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A Neurosurgeon's Guide to Cognitive Dysfunction in Adult Glioma

Cognitive decline is common among patients with low- and high-grade glioma and can significantly impact quality of life. Although cognitive outcomes have been studied after therapeutic interventions such as surgery and radiation, it is important to understand the impact of the disease process itself prior to any interventions. Neurocognitive domains of interest in this disease context include intellectual function and premorbid ability, executive function, learning and memory, attention, language function, processing speed, visuospatial function, motor function, and emotional function. Here, we review oncologic factors associated with more neurocognitive impairment, key neurocognitive tasks relevant to glioma patient assessment, as well as the relevance of the human neural connectome in understanding cognitive dysfunction in glioma patients. A contextual understanding of glioma-functional network disruption and its impact on cognition is critical in the surgical management of eloquent area tumors.

KEY WORDS: Malignant glioma, Glioma, Cognition, Functional mapping

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Gliomas exist within a microenvironment in which central nervous system (CNS) physiology contributes to tumor invasion and proliferation.^{1–8} In doing so, interactions between gliomas and their neuron microenvironment can significantly impact cognitive, language, and sensorimotor processing. Surgical resection is a mainstay of treatment and combination chemoradiation is the standard of care of both high and low grade glioma,^{9–11} all of which may lead to further significant cognitive decline in patients compounding on that already caused by the tumor itself. Normal neurocognitive function is associated with functional independence in patients with glioma,¹² yet cognitive dysfunction is common.

ABBREVIATIONS: **AED**, antiepileptic drug; **CNS**, central nervous system; **CVLT-II**, California Verbal Learning Test – Second Edition; **D-KEFS**, Delis-Kaplan Executive Function System; **IQ**, intelligence quotient; **MMSE**, Mini Mental Status Examination; **MoCA**, Montreal Cognitive Assessment; **NART**, National Adult Reading Test; **RCFT**, Rey Osterrieth Complex Figure Test and Recognition Trial; **TMT**, Trail Making Test; **WAIS**, Wechsler Adult Intelligence Scale; **WTAR**, Weschler Test of Adult Reading

Broadly speaking, cognitive dysfunction is defined as an impairment in 1 or more cognitive domains which include executive function, learning and memory, perceptual-motor function, language, and attention. In a meta-analysis of cognitive impairment in glioma patients beginning at the point of diagnosis, an impairment in at least 1 cognitive domain was seen in the majority of patients.¹³ Cognitive impairments experienced by patients with glioma are associated with lower rates of return to work, reduced independence despite high functional scales with Karnofsky Performance Scores, and lower quality of life.^{14,15} Unfortunately, patients may also have poor insight into their level of impairment.¹⁶ Cognitive outcomes are often studied in a cross-sectional manner, following therapeutic interventions such as surgery, chemotherapy, and brain irradiation. However, even prior to these therapies, gliomas disrupt network dynamics with neurological consequences.^{17–19} The widespread application of cognition testing throughout the trajectory of disease may be difficult due to a number of obstacles; however, routine testing can be a valuable addition to patient care. The focus of this review is to provide an overview of oncological factors associated influencing cognitive dysfunction for adult glioma patients.

FACTORS ASSOCIATED WITH NEUROCOGNITIVE IMPAIRMENT PRIOR TO TREATMENT

There are a number of factors associated with neurocognitive impairment in glioma patients, including older age, tumor location, extent of peritumoral edema, and tumor size.^{16,19-21} In this section, we review oncologic factors as well as common medications that may impact cognition.

Impact of Antiepileptic Medications

A majority of glioma patients use antiepileptic drugs (AEDs), especially those presenting with seizures. Historically, these agents were thought to impair cognitive function²²⁻²⁵ with the most common domains affected including attention, psychomotor speed, and memory.²⁴ However, some reports suggest that newer antiepileptics (eg, levetiracetam) may not be as deleterious as older agents (eg, phenytoin).^{22,23} For example, levetiracetam does not significantly impact cognition in epilepsy patients.²⁶⁻²⁸ De Groot et al²⁹ studied cognition in a matched cohort of high-grade glioma patients who received older AEDs (phenytoin and valproic acid), a newer AED (levetiracetam), or no AEDs prior to chemoradiation. Neither levetiracetam nor valproic acid were associated with cognitive impairments. Interestingly, patients on levetiracetam performed better on verbal memory tests than patients not on AEDs.²⁹ Further work, however, is needed to assess other novel AED medications, the impact of dosing on cognitive outcomes, as well as the interplay between seizure control and cognition.

Impact of Dexamethasone

Corticosteroids are a central part of symptomatic control in glioma patients. Although their association with neuropsychiatric symptoms including insomnia, mania, psychosis, and depression are well known, the interplay between dexamethasone and cognition is not well understood. In other surgical contexts, there are mixed results in regards to dexamethasone's impact on postoperative cognition. In a study by Glumac et al,³⁰ dexamethasone reduced the incidence of postoperative cognitive dysfunction after cardiac surgery. In a meta-analysis of studies examining the effects of dexamethasone on postoperative cognitive dysfunction, there were no differences in cognitive task performance between dexamethasone-treated and placebo-treated groups 30 d after surgery.³¹ The generalizability of these findings to glioma patients is questionable. In practice, dexamethasone significantly improves peritumoral edema and can improve a patient's functional and cognitive status, at least in the short term. The long-term effects of corticosteroid use on cognition require further study.

Impact of Glioma Location on Cognition

As early as the 2nd century AD, many have debated a localizationist view of the brain, which assigned mental abilities to specific brain regions. It was French neurologist Paul Broca and German neurologist Carl Wernicke who first observed specific

patterns of altered language following brain injury and stroke to the left frontal and temporal lobes. Awake cortical mapping with electrical stimulation, first described by Penfield and Boldrey in 1937 for epilepsy surgery, allowed for improvements in the correlation of location and function.³² Ojemann further advanced this technique in the 1970s.^{33,34}

Presently, the neural connections in the brain underlying mental and cognitive processes remain largely unknown. However, there are distinct patterns of neurocognitive impairment across cortical locations. For example, patients with left hemispheric lesions more frequently report depressive symptoms and more difficulty with memory.³⁵ Noll et al¹⁹ compared neurocognitive task performance between left- and right-sided temporal glioma. Left temporal gliomas frequently had impairment in verbal learning and memory, language tasks, executive function, and attention yet normal processing speed. Patients with right temporal gliomas demonstrated impairment of executive function, verbal learning and memory, processing speed, and fine motor control.¹⁹ Tucha et al¹⁶ reported on 139 patients with frontal or temporal untreated gliomas. Left-sided lesions exhibited more impairments in verbal short-term memory tasks whereas patients with bilateral and right-sided lesions more frequently demonstrated impaired visuospatial abilities.¹⁶ Hahn et al³⁵ reported increased memory loss and poorer verbal fluency and learning in patients with left-sided tumors. Wu et al³⁶ examined neurocognitive impairment associated with insular tumors and found lesions in this region were associated with worse visual confrontational naming. Noll et al¹⁹ reported that within the left temporal lobe, new learning appeared most impacted by tumors restricted to anterior temporal lobe. Delayed recall and recognition performance was lowest in tumors involving medial structures within the temporal lobe, suggesting site specific cognitive impairment even within a single cortical lobe.¹⁹ These results and lateralization of cognitive function appear consistent with those noted in the stroke literature.³⁷

Given how cognitive dysfunction impacts quality of life, there is a need to preserve function following therapeutic interventions and this goal must be balanced with the survival benefit associated with maximal extent of resection and chemo- and radiotherapy.^{11,38} Although there are a lack of guidelines for patient-specific cognitive testing, the localizationist view of cognition for glioma patients leads to the idea of site-specific preoperative and postoperative cognitive testing based on glioma location (Figure).

Influence of Growth Rate on Neurocognition

The concept of tumor rate of growth may explain differing patterns of neurological and cognitive symptom burden.³⁹ For slower growing low-grade gliomas, there is more time for glioma-neural network functional integration resulting in topographic reorganization of functional areas. Several reports have demonstrated that faster-growing gliomas are associated with more

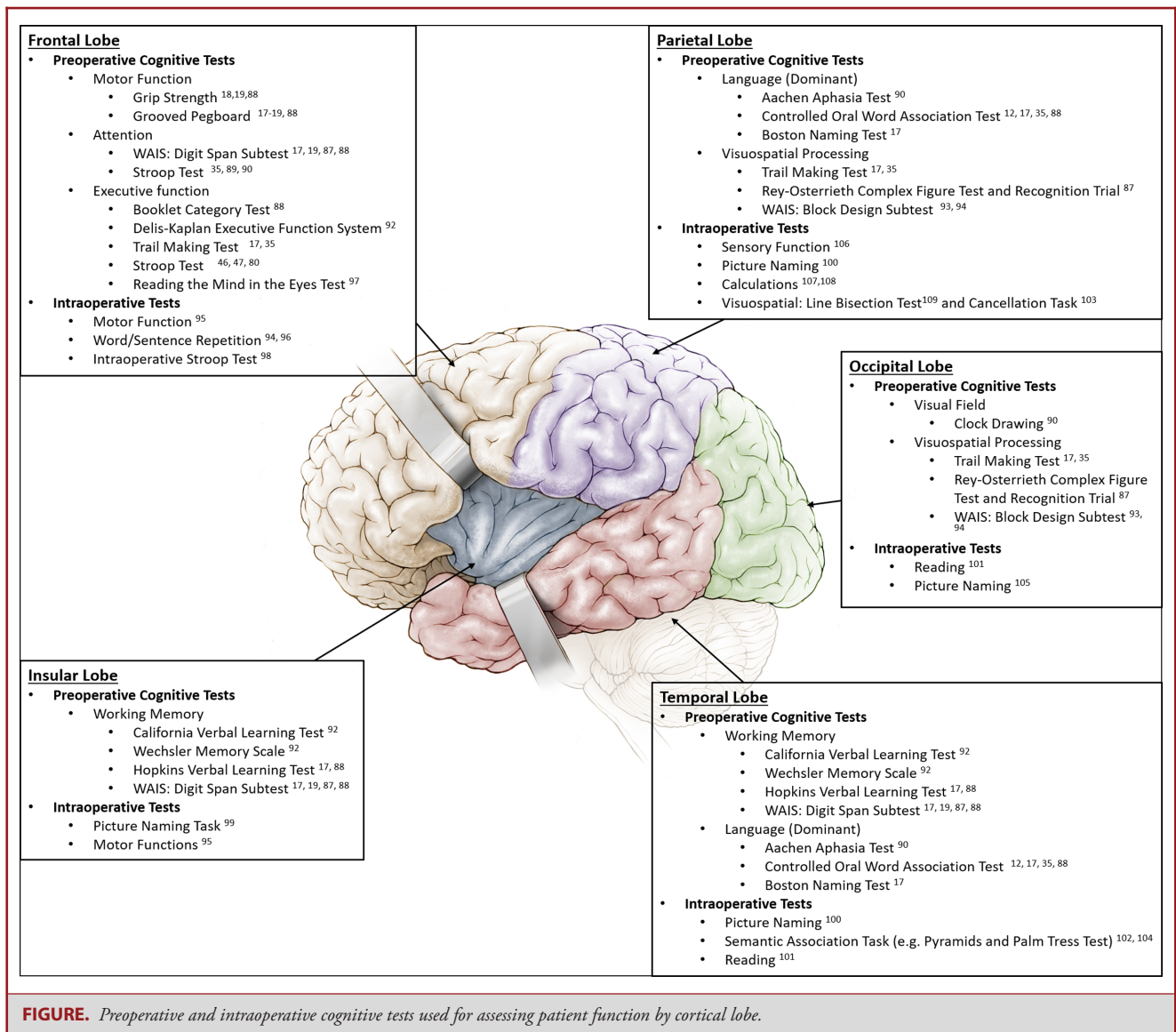


FIGURE. Preoperative and intraoperative cognitive tests used for assessing patient function by cortical lobe.

severe neurocognitive impairment when compared with low-grade gliomas.^{17,18,40,41} Wefel et al¹⁷ compared the severity of neurocognitive impairment between patients with IDH1-wildtype and IDH1-mutant malignant gliomas. IDH1-wildtype gliomas which were faster growing had poorer neurocognitive function compared to IDH1-mutant gliomas despite similar tumor size. Mean task performance for patients with IDH-wildtype gliomas was lower on measures of learning and memory, processing speed, language, executive functioning, and dexterity.¹⁷ As a correlate to faster growth potential, high-grade gliomas are also associated with a higher rate of neurocognitive impairments.^{18,21} Noll et al¹⁸ compared neurocognitive impairment rates between patients with newly diagnosed grade II to IV gliomas. Patients with grade IV tumors suffered more

frequent neurocognitive impairment when compared with grade II and III tumors.¹⁸

IMPACT OF GLIOMA ON THE HUMAN CONNECTOME

Neural network disruption results in neurocognitive impairment in glioma patients.^{42,43} New scientific inquiry into the mapping of cognitive functions and neurologic symptoms to specific brain regions has led to an emphasis on identifying functional networks as opposed to studies which focus on anatomic cortical correlations. This work has resulted in the development of a human brain “connectome,” which provides a

map of functional connections and may explain how lesions in different locations explain specific symptomatology.⁴⁴

In the context of glioma, this means that a tumor in a single location may cause global perturbation of network function. Zhang et al⁴⁵ examined cerebral hemispheric functional connectivity between 20 right-handed patients with frontal lobe glioma and healthy controls. Functional connectivity between the posterior cingulate cortex and temporal-parietal junction was decreased in the glioma group. Interestingly, left hemispheric functional connectivity was negatively impacted by right frontal tumors suggesting more widespread network dysfunction remote from the primary site of a glioma.⁴⁵ While long-distance inter-hemispheric connectivity may be impaired in glioma patients, local connectivity may be preserved and similar to healthy controls.⁴⁶

Differences in network connectivity between glioma subtypes are also apparent. Kesler et al⁴² compared network organization between IDH1-mutant and IDH1-wildtype malignant astrocytomas and found that patients with IDH1-wildtype tumors had lower connectivity in medial frontal, posterior parietal, and subcortical areas. These patients also had higher rates of neurocognitive impairment, although network connectivity was inversely associated with cognitive impairment in both cohorts.⁴²

One feature of the human connectome is the presence of “hubs” or areas of high-information throughput which may be relevant for quick processing of information.^{47,48} Derks et al⁴⁹ found wide-spread altered connectivity changes in glioma patients with higher rates of hub-to-non-hub connectivity and lower hub-to-hub connectivity when compared to healthy controls. In terms of surgical impact on language performance, Lee et al⁵⁰ found that removal of high connectivity sites that were negative for functional during intraoperative stimulation led to higher rates of transient postoperative decline on specific language tasks.

FUNCTIONAL REORGANIZATION OF NETWORKS DYNAMICS AND PRESERVATION OF NEUROCOGNITIVE FUNCTION

As gliomas grow, they alter networks dynamics and therefore cognition. However, neighboring networks may reorganize via neural plasticity allowing for functional recovery of both cognitive and language/motor activity.⁵¹ This process of functional reorganization and cortical plasticity is one reason that patient’s with slow-growing diffuse low-grade gliomas in areas considered to be “eloquent” often remain neurologically intact.⁵² Low-grade gliomas often grow to a very large size, with minimal symptoms.^{53,54} This is in contrast to glioblastoma, which grows rapidly and often presents with neurological deficits. Likewise, an ischemic stroke, usually results in some degree of neurological impairment, even though functional reorganization can still occur in a delayed fashion. The observation that cortical plasticity can occur in the setting of glioma infiltration has been confirmed intraoperatively with direct electrocortical stimulation.⁵⁵⁻⁵⁷

There are a few hypotheses for how functional network reorganization occurs in the setting of oncologic growth.⁵⁸ First, function might be preserved within the original network despite the tumor infiltration. This concept of functional integration may make achieving a gross total resection difficult without creating a lasting postoperative neurological deficit. Second, function may be redistributed to the adjacent nontumor cortical and subcortical networks. In this setting, an aggressive surgical resection can occur. Finally, areas remote from the lesional tissue could compensate for lost function. Some authors have argued that extent of subcortical violation limits functional connectivity and is therefore the biggest limiting factor to neuroplasticity.⁵⁵ As a result, when gliomas infiltrate the subcortical white matter, it may be critical to perform subcortical mapping or resect the tumor in a subtotal fashion.⁵⁹ In taking this approach, the surgeon can “stage” the resection of a slower growing low-grade glioma and return for repeat resection at a later date to remap the area and determine if function still remains.⁶⁰ Lesions initially deemed unresectable due to stimulation-confirmed involvement of functional tissue may later become resectable once functional networks have been re-established elsewhere.^{61,62} The exact timing of this process and the underlying mechanisms remain unknown.

NEUROCOGNITIVE TESTING DOMAINS

Neurocognitive testing aides in assessing domains of cognitive impairment in patients with gliomas. Testing is performed by specialized neuropsychologists, psychometrists, speech pathologists, or intraoperative physiologists and is carried out with the patient alone in a noise-controlled, comfortable environment which is free of distractions. Cognitive impairment interferes with an individual’s independence in completing everyday activities and is typically diagnosed when substantial decline is observed in one or usually more cognitive domains.⁶³ Global measures of cognitive impairment, such as the Folstein Mini Mental Status Examination (MMSE)⁶⁴ and the Montreal Cognitive Assessment (MoCA),⁶⁵ are commonly used screening tools. The MMSE and MoCA are both 10-min screening tools. A score below 20 on the MMSE and a score below 26 on the MoCA indicates cognitive impairment.^{64,65} These assessments have poor domain-specific sensitivity and specificity.⁶⁶

Utilizing a comprehensive neurocognitive testing battery can provide domain-specific information. A testing battery typically assesses the following domains in glioma patients: premorbid ability, general intellectual level, attention, memory, executive functioning, language, visual spatial functioning, motor functioning, and emotional functioning.⁶⁷ Tests are chosen depending on the referral question, the patient or caregivers’ complaints and symptoms, and information collected during the clinical interview. There is no consensus regarding which tasks to administer for glioma patients limiting interpretation of comparative studies.⁶⁸ Furthermore, normative standards and cut-off

TABLE. Neuropsychological Tests for Assessing Neurocognitive Domains in Glioma

Neurocognitive domains	Test	Functions and cognitive abilities	Example references
Attention	Digit span	Auditory attention	17,19,87,88
	Stroop test	Mental speed; selective attention; inhibitory control	35,89,90
	TMT-A	Selective and divided attention; visual search speed; scanning	17,35,88,91
Executive functions	BCT	Concept formation; abstract reasoning; problem-solving	88
	COWA	Verbal fluency	12,17,35,88
	D-KEFS	Problem-solving; flexible thinking; verbal and spatial fluency; concept formation; deductive reasoning; abstract thinking	92
	TMT-B	Cognitive flexibility; visuomotor speed	17,35,90
Learning and memory	Stroop test	Cognitive flexibility; resistance to interference; suppression of dominant verbal response	35,89,90
	CVLT-II	Verbal learning; information on acquisition, recall; retention, and retrieval of verbal information	92
	HVLT-R	Verbal memory; information on acquisition, recall; retention, recognition of verbal information	17,88
	RCFT (delayed recall)	Implicit visual-spatial memory	87
Language	WMS-III ^a	Auditory memory; visual memory; attention; working memory	92
	Digit span	Short-term auditory memory; working memory	87
	BNT	Category fluency; letter fluency;	17
	Subtests of AAT		
	Token test	Verbal comprehension; receptive language	17,88,90
	Naming	Word finding; expressive language	90
	Written language	Verbal academic skills	90
	Language comprehension	Auditory and reading comprehension	90
Visuospatial	Lexical word fluency	Phonological fluency	90
	RCFT (copy)	Visuoconstructional ability	87
	Block design	Spatial component in perception and motor execution	17,19,88
Processing speed	Clock drawing	Visuo-spatial and praxis abilities; visuospatial; Construction; abstract conceptualization	90
	TMT-A	Visual search speed; scanning	17,35,88,91
Motor	Grip strength	Hand strength	18,19,88
	Grooved pegboard	Manual dexterity; complex visual motor coordination	17-19,88
Intelligence	WAIS-III ^b	IQ; verbal comprehension; perceptual reasoning; processing speed; working memory	93,94
	American Nelson Test	Premorbid functioning	35

TMT = Trail Making Test; BCT = Booklet Category Test; COWA = Controlled Oral Word Association Test; D-KEFS = Delis-Kaplan Executive Function System; CVLT-II = California Verbal Learning Test, Second Edition; HVLT-R = Hopkins Verbal Learning Test - Revised; RAVLT = Rey Auditory Verbal Learning Test; WMS-III = Wechsler Memory Scale - Third Edition; AAT = Aachen Aphasia Test; BNT = Boston Naming Test - 2; RCFT = Rey Complex Figure and Recognition Trial; WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; WTAR = Wechsler Test of Adult Reading.

^aReferences used WMS-III. The WMS-IV is the most up-to-date version of this test.

^bReferences used WAIS-III. The WAIS-IV is the most up-to-date version of this test.

limits to define impairment are variable. The following domains and their corresponding measures have been commonly used in the assessment of adult glioma patients (reviewed in [Table](#)).⁶⁷

Intellectual Function and Premorbid Ability

The most widely used and established test of intelligence for adults is the Wechsler Adult Intelligence Scale (WAIS)-IV. It consists of 10 subtests measuring 4 cognitive domains to produce a full-scale intelligence quotient (IQ).⁶⁹ The following domains are assessed: verbal comprehension, working memory, perceptual

reasoning, and processing speed. Approximately 60 to 90 min are needed for completion. Verbal comprehension is assessed through the following subtests: similarities (describing how 2 words or concepts are similar), vocabulary (defining words presented), and information (general knowledge questions). Perceptual reasoning is assessed through block design (putting together blocks in a pattern according to a displayed model), matrix reasoning (viewing an array of pictures with a missing square and selecting a picture that fits the array from 5 options), and visual puzzles (viewing puzzles from a stimulus book and choosing from pieces

of which 3 could construct the puzzle). Working memory is assessed through the digit span subtest (listening to a sequence of numbers and repeating them as heard in reverse order and ascending order) and the arithmetic subtest (orally administered arithmetic word problems that are timed). Processing speed is assessed through timed tasks, such as the symbol search subtest (viewing rows of symbols and target symbols and marking whether or not target symbols appear in each row) and the coding subtest (transcribing a digit-symbol code using a key).⁶⁹

The WAIS IQ is highly correlated with tests of premorbid functioning when controlled for education,⁷⁰ and patients with gliomas are typically assessed as a baseline for future comparison. The National Adult Reading Test, Second Edition (NART-2)^{67,71} and the Weschler Test of Adult Reading (WTAR)⁷² are 2 commonly used measures of premorbid functioning that correlate with WAIS IQ scores. The NART-2 is used to estimate premorbid intellectual ability in adults ages 16 to 70 yr. The test requires the patient to read aloud 50 irregularly spelled words, with the accuracy of pronunciation used to predict IQ. Because the words are irregular, intelligent guesswork will not provide the correct pronunciation and performance therefore depends more on previous knowledge than on current cognitive capacity.⁷³ Similarly, the WTAR is used to assess premorbid intellectual functioning in individuals aged 16 to 89 yr. The test takes 5 to 10 min and involves reading 50 irregular words.⁷² Each item is individually presented on a word card, and examinees are asked to pronounce each word.⁷²

Attention and Processing Speed

This domain assesses a patient's ability to focus, divide, and sustain attention, as well as resist distraction.⁶⁷ The digit span subtest of the WAIS-IV has been found to be a valid and reliable measure of auditory attention, short-term memory, and mental manipulation.⁶⁹ The subtest involves: digit span forward, digit span backward, and digit span sequencing. A series of digits is read to the patient, who is required to then repeat the digits in the order they were presented (digit span forward).⁶⁹ The patient is then asked to recall digits presented in the reverse order (digit span backward), and lastly, the patient is required to repeat digits that are presented in sequential order from lowest to highest (digit span sequencing).⁶⁹ Processing speed, and visual and focused attention, is typically measured through the Trail Making Test (TMT).⁷⁴ The test usually takes less than 10 min to complete and involves 2 parts: Trail Making A (involves number sequencing) and Trail Making B (requires sequencing between letters and numbers).⁵ The test asks patients to connect circles numbered from 1 to 25 in order as quickly as possible. Scoring is based on the time it takes in seconds to complete the test.⁷⁴ The Stroop Color Word Test is another common assessment used in assessing attention as well as executive functioning. It involves 3 tasks: word reading, color naming, and color word naming.⁷⁵ In the last task, a patient is required to name as quickly as possible the ink color which is conflicting with the actual word. The task measures cognitive

flexibility, resistance to interference from outside stimuli, and the ability to suppress a dominant verbal response.

Memory

Memory tests assess visuo-spatial episodic memory, verbal memory, short-term memory, and working memory. A comprehensive assessment of memory is the Wechsler Memory Scale – Fourth Edition.⁷⁶ The test is co-normed with the WAIS-IV and provides 5 summary scores that assess the patient's auditory, visual, immediate, delayed, and visual working memory.⁷⁶ Auditory memory subtests (Logical Memory I and II and Verbal Paired Associates I and II) assess narrative memory both from free recall and a delayed recall to assess both short- and long-term narrative memory. The patient is presented with short stories and is asked to recall each story from memory immediately and after a delay period. This domain also assesses verbal memory for associated word pairs; the examiner reads word pairs to the patient and asks the patient to provide the corresponding word after reading the first word of each pair. A delayed condition to assess long-term recall is also given. The Visual Memory Index assesses memory for nonverbal stimuli by showing a series of designs to the patient and asking them to draw the design from memory immediately and after a delay period (Visual Reproduction I and II). Additional subtests in this domain assess spatial memory for unfamiliar visual material (Designs I and II) in which the patient is shown a grid with designs for several seconds and is then asked to select designs from a set of cards by placing them in a grid corresponding to the example image. The Visual Working Memory Index assesses visual-spatial working memory with the spatial addition subtest, where the patient is shown 2 grids with blue and red circles. The patient is asked to add or subtract the location of the circles based on a set of rules. Another subtest (symbol span) assesses visual working memory by briefly showing the patient a series of abstract symbols on a page and then asking the patient to select the symbols from an array of symbols in the same order they were presented in the previous page.

The California Verbal Learning Test – Second Edition (CVLT-II) is also used to assess memory.⁷⁷ The CVLT-II uses a shopping list format consisting of 16 words from 4 categories presented over 5 trials. After the 5 trials, an interference list is presented, followed by short-delay recall of the first list, and then long-delay recall after 20 min.

Executive Function

This domain encompasses a set of mental skills needed to achieve a goal, such as planning, organizing, focusing attention, judgment, reasoning, abstraction, self-regulation, and initiating or inhibiting a response.⁶⁷ The Delis-Kaplan Executive Function System (D-KEFS) is a comprehensive executive functioning measure that comprises of 9 tests designed to assess problem-solving, flexible thinking, verbal and spatial fluency, concept formation, planning and reasoning, verbal inhibition, hypothesis testing, deductive reasoning, and abstract thinking.⁷⁸ The Tower Test and TMT are subtests of the D-KEFS that are commonly

used to assess executive functioning.^{67,78} In addition to the TMT that was previously described, the Tower Test requires the patient to use verbal cues to deduce the meaning of made-up words. It measures deductive reasoning, integrating multiple pieces of information, hypothesis testing, and flexibility.⁵

Language

Tests that measure language for gliomas assess auditory comprehension, word retrieval deficits, and verbal association fluency. Common domain includes auditory language,⁶⁷ which is assessed using the Token Test.^{17,79,80} In this task, the patient is asked to follow simple commands (eg, “touch a circle”) which progresses toward more complex commands (eg, “before touching the yellow circle, pick up the red square”).¹⁷ Verbal fluency can be assessed by the Controlled Oral Word Association Test,⁷⁴ which measures the patient’s ability to maximally produce words belonging to a particular class.⁶⁷ It asks the patient to generate as many words as possible beginning with the letters F, A, and S in 1-min intervals. In category fluency, the patient is required to generate as many words as possible belonging to a particular category (eg, animals and fruits). Lastly, the Boston Naming Test-2 is used to assess confrontation naming and word retrieval.⁸¹

Visual Spatial and Visual Constructional Function

This domain evaluates visual perception and visuospatial abilities, including visual construction and visual integration.⁶⁷ Functioning in this domain is assessed through one of the following assessments: The Clock Test, the Block Design subtest of the WAIS-IV, or the Rey Osterrieth Complex Figure Test and Recognition Trial (RCFT). The Clock Test assesses visuospatial construction, visual perception, and abstract conceptualization.⁸² It involves 3 subtests including clock drawing, clock setting, and clock reading. It asks participants to draw a clock with all the numbers and set the hands of the clock to show a specific time. Following this, the patient is asked to copy a picture of a clock. The block design subtest of the WAIS-IV assesses 3-dimensional construction abilities.⁶⁹ It requires the patient to use colored blocks to construct replicas of designs that are shown from a stimulus book within a specified time limit. The copy phase of the RCFT assesses a patient’s visuo-constructional ability by evaluating accuracy of copying complex geometric figures.⁸³ The test consists of 4 trials, including copy, immediate recall, delayed recall, and recognition. The patient is asked to copy a figure and to reproduce the figure 3 min later and in a delayed fashion from memory.

Motor Function

Motor functioning is assessed through evaluation of a patient’s strength, coordination, and dexterity.⁶⁷ Typical tests used in this assessment include the grip strength test and the grooved pegboard. The test of grip strength uses a hand dynamometer to assess the patient’s strength in each hand.⁷⁴ The grooved pegboard test measures manual dexterity and requires complex visual-motor

coordination.¹¹ The test involves a board that consists of 25 randomly positioned keyholes. The patient must rotate the pegs to match the holes before the peg can be inserted into the keyhole on the board.¹¹

Emotion

Assessment of the patient’s emotional functioning is important to determine the patient’s emotional state during testing. Brain tumor patients have a higher level of depression and anxiety than the normal population,^{37,84} and these conditions are commonly evaluated to confirm the validity of cognitive testing as a highly anxious or depressive state can reduce performance.²¹ The Beck Depression Inventory⁸⁵ – Second Edition and the Beck Anxiety Inventory⁸⁶ are 2 of many common assessments that can be used in adults.

IMPLICATIONS FOR CURRENT AND FUTURE PRACTICE

Given the impact that glioma as well as oncologic therapy have on cognition, multidisciplinary cognitive rehabilitation is becoming recognized as a valuable component of care for glioma patients. There are 2 main interventional approaches underlying cognitive rehabilitation: retraining and functional compensation. Retraining involves strengthening impaired cognitive skills through repeatedly practicing cognitive tasks whereas functional compensation focuses on improving daily function through learned strategies that modify a patient’s environment or their approach toward achieving a goal. The goal of cognitive rehabilitation is to improve one’s autonomy, self-awareness, emotional coping, acceptance, and management of cognitive impairments. It has been proposed that cognitive retraining may facilitate functional network reorganization. This approach would permit neurosurgeons to offer “staged” procedures leaving tumor behind for later remapping after a period of network reorganization.

It must be pointed out that computerized cognitive training is a newly developing field of therapeutics for neurological and psychiatric disorders that uses frequent game like training sessions to drive CNS plasticity. It remains to be seen whether these tools impact outcomes. Furthermore, the idea of preventing treatment related cognitive impairments has gained popularity. Recently published data have begun to advocate for preoperative cognitive rehabilitation also known as “prehab,” as a means of preparing patients for oncologic interventions in an effort to reduce treatment-related cognitive impairments.^{85,86} More work is needed to determine if prehab may prevent cognitive impairments in glioma patients.

CONCLUSION

Low- and high-grade gliomas are characterized by neural network invasion that can lead to neurocognitive impairment prior to any therapeutic intervention. Neurocognitive testing is

valuable for assessing specific domains of cognition in patients with gliomas. Cognitive tasks may be selected in a patient- and site-specific manner based on symptoms and location of a tumor. More work is needed to elucidate how altered network dynamics impact specific neurocognitive domains and how neural networks may reorganize over time in response to tumor growth and surgical intervention.

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COMMENTS

These authors provide a brief introductory review cognition testing in glioma patients, that along with the entire series of manuscripts accompanying this one provides a very comprehensive review of this topic. In this manuscript, these authors argue that there may be benefit in more site-specific cognitive testing despite limited therapeutic options. Of course, the brain connectome shows widespread connections that can be impacted by focal lesions. Anticipating specific cognitive dysfunctions may be difficult for each focal lesion. Their review of specific cognitive tests is of good value to the neurosurgeon. Preoperative, intraoperative, and postoperative testing by the neurosurgical team and cognitive therapists may help guide therapeutic options and potentially modify tumor-specific therapies that are harming cognition. If anything, this manuscript emphasizes the complexity of the question at hand and illustrates the need for including cognitive therapists on our teams to care for these patients.

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The authors provide a nice overview of cognitive dysfunction in adult glioma as a guide for neurosurgeon. This is an interesting topic and of some importance to neurosurgeons. I appreciate the details in the domain description section about the steps and practical considerations of each task, in order to familiarize neurosurgeons with these tools. The authors point out that cognitive tasks are proprietary and unfortunately cannot reprint the specific images/stimuli from these tasks because they do not have permission to do so. I encourage them to follow up on this work with a review of the feasibility of an abbreviated neurocognitive testing paradigm for intraoperative use.

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