Neuro-Oncology Practice
5(3), 184–193, 2018 | doi:10.1093/nop/npx028 | Advance Access date 19 November 2017

Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma

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Abstract

Background. Cancer and treatment-related neurocognitive dysfunction has the potential to significantly disrupt the lives of survivors. While neurocognitive functioning is known to predict aspects of patient-reported quality of life in individuals with glioma, little is known regarding the association between neurocognitive functioning and clinician-rated functional independence.

Methods. Newly diagnosed patients with glioma in the left (n = 73; 49% glioblastoma) or right (n = 30; 57% glioblastoma) temporal lobe completed comprehensive neuropsychological testing. Clinicians rated patient functional independence using the Functional Independence Measure (FIM) and Karnofsky Performance Status (KPS) scale. Correlational and regression analyses were conducted to determine relationships between neurocognitive functioning and functional independence.

Results. Tests of verbal learning, executive function, and language comprehension were moderately to strongly associated with clinician-rated functional independence, particularly for items pertaining to need for assistance with memory, problem-solving, and language functions. Stepwise linear regression showed that tests of verbal learning, executive functioning, and language comprehension predicted FIM ratings, together accounting for 40% of variance ($P < .001$). A test of executive functioning also predicted KPS scores and accounted for 19% of variance ($P < .001$).

Conclusions. In patients with newly diagnosed temporal lobe glioma, neurocognitive functioning is associated with functional independence. Verbal learning, executive functioning, and language comprehension demonstrated the strongest associations across both measures of functional independence. These findings provide support for the ecological validity of neuropsychological assessment by demonstrating the real-world clinical significance of objectively assessed neurocognitive functioning in glioma patients.

Key words

brain tumor | cancer | functional status | neurocognitive function | neuropsychology

Although primary brain tumors are relatively rare, nearly 78,000 were expected to be diagnosed in 2016 with approximately 25,000 representing primary malignant glioma.[1] Accordingly, a sizeable number of patients require care each year, including interventions directed toward the tumor itself, as well as those aimed at prevention or amelioration of accompanying signs and symptoms. Unfortunately, prognosis remains poor for most patients with glioma, highlighting the importance of maximizing patient quality of life during the often limited survivorship period. Neurocognitive functioning is an important determinant of patient-reported quality of life and nearly all patients with glioma exhibit impaired neurocognitive functioning at some point in the disease.[2] However, the

relationship between neurocognitive functioning and ability to perform activities essential to independent daily living require further examination in this population.

Level of functional independence represents a key indicator of illness burden, generally referring to the ability to carry out day-to-day activities, including basic (eg, self-care, grooming) and instrumental (eg, medication and financial management, transportation) tasks.[3] Whereas quality of life indices are inherently subjective and tap a patient's inner experience (eg, feeling close to friends or family, experience of worry), measures of functional independence aim to evaluate the extent to which a patient is independently engaging in specific daily activities (eg, assistance required when eating, help needed to meet other basic daily needs). Functional independence inventories are often rated by an observer, such as an attending clinician, with support from accompanying collateral information helping to reduce confounding reporter bias. Unsurprisingly, patients with brain tumors exhibit reduced functional independence and autonomy in daily living, often necessitating supervision or assistance with both instrumental and basic activities.[4] While little empirical work has examined neurocognitive functioning in relation to clinician-rated functional independence in patients with brain tumors, neurocognitive impairment is a known predictor of functional independence deficits across numerous other neurological populations, including multiple sclerosis,[5] mild cognitive impairment,[6] and Alzheimer's disease.[7] In particular, executive functioning and learning and memory appear to have the strongest relationships with functional independence, underscoring the important role of these domains in successfully executing skill-based practical activities.[8,9]

Executive functioning and memory also represent the domains most frequently impaired in patients with primary brain tumors, particularly when lesions are located within frontal and temporal regions.[10–12] When considering temporal lobe tumors specifically, we previously demonstrated that 74% of patients exhibit significant neurocognitive impairment prior to treatment (ie, at least 1.5 standard deviations below normative means), most commonly in executive functioning and verbal learning.[10] Importantly, deficits in these domains were associated with patient-reported quality of life. Verbal learning predicted patient appraisal of general well-being and neurological symptoms, and executive functioning predicted patient perception of functional capacities. However, clinician-rated measures of functional independence were not included in the analyses.

The present study extends our prior work by characterizing relationships between neurocognitive functioning and clinician-rated functional independence in patients with newly diagnosed glioma of the temporal lobes. The focus on patients with lesions isolated to the temporal lobes was deliberate, as the temporal lobes represent one of the most common locations of glioma. Temporal lobe structures also support memory and higher order cognitive systems critical for maintaining functional independence. Limiting heterogeneity in lesion location allows for greater specificity of findings, yielding information particularly useful in the management and study of patients with glioma in this common lesion location. It was expected that neurocognitive functioning would be at least moderately associated with clinician-rated functional independence, given the numerous neurocognitive demands required to negotiate the varied tasks of daily living.[13] We further hypothesized that memory and executive functioning would show the greatest relationships with functional independence in light of findings in other neurological populations noted above. However, impairment in neurocognitive functioning was expected to occur more frequently than daily functional deficits given the sensitivity of neurocognitive functioning measures to changes that may not be readily observable to a clinician or fully appreciated by the patient or collateral informant.[14,15]

Materials and Methods

Participants

Inclusion/exclusion criteria and data collection procedures were conducted as previously described.[10] Briefly, newly diagnosed adult patients with glioma of the left temporal lobe or right temporal lobe were identified in the University of Texas MD Anderson Cancer Center (MDACC) neuropsychology and neurosurgery databases. Patients were included if they underwent comprehensive neuropsychological evaluation prior to treatment. One hundred three patients met criteria and completed presurgical neuropsychological evaluation between 2001 and 2010. The MDACC Institutional Review Board approved this retrospective study.

As described previously[16] and further detailed elsewhere,[17] volumetric analysis was performed on MRI scans with MedVision 1.41 software. FLAIR volume was considered representative of overall lesion volume, including tumor and perilesional edema.

Neurocognitive Testing

Neurocognitive testing was conducted as part of a comprehensive presurgical neuropsychological evaluation for clinical purposes. Table 1 lists the neuropsychological tests by domain that were routinely included in the clinical test battery and the sources of normative comparison groups.[18–25] The number of patients administered a given NCF test differed by instrument, as the evaluations utilized a flexible battery and were performed for clinical purposes. Sample sizes are described by test in the table accompanying the results. Approximately half of the total sample did not have data for the HVLT-R DR and HVLT-R Rec variables, as clinic practices initially utilized an earlier version of the HVLT that did not include the delayed memory trials. Nonetheless, HVLT-R TR trials are identical between versions, and HVLT-R normative data were used for all HVLT variables, as indicated in Table 1.

All neurocognitive test scores were converted to z-scores (M = 0, SD = 1) using published normative data stratified by age and other demographic characteristics when appropriate (see Table 1). Performance on an individual neurocognitive functioning test that fell at or below a z-score of -1.5 was considered indicative of clinically

Table 1 Neurocognitive Tests Grouped by Principal Domain

Test	Abbreviation	Norms
Attention		
WAIS-R/III Digit Span	Digit Span	Wechsler[18,19]
Learning and Memory		
HVLT-R Total Recall	HVLT-R TR	Benedict et al.[20]
HVLT-R Delayed Recall	HVLT-R DR	Benedict et al.[20]
HVLT-R Recognition Discrimination Index	HVLT-R Rec	Benedict et al.[20]
Processing Speed		
WAIS-R/III Digit Symbol	Digit Symbol	Wechsler[18,19]
Trail Making Test Part A	TMTA	Tombaugh[21]
Executive Function		
Trail Making Test Part B	TMTB	Tombaugh[21]
WAIS-R/III Similarities	Similarities	Wechsler[18,19]
MAE Controlled Oral Word Association	COWA	Ruff et al.[22]
Language		
MAE Visual Naming or Boston Naming Test	Naming	Benton et al.[23]; Heaton et al.[24]
MAE Token Test	Token	Benton et al.[23]
Visuospatial Function		
WAIS-R/III Block Design	Block Design	Wechsler[18,19]
Motor Function		
Grip Strength right hand	Grip-right	Heaton et al.[24]
Grip Strength left hand	Grip-left	Heaton et al.[24]
Grooved Pegboard right hand	Peg-right	Trites[25]
Grooved Pegboard left hand	Peg-left	Trites[25]
Clinical Trial Battery Composite	CTB Comp	Mean of *z* scores from the HVLT-R, COWA, and TMT using the above norms

Abbreviations: WAIS-R/III, Wechsler Adult Intelligence Scale-Revised or Third Edition; HVLT-R, Hopkins Verbal Learning Test-Revised; MAE, Multilingual Aphasia Examination.
Note. Norms refer to sources of normative comparison groups.

significant impairment, consistent with common convention in neuropsychological practice. CTB Comp is the mean of z-scores for COWA, TMTA, TMTB, HVLT-R TR, HVLT-R DR, and HVLT-R Rec. CTB Comp z-scores at or below -0.70 were considered indicative of impairment based on the results of prior receiver operating characteristic analyses (unpublished data).

Functional Independence

At the time of neuropsychological evaluation, neuropsychologists completed the Functional Independence Measure (FIM) based on clinical interview with the patient, collateral information provided by family or a caregiver where possible, and medical record review. All neuropsychologists were trained in the administration and scoring of the FIM using the standardized FIM User Manual and scoring rubric. The FIM is an 18-item inventory measuring degree of disability and burden of care, including 13 items reflecting physical functions and 5 items reflecting cognitive functions (see Table 2).[26] Items are scored on a Likert-type scale from 1 (total dependence) to 7 (total independence), yielding a total score on an ordinal scale ranging from 18 to 126. Higher scores indicate better functional ability and less dependence upon caregiver assistance. The FIM has been validated in numerous neurological populations.[27–33] While existing data pertaining to the validity of the FIM in patients with glioma are limited, preliminary evidence suggests that total scores are sensitive to change in daily functioning in a small sample of individuals with brain tumors of heterogeneous histologies.[34] The FIM was unavailable for 4 patients.

Functional independence was also evaluated with the Karnofsky Performance Status (KPS) scale.[35,36] The KPS is a clinician-rated scale commonly utilized in oncology settings, including clinical trials.[37,38] The treating physician completed the KPS based upon interview and neurologic exam, yielding a general rating of patient ability to carry out daily activities and the presence of overt signs and symptoms of disease. Ratings lie on an ordinal scale ranging from 0 to 100 in 10-point increments, with a score of 100 reflecting no complaints or evidence of disease and a score of 0 reflecting death. KPS scores were extracted from medical records of the neurological or neurosurgical encounter

Table 2 Functional Independence Measure Subscales and Items

Physical Items	Cognitive Items
Self-Care	*Communication*
1. Eating	14. Comprehension
2. Grooming	15. Expression
3. Bathing	*Social Cognition*
4. Dressing, upper body	16. Social Interaction
5. Dressing, lower body	17. Problem-Solving
6. Toileting	18. Memory
Sphincter Control	
7. Bladder Management	
8. Bowel Management	
Transfers	
9. Bed/Chair/Wheelchair	
10. Toilet	
11. Tub/Shower	
Locomotion	
12. Walk/Wheelchair	
13. Stairs	

within closest proximity to the date of neuropsychological evaluation (usually the same day but within 1 week). KPS ratings were unavailable for 28 patients.

Statistical Analysis

Independent-samples *t* tests or Pearson's χ^2 tests were used to compare clinical characteristics between left temporal lobe and right temporal lobe patient groups, and those with and without KPS scores, to assess for potential biases in the sample. Relationships between measures of functional independence and age, education, lesion volume, and steroid and antiepileptic medication use were determined with Spearman (ρ) correlations and Mann Whitney U tests. Associations between FIM and KPS scores, individual FIM items, and measures of neurocognitive functioning were determined with Spearman correlations. Using Cohen's guidelines, correlation coefficients of 0.1, 0.3, and 0.5 corresponded to weak, moderate, and strong associations, respectively.[39] Separate stepwise multiple regression analyses were conducted with neurocognitive measures as predictors of FIM and KPS. The HVLT-R DR, HVLT-R Rec, and CTB Comp variables were excluded because of the reduced sample sizes on these measures. Patients were included in regression analyses only if they completed all other neurocognitive functioning measures and the FIM (n = 86) or KPS (n = 65). Despite sample size limitations, particularly for analyses involving KPS, regression analyses were adequately powered. Considering an alpha of 0.05, a desired power of 0.80, and 14 predictors (all included neurocognitive functioning tests), power analysis determined that a sample size of 66 was adequate for detecting moderate to large effect sizes in multiple regression analyses. For all regression procedures, a predictor was deleted if alpha > 0.10 and added if alpha < 0.05. Adjusted R^2 was used to determine the amount of variance accounted for by the models, correcting for the number of predictors in the model. Statistical analyses were performed with SPSS 21.0 (IBM Corp).[40] Given the exploratory nature of the study, two-sided tests were used with a significance level of $P < .05$.

Results

Patient Characteristics

Demographic and clinical characteristics are presented in Table 3. The majority of patients were diagnosed with high-grade tumors (78%) and 71% of tumors were located in the left temporal lobe. Patient characteristics did not significantly differ between left temporal lobe and right temporal lobe groups.

Neurocognitive Functioning and Functional Independence

Descriptive data regarding neurocognitive test performances and ratings of functional independence are presented in Table 4. Most patients (74%) exhibited clinically significant neurocognitive impairment on at least one test, most frequently in verbal learning (HVLT-R TR, 44%), memory (HVLT-R DR, 37%), and executive functioning (TMTB, 36%). Nearly 20% exhibited impairment on the composite, CTB Comp.

On average, functional independence ratings on FIM total and KPS scores indicated a relatively high level of general functional independence, particularly regarding physical functioning. Specifically, 82% of patients had KPS ratings of at least 90, 12% had ratings of 80, and no patients had ratings below 70. Regarding the FIM, over 90% of patients received maximal ratings of 7 on all individual items in the Physical domain (i.e. items 1–13). In contrast, maximal scores were less frequent across Cognitive items on the FIM, with 54% receiving a rating of less than 7 on the Memory item, 21% on the Comprehension item, and 17% on the Expression and Problem-Solving items. However, relatively few patients (8%) were rated below 7 on the Social Interaction item.

Associations Between Clinical Characteristics, Neurocognitive Functioning, and Functional Independence

Age showed a significant moderate inverse association with functional independence on the FIM [$\rho(97) = -0.38$, $P < .001$] and a weak association with KPS [$\rho(73) = -0.23$, $P = .048$]. Functional independence ratings were not significantly associated with education, lesion volume, tumor grade, or steroid use for either measure. Patients with history of seizures showed better functional independence on the KPS than those without seizures, though medians were equivalent [Median = 90.0 vs 90.0; U(74) = 907.00, $P = .035$]. Those taking antiepileptic medications also

Table 3 Demographic and Clinical Characteristics

	LTL (N = 73)	RTL (N = 30)	Total (N = 103)
Age, years			
Mean (SD)	51.3 (14.4)	53.6 (11.1)	52.0 (13.5)
Range	18–78	25–73	18–78
Gender, % Male	56.2	63.3	58.3
Race, % White	87.7	93.3	89.3
Handedness, % Right	86.3	83.3	85.4
Education, years			
Mean (SD)	14.6 (2.6)	14.6 (2.0)	14.6 (2.4)
Range	7–20	11–19	7–20
Histology, %			
Glioblastoma	49.3	56.7	51.5
Astrocytoma	21.9	23.3	22.3
Oligodendroglioma	16.4	10.0	14.6
Other	12.3	10.0	11.7
WHO Tumor Grade, %			
IV	50.7	56.7	52.4
III	27.4	20.0	25.2
II	20.5	23.3	21.4
I	1.4	0.0	1.0
Lesion Volume, cm^3			
FLAIR, Mean (SD)[1]	47.1 (44.1)	55.8 (47.2)	49.6 (45.0)
Seizure History, % yes	43.8	36.7	41.7
Antiepileptic Drug, % yes[2]	64.5	70.4	66.0
Steroid, % yes[3]	56.9	56.0	57.3
KPS, %			
>80	96.0	94.0	94.6

Abbreviations: LTL, left temporal lobe; RTL, right temporal lobe.
[1]LTL n = 71; RTL n = 29.
[2]LTL n = 62; RTL n = 27.
[3]LTL n = 58; RTL n = 25.

showed better functional independence on the KPS than those not on the medications, though medians were again equivalent [Median = 90.0 vs 90.0; U(68) = 665.00, $P = .023$]. Distribution of tumor grade did not differ by seizure status or antiepileptic drug use. FIM scores did not differ by seizure status or antiepileptic use.

Associations between tests of neurocognitive functioning and functional independence measures are displayed in Table 5. Significant associations were found between the FIM and 13 of 17 neurocognitive functioning tests. Of these, the FIM was moderately to strongly associated with verbal learning, executive functioning, language comprehension, and the composite measure. Regarding the KPS, significant associations were identified for 6 of 17 neurocognitive functioning tests. Relationships were moderate for attention, verbal learning, executive functioning, and language comprehension.

Relationships between individual items on the FIM and tests of neurocognitive functioning were also examined for exploratory purposes. Associations between Physical items and neurocognitive functioning tests were non-significant or weak ($\rho < 0.21$). In contrast, numerous significant and moderate-to-strong relationships were found between neurocognitive functioning tests and Cognitive items from the FIM, with the exception of the Social Interaction item. The Comprehension item was strongly associated with a language comprehension test [Token: $\rho(98) = 0.51$, $P < .001$] and moderately associated with tests of auditory attention [Digit Span: $\rho(98) = 0.40$, $P < .001$], verbal learning [HVLT-R TR: $\rho(98) = 0.42$, $P < .001$], and executive functioning [TMTB: $\rho(94) = 0.45$; Similarities: $\rho(94) = 0.38$; COWA: $\rho(97) = 0.44$; all $P < .001$]. The Expression item was moderately associated with tests of auditory attention [Digit Span: $\rho(98) = 0.39$, $P < .001$], verbal learning [HVLT-R TR: $\rho(98) = 0.35$, $P < .001$], and expressive language and language comprehension [Naming: $\rho(97) = 0.35$; Token: $\rho(98) = 0.41$; all $P < .001$]. The Problem-Solving item was moderately associated with

Table 4 Neurocognitive Test Scores and Functional Independence Ratings

	N	Mean (SD)	Range	% Impaired
Neurocognitive Test[1]				
Digit Span	103	-0.43 (0.86)	-2.33–2.33	18.4
HVLT-R TR	103	-1.28 (1.53)	-6.16–1.37	43.7
HVLT-R DR	51	-1.22 (1.82)	-5.47–1.22	37.3
HVLT-R Rec	51	-0.86 (1.84)	-7.71–0.86	18.4
Digit Symbol	102	-0.04 (1.00)	-2.33–2.33	10.8
TMTA	101	-0.30 (1.99)	-14.75–1.79	13.9
TMTB	97	-1.26 (2.48)	-11.91–2.06	36.1
Similarities	98	-0.21 (0.86)	-2.33–2.33	14.3
COWA	102	-0.57 (1.13)	-3.66–1.61	15.7
Naming	101	-0.65 (1.30)	-5.20–1.80	18.8
Token	97	-0.05 (1.11)	-2.33–0.92	17.6
Block Design	101	-0.04 (0.92)	-2.00–2.67	6.9
Grip-right	98	0.46 (1.23)	-2.00–3.00	3.0
Grip-left	97	0.62 (1.31)	-3.09–3.00	1.0
Peg-right	101	-0.82 (1.89)	-11.25–1.66	24.0
Peg-left	101	-0.85 (1.97)	-14.96–1.33	24.8
CTB Comp	49	-0.80 (1.03)	-3.86–1.06	19.4
Functional Independence[2]				
FIM	99	Median = 125	108.00–126.00	—
KPS	75	Median = 90.00	70.00–100.00	—

Abbreviations: See Table 1 for abbreviations of neurocognitive tests. FIM, Functional Independence Measure; KPS, Karnofsky Performance Status scale.
[1]*z* scores
[2]Raw scores

language comprehension [Token: $\rho(98) = 0.36$, $P < .001$]. The Memory item was strongly associated with verbal learning [HVLT-R TR: $\rho(98) = 0.55$, $P < .001$] and moderately associated with executive functioning [Similarities: $\rho(94) = 0.39$, $P < .001$] and language comprehension [Token: $\rho(98) = 0.43$; $P < .001$].

Neurocognitive Predictors of Functional Independence

Regression analyses were conducted on subsamples. For the FIM, patients were included if they completed all neurocognitive functioning predictors and had FIM ratings (n = 86). For the KPS, patients were included if they completed all neurocognitive functioning predictors and had KPS ratings (n = 65). Given the reduced sample size for KPS analyses, preliminary analyses were conducted to determine the representativeness of the subsample to the broader overall sample. Patient characteristics and neurocognitive test performances did not significantly differ between those with and without KPS scores. Given that age was significantly associated with KPS and FIM, and antiepileptic use was significantly associated with KPS, these variables were included as predictors in regression analyses along with neurocognitive functioning tests. Results of stepwise linear regression analyses are summarized in Table 6. Tests of verbal learning [HVLT-R TR: $F(1,83) = 35.28$, $P < .001$], executive functioning [TMTB: $F(2,82) = 23.87$, $P < .001$], and language comprehension [Token: $F(3,81) = 19.86$, $P < .001$] were significant predictors of FIM scores, together accounting for 40% of the variance. For the KPS, executive functioning was the only significant predictor [TMTB: $F(1,61) = 15.54$, $P < .001$], accounting for 19% of the variance. Age and antiepileptic use were not significant predictors in any models.

Discussion

Most neurocognitive tests exhibited significant relationships with measures of functional independence, though as hypothesized, associations were strongest for measures of verbal learning and executive functioning. These represent the same domains that we previously demonstrated to be most frequently impaired in newly diagnosed patients with temporal lobe glioma.[10] Language comprehension also appeared related to functional independence in patients with temporal lobe glioma, though to a lesser extent than verbal learning and executive functioning. Taken together, these findings suggest a central role for

memory, executive functioning, and language comprehension in maintaining functional independence. In other words, as gliomas compromise both local and distributed networks involving the temporal lobes, reductions in patient ability to comprehend, acquire new information, and flexibly reason translate to problems executing basic and instrumental daily activities.

Table 5 Correlations Between Neurocognitive Tests and Measures of Functional Independence

Test	FIM	KPS
Digit Span	0.39***	0.30**
HVLT-RTR	0.49***	0.37**
HVLT-R DR	0.29*	0.12
HVLT-R Rec	0.25	0.07
Digit Symbol	0.32**	0.26*
TMTA	0.11	0.21
TMTB	0.42***	0.42***
Similarities	0.39***	0.23
COWA	0.32**	0.28*
Naming	0.25*	0.08
Token	0.47***	0.31**
Block Design	0.35**	0.08
Grip-right	-0.08	-0.01
Grip-left	-0.21*	-0.19
Peg-right	0.21*	0.15
Peg-left	0.14	0.12
CTB Comp	0.42**	0.23

Abbreviations: See Table 1 for abbreviations of neurocognitive measures. FIM, Functional Independence Measure; KPS, Karnofsky Performance Status scale.
Data represent Spearman rank-order correlation coefficients (ρ).
*$P < .05$. **$P < .01$. ***$P < .001$.

Notably, relationships between tests of neurocognitive functioning and functional independence were stronger for the FIM than KPS. This likely pertains, at least in part, to differences in scale composition. Whereas the KPS is a global scale comprised of a unitary construct of overall functional status, the FIM contains items each rated with respect to discreet aspects of patient functioning. Further, 5 of the FIM's 18 items pertain to the Cognitive domain, broadly categorized as "Communication" (Comprehension, Expression) and "Social Cognition" (Social Interaction, Problem-Solving, Memory). Neurocognitive tests were largely unrelated to the 13 items within the Physical domain. In contrast, the Cognitive FIM items (with the exception of Social Interaction) were moderately to strongly associated with various tests of language, attention, verbal learning, and executive functioning. As such, the FIM appears better suited to capture changes in functional independence related to neurocognitive functioning impairment than the KPS, at least in patients with newly diagnosed temporal lobe lesions. Taken together, results indicate that performance on objective neurocognitive tests appears robustly related to increased need for assistance in cognitively demanding domains of daily living.

Although age was associated with functional independence, relationships between neurocognitive functioning and functional independence were independent of age. Specifically, relationships between neurocognitive functioning and functional independence ratings remained significant despite the fact that neurocognitive test scores were age-adjusted and age was included in all regression analyses as a predictor alongside all neurocognitive tests. Interestingly, patients with seizures and those taking antiepileptic medications showed better functional independence on the KPS than those without seizures or not on this class of medication. A potential explanation of this finding includes the fact that seizures tend to occur more frequently in patients with lower grade lesions who also tend to show better preserved neurocognitive functioning and performance status. However, functional status, seizure status, and antiepileptic use did not differ between high-grade

Table 6 Predictors of Functional Independence

Functional Independence Measure (FIM)	Neurocognitive Predictor(s)	Unstandardized B	Standard Error B	Standardized β	*P* value	Adjusted R^2
FIM[1]						
Model 1	HVLT-RTR	1.19	0.20	0.54	< .001	0.29
Model 2	HVLT-RTR	0.91	0.21	0.42	< .001	0.35
	TMTB	0.37	0.12	0.29		
Model 3	HVLT-RTR	0.64	0.23	0.29	< .001	0.40
	TMTB	0.34	0.12	0.26		
	Token	0.80	0.29	0.27		
KPS[2]						
Model 1	TMTB	1.37	0.36	0.44	< .001	0.19

Note. See Tables 1 and 3 for abbreviations. HVLT-R DR, HVLT-R Rec, and CTB Comp were excluded due to reduced sample size for these variables.
[1] n = 85.
[2] n = 64.

and low-grade patients, though this may relate to the relatively few patients with low-grade tumors in the sample. Accordingly, the significance of relationships between functional independence, neurocognitive functioning, and seizure status and antiepileptic use remains unclear and requires further investigation in independent and larger samples. Regardless, regression analyses demonstrated that relationships between neurocognitive functioning and functional independence were independent of potential confounds, including age, seizure status, and medication use.

The main findings dovetail with our prior demonstration of the importance of verbal learning and executive functioning to the health-related quality of life of patients with temporal lobe glioma.[10] However, based on the current results, tests of neurocognitive functioning appear to be far better predictors of functional independence than quality of life in this population. That is, up to 40% of variance in patient functional independence was accounted for by objective neurocognitive tests of learning, executive functioning, and language comprehension, while neurocognitive test results accounted for only 6% to 13% of variance in quality of life. This adds to the growing body of literature supporting the validity of neurocognitive testing in patients with glioma. Specifically, other studies have shown that neurocognitive functioning is sensitive to disease progression,[41,42] varies by genetic tumor subtype,[43] and is a strong predictor of overall survival.[44] In addition to such criterion-related validity, the present data support the ecological validity of neurocognitive testing in this population—namely, that reductions in neurocognitive functioning are not only accompanied by decrements in patient self-reported well-being, but also signal declining ability to perform important "real-world" functions.

It is important to note that these relationships were observed within the context of relatively restricted ranges on the total scores from the functional independence measures, particularly for the KPS. That is, only 5% of patients had ratings below 80 on the KPS, indicating that most were considered capable of completing normal activities with only minor signs or symptoms. Similarly, when considering the Physical domain on the FIM, nearly all patients were rated as completely independent across individual items (ie, scores of 7). This may relate, in part, to the fact that the KPS and Physical subscale of the FIM emphasize physical aspects of patient functioning that tend to be infrequently compromised in patients with temporal lobe lesions at baseline. Indeed, less than 5% of the sample exhibited significant upper extremity grip weakness and less than 25% had significant manual dexterity impairment on objective testing.

Relatively preserved physical functional independence is not entirely surprising given that patients are newly diagnosed, harbor temporal lobe lesions, and are assessed prior to surgery. It is possible that functional independence ratings will change following neurosurgery, as some physical functions may be more likely to become impacted. Similarly, patients with lesions resulting in greater motor impairment (eg, those involving perirolandic regions or corticospinal tracts) may be particularly likely to exhibit reductions in functional independence on these physically oriented scales. Future work is needed to investigate longitudinal changes in functional independence and relationships with neurocognitive and motor abilities, as well as such relationships in patients with other lesion locations.

In contrast to the relatively preserved functional independence on the KPS and the Physical domain of the FIM, greater variance was noted when examining items from the Cognitive domain of the FIM. Specifically, a sizeable proportion of patients (17% to 54%) were rated as modified independent or dependent across Memory, Comprehension, and Problem-Solving items, indicating some need for assistance in associated daily functions. For example, some patients and caregivers report that patients may need reminders, rely upon written notes, require cueing and prompting for task completion, assistance with medication and financial management, and may even be unable to make independent informed decisions. While we hypothesized that objective neuropsychological testing would reveal that neurocognitive impairment occurs more frequently than reductions in functional independence, rates of impairment on neurocognitive tests analogous to FIM Cognitive items were actually similar to rates of functional deficits. However, it should be noted that correspondence between neurocognitive function and functional activity is not exact. For example, reductions in FIM activities labeled "memory" (eg, difficulty executing requests without being reminded) can be due to impairment in multiple aspects of cognitive function including memory function, but also executive function, attention, and/or language processes. It should be emphasized that the intention of the FIM is not to diagnose disorders of cognition but to rather identify severity of disability.

As with our previous work,[10] the greatest limitation of the study pertains to sample size variation across measures. Patients were referred for clinical purposes, clinical practices changed over time, and the battery of measures was necessarily flexible to accommodate for unique referral questions and patient needs. Unfortunately, this means that not all patients were administered each neurocognitive functioning test and not every patient received evaluation of functional independence with the FIM and KPS. The sample size was particularly reduced for delayed memory tests given changes in the test form utilized in clinical practice. This may account for the lack of association between delayed verbal memory tests and functional independence, which was expected given the strong associations between verbal learning and functional independence. Additionally, results of regression analyses should be interpreted with some caution given that sample sizes were reduced, as only patients completing all neurocognitive functioning tests and having functional independence measures could be included in analyses. Nonetheless, the subsamples involved in regression analyses were similar to the broader sample on relevant characteristics, and results of regression analyses were consistent with the correlational analyses involving the larger sample.

The functional independence measures relied primarily upon patient report of functioning and/or the presence of signs and symptoms from relatively brief clinical examination. Further, the FIM has not been well-validated in patients with glioma. In turn, it is possible that the information captured from these functional independence measures may not sufficiently reflect a patient's veridical functional capabilities in relevant daily domains. While caregiver report may help improve the ecological validity of clinician functional independence ratings, caregiver reports were not available for all patients.

Additionally, data regarding usage of caregiver reports were not recorded, precluding examination of the potential impact of such information upon clinician ratings. Accordingly, future studies are needed that capture caregiver reports and examine the convergent and criterion-related validity of the FIM and other measures of functional independence in this population. This work would also benefit from inclusion of performance-based measures akin to actual tasks performed in daily living, as these measures improve ecological validity and sensitivity to reductions in functional independence.[45]

Clinicians often evaluate patient functional independence within the broader context of questions of disability. Determination of capacity is essential to understanding the objective impact of disease upon functional independence, and ultimately, disability status. The World Health Organization (WHO) makes a useful distinction between "capacity" to participate and "performance/participation restriction" when describing disability (for detailed discussion see WHO[46]). To assess "capacity," one needs to establish a "standardized environment" independent of "contextual factors," such as environmental contributors and psychosocial characteristics. That is to say, formal assessment of capacity requires establishment of a "sterile" environment in which the person can objectively demonstrate the ability (or lack thereof) to perform a specific behavior of interest. In this regard, formal neuropsychological evaluation involving standardized neurobehavioral tasks provides an optimal setting to discern the impact of a particular disease/illness upon neurofunctional capacity, free from the influence of contextual factors. Importantly, these results provide evidence that capacity as measured with formal neurocognitive functioning testing is associated with patient functional independence in real-world context, supporting the use of neuropsychological testing to inform questions of disability in patients with glioma.

Overall, the findings support the primary study hypothesis that neurocognitive functioning is strongly related to functional independence in patients with temporal lobe glioma, even prior to treatment when patient physical independence is relatively preserved. Clinically, the current results add support for the routine assessment of neurocognitive functioning in patients with glioma and the meaningfulness of changes in cognitive function to patient independence. Given that reduced functional independence is also associated with increased caregiver distress,[47] neuropsychological evaluation may help identify patients at risk for early functional disability and provide caregivers with important information to help maximize the quality of life of those affected by this often devastating disease.

Funding

Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health under Award Number R01NR014195 (J.S. Wefel). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest statement. None declared.

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