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

Gliomas make up the majority of primary intrinsic brain tumors. Molecular characterization and epidemiology studies have greatly enhanced our understanding of molecular drivers of progression with implications for overall and progression-free survival. 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. 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.

Classically, language processing is thought to occur through dorsal and ventral streams along the dominant hemisphere perisylvian network. 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. 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 is 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.18-26 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 al28 studied the impact of gliomas on white matter integrity and showed large-scale white matter alterations characterized by edema, degra- dation, 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 diagnosis34,35 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
may elicit a multitude of transient language alterations, such as dysphasia, aphasia, dysarthria, and phonological paraphasias. Several reports have illustrated immediate and short-term postoperative language outcomes; however, the published incidence is dependent on one's definition of aphasia. 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.

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

**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). Therapeutic radiation with a total dose of ≤60 Gray (Gy) has yielded longer survival in glioma patients. However, the beneficial effect of radiation must be balanced with a higher risk of developing late delayed cognitive and language declines. The same may be true for patients with brain metastases, as Kerklaan et al 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). 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.

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. 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.
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. 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.

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. The ε4 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. 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. Long-term brain tumor carriers of at least one ApoE ε4 allele, who received standard chemotherapy alone or in combination with radiotherapy, display poor verbal memory and executive functions compared to non-ε4 carriers. Although the mechanistic significance of the ApoE ε4 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. Mechanically, the adverse effect of the ε4 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.

The prefrontal cortex (PFC) has been studied extensively for its neuroanatomic connections, electrophysiological properties, and imaging correlates with cognitive domains of clinical importance. The PFC is therefore regarded as a critical region of the brain for higher-order cognitive processes such as executive function. 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. 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. 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 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. 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. 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). Across several chronic disease models, a multitude of studies have documented restoration of motor and language dysfunction following stroke, epilepsy, and glioma. 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. 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. 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. 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. 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 contralateral 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 al13 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 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 reports98 demonstrate robust contralateral hemisphere language activation.

There has been some thought that network level plasticity may occur quickly, as Duffau and colleagues107,108 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 neuropsylic 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 GABAAergic 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 ischemia117-119; data suggesting this mechanism is 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
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. Intraoperative electrical stimulation before and after glioma resection has uncovered functional reorganization of cortical language sites. Disruption of functional networks plus regional hyperexcitability induced by surgical lesioning itself may result in acute network remodeling in glioma patients.

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. 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. There is also strong preclinical evidence that malignant glioma cells can electrically integrate into neural circuitry through bona fide neogliomai synapses and that excitatory neuronal activity can promote glioma growth and invasion. Moreover, a recent study reported a specific population of cells in glioblastoma that differentially supported synaptogenesis. 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 history 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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