related cognitive dysfunction, or 'chemobrain'. *Oncology (Williston Park)*. 2014;28(9):797-804.
63. Gibson EM, Nagaraja S, Ocampo A, et al. Methotrexate chemotherapy induces persistent Tri-glial dysregulation that underlies chemotherapy-related cognitive impairment. *Cell*. 2019;176(1-2):43-55.e13.e13.
64. Geraghty AC, Gibson EM, Ghanem RA, et al. Loss of adaptive myelination contributes to methotrexate chemotherapy-related cognitive impairment. *Neuron*. 2019;103(2):250-265.e8.
65. Wefel JS, Noll KR, Scheurer ME. Neurocognitive functioning and genetic variation in patients with primary brain tumours. *Lancet Oncol*. 2016;17(3):e97-e108.
66. Tucker-Drob EM, Briley DA, Harden KP. Genetic and environmental influences on cognition across development and context. *Curr Dir Psychol Sci*. 2013;22(5):349-355.
67. Koten JW Jr, Wood G, Hagoort P, et al. Genetic contribution to variation in cognitive function: an FMRI study in twins. *Science*. 2009;323(5922):1737-1740.
68. de Geus EJ, Wright MJ, Martin NG, Boomsma DI. Genetics of brain function and cognition. *Behav Genet*. 2001;31(6):489-495.
69. Pietropaolo S, Crusio WE. Genes and cognition. *Wiley Interdiscip Rev Cogn Sci*. 2011;2(3):345-352.
70. Liu Y, Zhou R, Sulman EP, et al. Genetic modulation of neurocognitive function in glioma patients. *Clin Cancer Res*. 2015;21(14):3340-3346.
71. Correa DD, Satagopan J, Cheung K, et al. COMT, BDNF, and DTNBP1 polymorphisms and cognitive functions in patients with brain tumors. *Neuro Oncol*. 2016;18(10):1425-1433.
72. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology*. 2003;12(6):612-619.
73. Castel H, Denouel A, Lange M, Tonon MC, Dubois M, Joly F. Biomarkers associated with cognitive impairment in treated cancer patients: potential predisposition and risk factors. *Front Pharmacol*. 2017;8:138.
74. Correa DD, Satagopan J, Baser RE, et al. APOE polymorphisms and cognitive functions in patients with brain tumors. *Neurology*. 2014;83(4):320-327.
75. Correa DD, Kryza-Lacombe M, Zhou X, et al. A pilot study of neuropsychological functions, APOE and amyloid imaging in patients with gliomas. *J Neurooncol*. 2018;136(3):613-622.
76. Seripa D, Bizzarro A, Pilotto A, et al. TOMM40, APOE, and APOC1 in primary progressive aphasia and frontotemporal dementia. *J Alzheimers Dis*. 2012;31(4):731-740.
77. Mesulam M. Primary progressive aphasia: a dementia of the language network. *Dement Neuropsychol*. 2013;7(1):2-9.
78. Ryan L, Walther K, Bendlin BB, Lue LF, Walker DG, Glisky EL. Age-related differences in white matter integrity and cognitive function are related to APOE status. *Neuroimage*. 2011;54(2):1565-1577.
79. Lane RM, Farlow MR. Lipid homeostasis and apolipoprotein e in the development and progression of alzheimer's disease. *J Lipid Res*. 2005;46(5):949-968.
80. Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behav*. 2006;5(4):311-328.
81. Miller EK. The prefontral cortex and cognitive control. *Nat Rev Neurosci*. 2000;1(1):59-65.

82. Altshuler DB, Wang L, Zhao L, et al. BDNF, COMT, and DRD2 polymorphisms and ability to return to work in adult patients with low- and high-grade glioma. *Neurooncol Pract.* 2019;6(5):375-385.
83. Nkam I, Ramoz N, Breton F, Mallet J, Gorwood P, Dubertret C. Impact of DRD2/ANKK1 and COMT polymorphisms on attention and cognitive functions in schizophrenia. *PLoS One*. 2017;12(1):e0170147.
84. Zhang X, Li J, Qin W, Yu C, Liu B, Jiang T. The catechol-o-methyltransferase val158met polymorphism modulates the intrinsic functional network centrality of the parahippocampal cortex in healthy subjects. *Sci Rep*. 2015;5(1): 10105.
85. Martinho E Jr, Michelon L, Ayres AM, et al. BDNF gene polymorphism, cognition and symptom severity in a brazilian population-based sample of first-episode psychosis subjects. *Braz J Psychiatry*. 2012;34(Suppl 2):S219-S225.
86. Qiu WH, Wu HX, Yang QL, et al. Evidence of cortical reorganization of language networks after stroke with subacute broca's aphasia: a blood oxygenation level dependent-functional magnetic resonance imaging study. *Neural Regen Res*. 2017;12(1):109-117.
87. Chamoun RB, Mikati MA, Comair YG. Functional recovery following resection of an epileptogenic focus in the motor hand area. *Epilepsy Behav*. 2007;11(3):384-388.
88. Helmstaedter C, Elger CE, Vogt VL. Cognitive outcomes more than 5 years after temporal lobe epilepsy surgery: remarkable functional recovery when seizures are controlled. *Seizure*. 2018;62:116-123.
89. Warburton E, Price CJ, Swinburn K, Wise RJ. Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. *J Neurol Neurosurg Psychiatry*. 1999;66(2):155-161.
90. Pillai JJ. Insights into adult postlesional language cortical plasticity provided by cerebral blood oxygen level-dependent functional MR imaging. *AJNR Am J Neuroradiol.* 2010;31(6):990-996.
91. Szaflarski JP, Eaton K, Ball AL, et al. Poststroke aphasia recovery assessed with functional magnetic resonance imaging and a picture identification task. *J Stroke Cerebrovasc Dis*. 2011;20(4):336-345.
92. Cao Y, Vikingstad EM, George KP, Johnson AF, Welch KM. Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke*. 1999;30(11):2331-2340.
93. Xing S, Lacey EH, Skipper-Kallal LM, et al. Right hemisphere grey matter structure and language outcomes in chronic left hemisphere stroke. *Brain*. 2016;139(Pt 1):227-241.
94. Meltzer JA, Wagage S, Ryder J, Solomon B, Braun AR. Adaptive significance of right hemisphere activation in aphasic language comprehension. *Neuropsychologia*. 2013;51(7):1248-1259.
95. Anglade C, Thiel A, Ansaldo AI. The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: a critical review of literature. *Brain Inj.* 2014;28(2):138-145.
96. Heiss WD. WSO leadership in stroke medicine award lecture vienna, september 26, 2008: functional imaging correlates to disturbance and recovery of language function. *Int J Stroke*. 2009;4(2):129-136.
97. Hamberger MJ, Cole J. Language organization and reorganization in epilepsy. *Neuropsychol Rev.* 2011;21(3):240-251.
98. Traut T, Sardesh N, Bulubas L, et al. MEG imaging of recurrent gliomas reveals functional plasticity of hemispheric language specialization. *Hum Brain Mapp*. 2019;40(4):1082-1092.
99. Rosenberger LR, Zeck J, Berl MM, et al. Interhemispheric and intra-hemispheric language reorganization in complex partial epilepsy. *Neurology*. 2009;72(21):1830-1836.
100. Cousin E, Baciu M, Pichat C, Kahane P, Le Bas JF. Functional MRI evidence for language plasticity in adult epileptic patients: preliminary results. *Neuropsychiatr Dis Treat*. 2008;4(1):235-246.
101. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. *Ann NY Acad Sci.* 1977;299:355-369.
102. Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. *Brain*. 2007;130(Pt 4):898-914.
103. Fisicaro RA, Jost E, Shaw K, Brennan NP, Peck KK, Holodny AI. Cortical plasticity in the setting of brain tumors. *Top Magn Reson Imaging*. 2016;25(1):25-30.
104. Southwell DG, Hervey-Jumper SL, Perry DW, Berger MS. Intraoperative mapping during repeat awake craniotomy reveals the functional plasticity of adult cortex. *J Neurosurg*. 2016;124(5):1460-1469.
105. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol*. 2005;4(8):476-486.
106. Rosenberg K, Liebling R, Avidan G, et al. Language related reorganization in adult brain with slow growing glioma: fMRI prospective case-study. *Neurocase*. 2008;14(6):465-473.
107. Duffau H. Acute functional reorganisation of the human motor cortex during resection of central lesions: a study using intraoperative brain mapping. *J Neurol Neurosurg Psychiatry*. 2001;70(4):506-513.
108. Duffau H, Denvil D, Capelle L. Long term reshaping of language, sensory, and motor maps after glioma resection: a new parameter to integrate in the surgical strategy. *J Neurol Neurosurg Psychiatry*. 2002;72(4):511-516.
109. Sarubbo S, Le Bars E, Moritz-Gasser S, Duffau H. Complete recovery after surgical resection of left wernicke's area in awake patient: a brain stimulation and functional MRI study. *Neurosurg Rev.* 2012;35(2):287-292; discussion 292.
110. Coget A, Deverdun J, Bonafe A, et al. Transient immediate postoperative homotopic functional disconnectivity in low-grade glioma patients. *NeuroImage: Clinical*. 2018;18:656-662.
111. Chivukula S, Pikul BK, Black KL, Pouratian N, Bookheimer SY. Contralateral functional reorganization of the speech supplementary motor area following neurosurgical tumor resection. *Brain Lang.* 2018;183:41-46.
112. Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. *Science*. 1991;251(4996):944-947.
113. Hoyer EH, Celnik PA. Understanding and enhancing motor recovery after stroke using transcranial magnetic stimulation. *Restor Neurol Neurosci.* 2011;29(6):395-409.
114. Butefisch CM, Netz J, Wessling M, Seitz RJ, Homberg V. Remote changes in cortical excitability after stroke. *Brain*. 2003;126(2):470-481.
115. Paik NJ, Yang E. Role of GABA plasticity in stroke recovery. *Neural Regen Res*. 2014;9(23):2026-2028.
116. Ghinda CD, Duffau H. Network plasticity and intraoperative mapping for personalized multimodal management of diffuse low-grade gliomas. *Front Surg* 2017;4:3.
117. Butefisch CM. Plasticity in the human cerebral cortex: lessons from the normal brain and from stroke. *Neuroscientist*. 2004;10(2):163-173.
118. Di Lazzaro V, Profice P, Pilato F, et al. Motor cortex plasticity predicts recovery in acute stroke. *Cereb Cortex*. 2010;20(7):1523-1528.
119. Alia C, Spalletti C, Lai S, et al. Neuroplastic changes following brain ischemia and their contribution to stroke recovery: novel approaches in neurorehabilitation. *Front Cell Neurosci*. 2017;11:76.
120. Lledo PM, Alonso M, Grubb MS. Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Rev Neurosci.* 2006;7(3):179-193.
121. Lindvall O, Kokaia Z. Neurogenesis following stroke affecting the adult brain. *Cold Spring Harb Perspect Biol.* 2015;7(11):a019034.
122. Font MA, Arboix A, Krupinski J. Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Curr Cardiol Rev*. 2010;6(3):238-244.
123. Sandvig I, Augestad IL, Haberg AK, Sandvig A. Neuroplasticity in stroke recovery. The role of microglia in engaging and modifying synapses and networks. *Eur J Neurosci.* 2018;47(12):1414-1428.
124. Venkatesh HS, Johung TB, Caretti V, et al. Neuronal activity promotes glioma growth through neuroligin-3 secretion. *Cell*. 2015;161(4):803-816.
125. Venkatesh HS, Morishita W, Geraghty AC, et al. Electrical and synaptic integration of glioma into neural circuits. *Nature*. 2019;573(7775):539-545.
126. Venkataramani V, Tanev DI, Strahle C, et al. Glutamatergic synaptic input to glioma cells drives brain tumour progression. *Nature*. 2019;573(7775):532-538.
127. John Lin CC, Yu K, Hatcher A, et al. Identification of diverse astrocyte populations and their malignant analogs. *Nat Neurosci.* 2017;20(3):396-405.