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Impact of Subventricular Zone Invasion on Preoperative Cognitive Decline in Patients with Diffuse Glioma

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BACKGROUND AND OBJECTIVES: To assess the impact of subventricular zone (SVZ) invasion on neurocognitive dysfunction in patients with diffuse glioma.

METHODS: We analyzed neuropsychological assessments of 129 patients with World Health Organization grade 2-4 treatment-naive diffuse glioma (2017-2023). Univariable and multivariable regression analyses were used to identify factors associated with cognitive dysfunction. A nomogram was developed to predict cognitive impairment probabilities, and the model's predictive accuracy was assessed using area under the curve. Statistical analyses were performed using IBM SPSS 20 and R. A *P*-value of <.05 was considered significant.

RESULTS: SVZ invasion (SVZ+) was present in 64 patients and was linked to more cognitive deficits compared with SVZ− (65 patients). In low-grade gliomas, SVZ+ increased risks of language and visual learning impairments, whereas in high-grade tumors, it heightened language and auditory learning vulnerabilities. In right hemispheric tumors, SVZ+ conferred worse global cognition, executive, and language function; in left hemispheric tumors, SVZ+ increased risks of language and auditory learning impairments. Frontal horn of SVZ+ was related to working memory decline, and body part of SVZ+ was related to emotional deficits. SVZ+ was an independent predictor of cognitive decline alongside age, T2 volume, and World Health Organization grade. A final model and nomogram composed of age, T2 volume, and SVZ invasion achieved moderate predictive accuracy (area under the curve 0.749) for cognitive dysfunction.

CONCLUSION: SVZ invasion affects preoperative neurocognitive function independent of tumor laterality and grade, with distinct SVZ subregions associated with specific cognitive impairments. These findings highlight the need for precise tumor mapping considering the SVZ to evaluate neurocognitive outcomes and consider preventive or rehabilitative interventions.

KEY WORDS: Cognitive function, Diffuse glioma, Gliomagenesis, Oncofunctional balance, Subventricular zone, White matter tract

ABBREVIATIONS: CTX, cortex; **HGG,** high-grade glioma; **LGG,** lower grade glioma; **NPA,** neuropsychological assessments; **SVZ,** subventricular zone; **WHO,** World Health Organization.

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The intricate relationship between gliomas and the subventricular zone (SVZ) has been a focal point in neuro-oncological research, with notable attention paid to the impact of SVZ involvement on clinical outcomes.[1-5] Previous research has demonstrated that patients with high-grade glioma (HGG) involving the SVZ experienced reduced overall survival and progression-free survival.[1] Further studies have indicated that SVZ involvement similarly affects low-grade glioma, leading to poorer survival.[2-4] On the other hand, researchers have shown that cognitive, emotional, and physical functioning are predictors of poor outcomes, highlighting the possible relationship between cognitive impairments and the severity of tumor infiltration.[6-10] Although existing literature has explored the connection between SVZ involvement and cognitive decline, both leading to worst survival, a notable gap persists regarding the cognitive consequences associated with SVZ-invaded gliomas.

Previous evidence suggests the role of neurogenesis of stem cells in the SVZ to cognitive function and diseases. Investigation of SVZ neurogenesis in an Alzheimer's disease mouse model has shown that neural stem cell proliferation and migration in the SVZ decline in the early stage of mouse development.[11-13] On the other hand, transplantation of SVZ-derived neural stem cell has been shown to protect against hippocampus degeneration and reverse cognitive dysfunction in a temporal lobe epilepsy mouse model.[14] These findings provide direct evidence supporting the role of neural stem cells in the SVZ in relation to cognitive functions in different disease models. However, to our knowledge, no study has addressed SVZ invasion and cognitive dysfunction in a diffuse glioma model.

Although several studies have documented cognitive impairment in patients with diffuse glioma before treatment,[15,16] the specific impact of glioma involving SVZ invasion on cognitive function remains unknown. Neuroanatomically, the SVZ is surrounded by deep nuclei, including the caudate, basal ganglion, thalamus, and hippocampus, as well as long association fibers, callosal fibers, and projection fibers.[17,18] The concept that deep white matter injury may significantly impair cognitive recovery has been demonstrated in a human glioma study.[19] We therefore hypothesized that patients with SVZ-invaded glioma have worsened cognitive function than noninvaded ones. In this retrospective study, we aimed to test the hypothesis by comprehensively analyzing neurocognitive decline in patients with treatment-naïve diffuse glioma.

METHODS

This is a single-center study in which we retrospectively collected neuropsychological assessments (NPA) of patients with treatment-naïve diffuse glioma from the awake craniotomy database. Written informed consent was obtained from each patient. This study was approved by the Institutional Review Board (No. 202300907B0). The data that support the findings of this study are available from the corresponding author (K.T.C.), on reasonable request. The study does not include data linkage across 1 or more database.

Study Population

A retrospective cohort study of consecutive patients with pathology-proven diffuse glioma (World Health Organization [WHO] grade 2 to 4), located in or near the cerebral eloquent cortex (CTX) who underwent awake neurosurgery was reviewed from 2017 to 2023. Patients younger than 18 years of age, those with other pathologies, incomplete medical records, or who were unable or refused to participate in NPA were excluded from the study. NPAs were performed before any diagnostic or therapeutic interventions, including biopsy, surgical resection, chemotherapy, or radiation therapy. Each patient received T1-weighted MRI after contrast enhancement and T2 fluid-attenuated inversion recovery imaging for volumetric analysis before surgical resection.

Patient factors, including age, sex, years of education, handedness, and preoperative neuropsychological evaluation, were recorded. Tumor factors, including tumor volume, laterality, lobar involvement, sum of involved lobes, motor or speech eloquent regions invasion, SVZ invasion, and pathology grading were also documented. Tumors involving the primary motor CTX, supplementary motor area, premotor region, and their associated subcortical white matter tracts were recorded as invading motor eloquent regions. Tumors involving the left frontal, parietal, and temporal operculum and their interconnected long association fibers were recorded as invading speech eloquent regions.[20]

To determine SVZ invasion, we referenced Jafri's classification.[1] Grade 4 gliomas (glioblastoma) were classified into 4 groups based on the association of T1 enhancing tumor with CTX and SVZ: Jafri I (CTX+, SVZ+), Jafri II (CTX−, SVZ+), Jafri III (CTX+, SVZ−), and Jafri IV (CTX−, SVZ−). Although originally designed for assessing glioblastoma, this classification has been adapted by others to evaluate low-grade glioma by focusing on nonenhanced lesions (T2 fluid-attenuated inversion recovery high signal area).[2] For SVZ+ tumors, the anatomic subregion (frontal horn [SVZ-F], body [SVZ-B], trigone/occipital horn [SVZ-Tr], and temporal horn [SVZ-T]) was recorded.[2,4]

Neuropsychological Tests

The NPAs were performed by senior neuropsychologists before treatments. The NPA encompasses 10 cognitive domains and used internationally recognized tests specifically designed to assess cognitive impairments within each domain. These domains include orientation, global cognition, language, auditory learning, visual learning, spatial perception, executive function, processing speed, working memory, and emotional state. Detailed tests per domain were listed.[21] (**Supplemental Digital Content 1: Table 1** [http://links.lww.com/NEU/E940]). Each neuropsychological test was scored based on standardized criteria and subsequently transformed into *Z*-scores, using the mean and SD derived from age and education-adjusted published norms.[22] These scores were then categorized into 4 groups: deficit (<-1.5 SD), borderline (−1 to −1.5 SD), normal (± 1 SD), and instances where testing feasibility was compromised. Impairment within a specific domain was established by the presence of subtest scores falling below −1.5 SD (indicative of a deficit) within that domain, consistent with established literature.[10,23] If all subtests within a domain yielded "unable to test" results, the domain was designated as "NA" (not assessable) rather than as a deficit. The total count of defective domains for each patient was then summarized for further analysis.

Statistical Analysis

The primary objective was to compare the number of defective cognitive domains between patients with SVZ-invaded (SVZ+) and noninvaded (SVZ−) gliomas. Secondary analyses examined the impact of tumor grade, hemisphere invasion, and SVZ subregion involvement on cognitive decline. Continuous data were expressed as mean ± SD, and categorical data as percentages. χ^2 tests were used for categorical comparisons, whereas the 2-sample independent *t*-test evaluated the difference between the 2 groups for continuous variables. Cognitive dysfunction was analyzed using both continuous (0-10 defective domains) and categorical (≥4 vs 0-3 defective domains) outcomes. Multivariable linear regression analysis was used to identify factors associated with the total number of defective domains, whereas binary logistic regression was used to determine factors linked to ≥4 defective domains. Variables with $P < .05$ in univariable analysis were included in the multivariable models. The area under receiver operating characteristic curve assessed the predictive accuracy of the final model, and a nomogram was developed to estimate the probabilities of cognitive impairment. Statistical analyses were performed using IBM SPSS 20, and R for statistical plot with R packages "forestplot", "ggplot2" and "rms". A *P*-value of <.05 from a 2-sided test was considered significant.

RESULTS

Patient Cohort

A total of 129 eligible patients consisted of 64 SVZ+ and 65 SVZ− diffuse gliomas. Overall, the SVZ+ tumors were left-sided (79%, $P = .002$), invaded speech eloquent regions (40.6%, $P = .01$), were more likely to be locate in the temporal lobe (34.4%, $P = .038$) and limbic & paralimbic lobe (50%, $P < .001$), presented with more lobar invasion (1.8 ± 0.9, $P < .001$), and had larger T2 volumes (109.3 ± 62.4, $P < .001$) compared with the SVZ− tumors (Table 1). Conversely, the SVZ− tumors had a higher paracentral lobule involvement (16.9%, $P = .021$) than the SVZ+ tumors. There was no difference between SVZ+ and SVZ− regarding tumor grading, age, and years of education of the patients. However, among SVZ+ tumors, the event rate increased along with higher tumor grading. Regarding cognitive dysfunction, the SVZ+ patients presented with discernible deficits in language (62.5% vs 24.6%, $P < .001$), auditory learning (76.6% vs 56.9%, $P = .029$), and showed a trend toward visual learning impairments ($P = .069$) compared with the SVZ− group. The total number of defective domains was significantly higher in the SVZ+ group than in the SVZ− group (3.9 ± 2.1 vs 2.7 ± 2.2, $P = .002$, Table 1, Figure 1A). Figure 1B summarizes the odds ratio (OR) of SVZ+ vs SVZ− in each cognitive domain. Dysfunctions in language (OR 1.60, $P < .001$), auditory learning (OR 2.47, $P = .018$), and visual learning (OR 2.24, $P = .044$) were significantly higher in the SVZ+ patients compared with the patients with SVZ− diffuse gliomas.

Univariable Analyses: WHO Grade and SVZ Invasion

We then stratified the patients into 2 subgroups according to WHO grading. WHO grade 2 and 3 gliomas were classified as lower grade glioma (LGG), whereas WHO grade 4 gliomas were classified as HGG. Among LGGs, the SVZ+ group had more WHO grade 3 gliomas (55.4%, $P = .04$, data not shown), was predominantly left-sided (82.1%), was more likely to be located in the temporal lobe (38.3%, $P = .078$), and involved speech eloquent regions (48.7%, $P = .001$) than the SVZ− group (**Supplemental Digital Content 1: Table 2** [http://links.lww.com/NEU/E940]). In both LGGs and HGGs, the SVZ+ group had higher limbic and paralimbic lobe involvement, affected more lobes, had higher T2 volumes, and had more defective domains than the SVZ− groups (**Supplemental Digital Content 1: Table 2** [http://links.lww.com/NEU/E940]). Regarding cognitive impairment, in LGGs, patients with SVZ+ had an increased risk of language (OR 7.50, $P < .001$) and visual learning dysfunction (OR 4.38, $P = .014$), whereas in HGGs, patients with SVZ+ had greater language (OR 8.56, $P = .003$) and auditory learning vulnerabilities (OR 3.85, $P = .039$) than patients without SVZ invasion (Figure 2A).

Univariable Analyses: Tumor Laterality and SVZ Invasion

Another subgroup analysis was performed based on tumor laterality. A detailed factor analysis comparing tumors with or without SVZ invasion in left and right hemispheric glioma is provided in supplementary materials (**Supplemental Digital Content 1: Tables 3 and 4** [http://links.lww.com/NEU/E940]). In brief, in both left and right hemispheric gliomas, the SVZ+ group was more likely to be located in the limbic and paralimbic lobe, involved more lobes, and had larger T2 volumes than the SVZ− group. In right hemispheric SVZ+ gliomas, there were older patients, more temporal lobe and less paracentral lobule involvement, and more defective domains compared with the SVZ− group. As expected, language (68.6%, $P = .022$) and auditory learning (76.5%, $P = .043$) impairments were significantly higher in the left hemispheric SVZ+ group than in the SVZ− group (**Supplemental Digital Content 1: Table 3** [http://links.lww.com/NEU/E940]). Surprisingly, there were significantly higher global cognition (23.1%, $P = .022$), language (38.5%, $P = .017$), and executive function (61.5%, $P = .012$) impairments in the right hemispheric SVZ+ group compared with the SVZ− group (**Supplemental Digital Content 1: Table 4** [http://links.lww.com/NEU/E940]). Figure 2B summarizes the OR of SVZ+ vs SVZ− on cognitive function according to tumor laterality. In left hemispheric gliomas, SVZ invasion increased the likelihood of language (OR 3.13, $P = .012$) and auditory learning (OR 2.89, $P = .024$) impairments, whereas in right hemispheric gliomas, SVZ invasion conferred worse global cognition (OR 21, $P = .022$), language (OR 9.06, $P = .017$), and executive function (OR 6.67, $P = .006$).

Univariable Analyses: Subregions of SVZ Invasion

For those with SVZ+, involvement of the frontal horn and body of the lateral ventricle was associated with significant deficits in working memory ($P = .021$). Moreover, involvement of the body

TABLE 1. Clinical Characteristics and NPA Performances Between patients with SVZ+ and SVZ− Treatment-Naïve Glioma

Factors	All (n = 129)	SVZ+ (n = 64)	SVZ− (n = 65)	*P*-value
Age (y)	48.3 ± 15.2	48.9 ± 13.9	47.6 ± 16.5	.631
Sex = Male	71 (55)	36 (56.2)	35 (53.8)	.922
Education (y)	13.3 ± 5.2	13.7 ± 6.2	13.0 ± 4.1	.499
Handedness				.85
LH	3 (2.3)	1 (1.6)	2 (3.1)	
RH	124 (96.1)	62 (96.9)	62 (95.4)	
Both	2 (1.6)	1 (1.6)	1 (1.5)	
Tumor laterality				.002[a]
Left	85 (65.9)	51 (79.7)	34 (52.3)	
Right	44 (34.1)	13 (20.3)	31 (47.7)	
Lobar involvement				
Frontal	67 (51.9)	37 (57.8)	30 (46.2)	.251
Parietal	10 (7.8)	3 (4.7)	7 (10.8)	.324
Temporal	33 (25.6)	22 (34.4)	11 (16.9)	.038[a]
Insula	38 (29.5)	20 (31.2)	18 (27.7)	.803
Limbic & paralimbic	40 (31)	32 (50)	8 (12.3)	<.001[a]
Paracentral lobule	13 (10.1)	2 (3.1)	11 (16.9)	.021[a]
Involved lobe counts	1.6 ± 0.8	1.8 ± 0.9	1.3 ± 0.5	<.001[a]
Sum of involved lobes				.003[a]
1	77 (59.7)	30 (46.9)	47 (72.3)	
2	35 (27.1)	19 (29.7)	16 (24.6)	
3	14 (10.9)	12 (18.8)	2 (3.1)	
4	3 (2.3)	3 (4.7)	0	
Eloquent				
Motor	34 (26.4)	14 (21.9)	20 (30.8)	.344
Speech	38 (29.5)	26 (40.6)	12 (18.5)	.010[a]
T1 C+ volume (mL)	16.5 ± 26.4	19.1 ± 29.7	13.9 ± 22.6	.258
T2 volume (mL)	80.1 ± 61.1	109.3 ± 62.4	50.9 ± 43.6	<.001[a]
WHO grade				
2	43 (33.3)	17 (26.6)	26 (40)	.152
3	35 (27.1)	22 (34.4)	13 (20)	.101
4	51 (39.5)	25 (39.1)	26 (40)	1
Frequency of deficit (%)				
Orientation	29 (22.5)	17 (26.6)	12 (18.5)	.373
Global cognitive	26 (20.2)	17 (26.6)	9 (13.8)	.114

TABLE 1. Continued.

Factors	All (n = 129)	SVZ+ (n = 64)	SVZ− (n = 65)	*P*-value
Language	56 (43.4)	40 (62.5)	16 (24.6)	<.001[a]
Auditory learning	86 (66.7)	49 (76.6)	37 (56.9)	.029[a]
Visual learning	36 (27.9)	23 (35.9)	13 (20)	.069
Spatial perceptual	40 (31)	23 (35.9)	17 (26.2)	.312
Executive	42 (32.6)	24 (37.5)	18 (27.7)	.317
Processing speed	18 (14)	9 (14.1)	9 (13.8)	1
Working memory	47 (36.4)	27 (42.2)	20 (30.8)	.244
Emotional state	44 (34.1)	19 (29.7)	25 (38.5)	.387
Sum of defective domain	3.3 ± 2.2	3.9 ± 2.1	2.7 ± 2.2	.002[a]

NPA, neuropsychological assessments; SVZ, subventricular zone; WHO, World Health Organization.
[a]$P < .05$.

of the lateral ventricle was associated with a significant deficit in emotional state ($P = .021$). In contrast, involvement of the trigone of lateral ventricle and temporal horn was not found to be associated with an increased risk of cognitive decline compared with other subregions (**Supplemental Digital Content 1: Table 5** [http://links.lww.com/NEU/E940]).

Multivariable Analyses: Independent Predictive Factors Contributing to Cognitive Decline

To identify independent factors associated with cognitive dysfunction, continuous and categorical dependent variables were used in separate models. Table 2 summarizes the results of using sum of defective domains as a continuous dependent variable. In the total population, older age ($P = .037$), SVZ invasion ($P = .032$), and WHO grade 4 (compared with WHO grade 2, $P = .023$) were independent risk factors associated with more defective cognitive domains. Considering only the SVZ+ group, older age ($P = .025$) and WHO grade 4 (compared with WHO grade 2, $P = .004$) were risk factors associated with worse cognitive function. Conversely, in the SVZ− group, tumor involvement of the parietal lobe ($P = .002$) was a risk factor, whereas education ($P = .057$) was a protective factor against cognitive dysfunction. Table 3 summarizes the results of using 0-3 vs ≥4 defective cognitive domains as a categorical dependent variable. By adjusting for statistically significant factors from the univariable analyses, an increase in age by 1 year and an increase in T2 volume by 1 mL resulted in a 3% and 1% increased risk, respectively, of having ≥4 defective domains ($P = .012$ and $.008$). Although no longer statistically significant after adjusting for age and T2 volume, SVZ invasion still showed a positive trend of increasing the risk of having ≥4 defective domains (adjusted OR 1.99, $P = .115$).

A model composed of age, T2 volume, and SVZ invasion was used to predict the risk of having ≥4 defective domains using the receiver operating characteristic curve analysis. The area under curve value was 0.749, indicating a moderately performing model ($P < .001$, **Supplemental Digital Content 1: Figure 1** [http://links.lww.com/NEU/E940]). Finally, we created a nomogram with age, SVZ invasion, and T2 volume for predicting the probability of having ≥4 defective domains (Figure 3).

DISCUSSION

Our results demonstrated that tumors with SVZ invasion had a significant influence on cognitive function, regardless of tumor grade and tumor laterality. Patients with SVZ+ gliomas exhibited an increased number of cognitive deficits and more substantial impairments in cognitive domains, particularly in language, auditory learning, and visual learning, compared with SVZ− patients. The observed cognitive impairments in SVZ+ patients are consistent with existing literature emphasizing the role of SVZ neurogenesis in cognitive processes and the underlying neuropathological changes.[11] Previous research has already demonstrated that glioma infiltration into the SVZ is linked to poorer clinical outcomes.[2-4] Our study builds on this by specifically highlighting the cognitive consequences of such infiltration, thereby filling a notable gap in current knowledge.

The classification of tumors based on their specific location within the SVZ provided further insights. Gliomas involving the frontal horn of the lateral ventricle were associated with significant deficits in working memory, whereas those in the body of the lateral ventricle were linked to both working memory and emotional state deficits. These findings are partially supported by previous literature, which indicates that gliomas in the frontal lobe and cingulate gyrus, located near the anterior frontal horn of the lateral ventricle, are associated with working memory deficits and

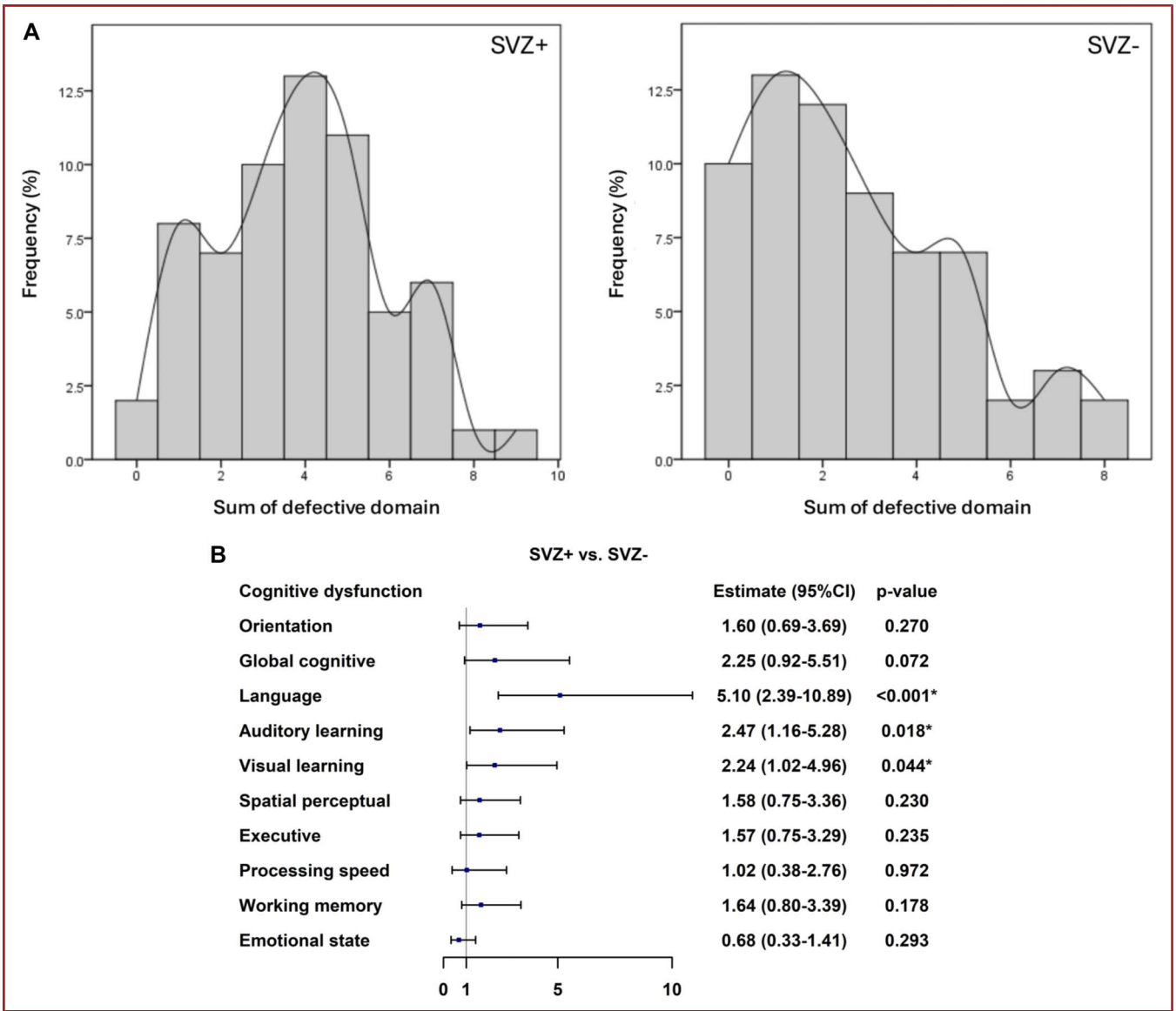

FIGURE 1. *Quantified cognitive impairments* **A** *and odds ratios* **B** *of cognitive dysfunction comparing patients with SVZ+ with patients with SVZ− glioma. SVZ, subventricular zone.*

difficulties in identifying angry expressions.[24,25] In addition, gliomas in the insular regions, near the body of the frontal horn, influence facial emotion recognition.[26,27] This location-based classification helps understand how SVZ invasion affects cognitive function.

We also revealed lateralized effects on cognitive functions. SVZ invasion in the left hemisphere was predominantly associated with deficits in language and auditory learning, whereas right hemisphere invasion was linked to impairments in global cognition, language, and executive function (Figure 2B, **Supplemental Digital Content 1: Tables 3 and 4** [http://links.lww.com/NEU/E940]). Although language traditionally localizes to the left hemisphere, our findings corroborate emerging evidence of bilateral language network involvement, particularly through white matter tract connectivity including nondominant inferior fronto-occipital fasciculus and inferior frontal parietal lobule.[28-33] These findings could enhance our understanding of brain hemisphere specialization and underscore the need for tailored therapeutic approaches based on tumor laterality. Besides, right hemispheric SVZ invasion exhibited more severe cognitive impairment patterns compared with SVZ− cases than left SVZ invasion. This hemispheric asymmetry aligns with established functional lateralization research, where right hemisphere's role in visuospatial processing, awareness, and attention may influence neuropsychological assessment

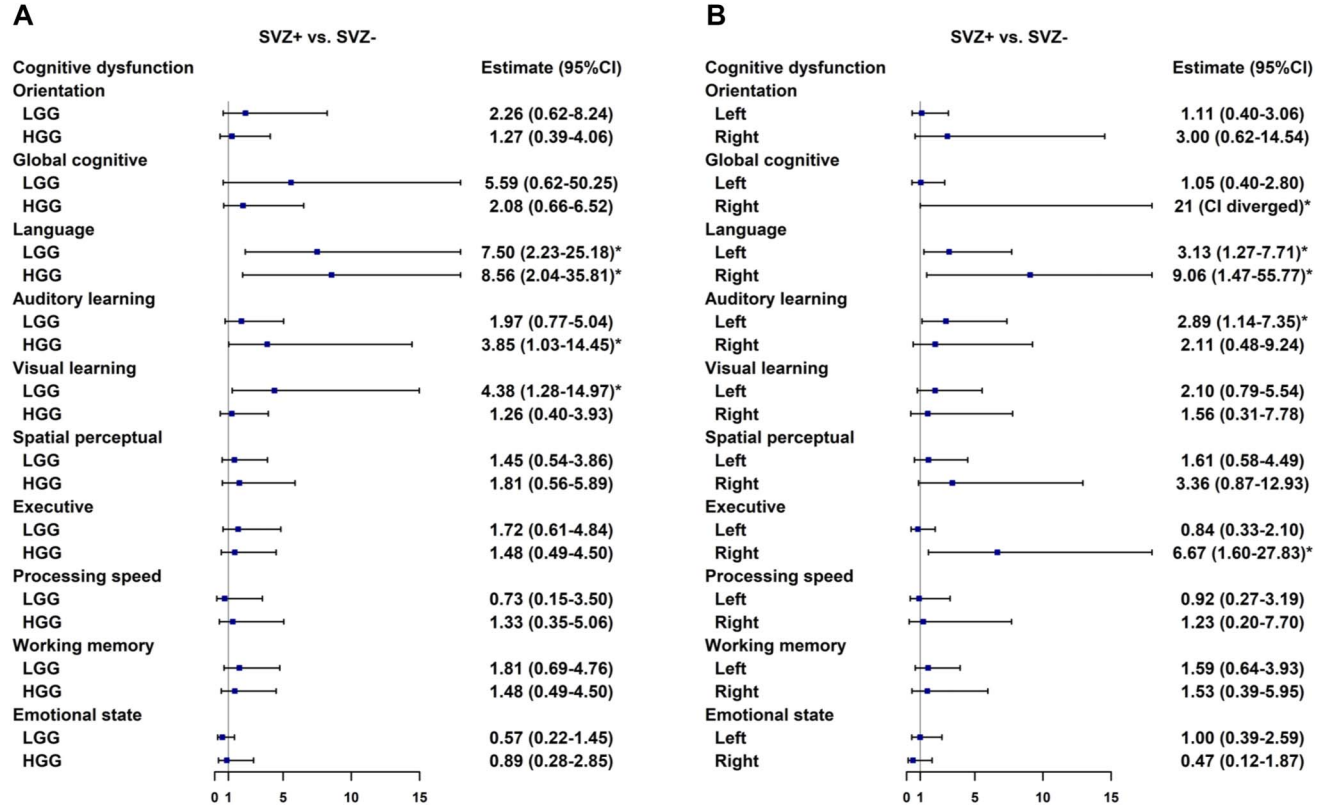

FIGURE 2. *Subgroup analyses according to* **A** *tumor grading: lower grade vs high-grade glioma and* **B** *tumor laterality: left-sided vs right-sided tumors. HGG, high-grade glioma; LGG, lower grade glioma; SVZ, subventricular zone.*

outcomes.[28-36] These findings suggest that further investigation into visuospatial function impact in patients with right hemispheric SVZ+ glioma is warranted.

From a biological perspective, there may be 2 interpretations regarding the issue of SVZ invasion in diffuse glioma. First, oligodendrocyte precursor cells or radial glial cells have been hypothesized as the origin of gliomagenesis.[37] Tumors with SVZ invasion are found to have a propensity of invasive proliferation,[37] suggesting a more malignant phenotype than non-SVZ-invaded tumors, which may negatively affect cognitive function. Second, the neural stem cells in the SVZ have been associated with cognitive decline when depleted and cognitive rescue when regenerated, as shown in preclinical studies.[11-14,38] Tumors invading the SVZ may impair normal SVZ function, leading to a reduced ability to preserve cognitive function in response to the destruction and invasion by malignant tumor cells. More studies are needed to address the biological mechanisms underlying the impact of SVZ invasion on cognitive decline. Collectively, in treatment-naïve patients, SVZ-invading gliomas are associated with worse cognitive outcomes due to their biological aggressiveness and preferential involvement of neurogenic and functionally critical brain regions. These tumors impair both the "hardware" (neural circuits) and "software" (neurogenesis) of cognition, even before any treatment-related neurotoxicity occurs.

The relationship between SVZ invasion and cognitive function has direct implications for preoperative patient counseling. This knowledge enables clinicians to provide more precise prognostic information and enhances the informed consent process by identifying patients at higher risk of specific cognitive deficits. For instance, our findings of worse cognitive performance in SVZ-invaded tumors, even in small ones, help clinicians better prepare patients and families for potential cognitive challenges and guide expectations for postoperative recovery.

Limitations

Study limitations include potential selection bias from retrospective design, data incompleteness, and generalizability concerns due to awake craniotomy patient selection. Although cognitive deficits are comprehensively analyzed, extent of white matter connectivity disruption and underlying biological mechanisms remain unexplored. Future directions should encompass prospective multicenter validation studies and investigation of molecular

TABLE 2. Factors Associated With Sum of Cognitive Dysfunction (0-10)[a]

	All (n = 129)		SVZ+ (n = 64)		SVZ− (n = 65)	
Factors	**B (95% CI)**	***P* value**	**B (95% CI)**	***P* value**	**B (95% CI)**	***P* value**
Age (y)	0.03 (0.00, 0.05)	.037[b]	0.04 (0.01, 0.07)	.025[b]	0.00 (−0.04, 0.04)	.993
Education (y)					−0.13 (−0.27, 0.00)	.057
SVZ invasion	0.82 (0.07,1.56)	.032[b]				
Location: parietal	0.97 (−0.28, 2.23)	.127			2.30 (0.82, 3.78)	.002[b]
Location: paracentral	−0.50 (−1.61, 0.06)	.372			−0.48 (−1.65~0.69)	.42
Speech eloquent	0.60 (−0.14, 1.35)	.114			0.75 (−0.43,1.93)	.211
T1 C+ volume (mL)	0.002 (−0.01, 0.02)	.737				
T2 volume (mL)	0.003 (−0.00, 0.01)	.337				
WHO (Grade 2 = ref)						
WHO 3	0.23 (−0.61, 1.07)	.598	0.52 (−0.62, 1.66)	.372	0.74 (−0.44, 1.93)	.219
WHO 4	1.05 (0.14,1.95)	.023[b]	1.65 (0.62, 2.79)	.004[b]	0.63 (−0.58, 1.83)	.31

SVZ, subventricular zone; WHO, World Health Organization.
[a]Univariate factors with $P < .05$ were selected into multivariable linear regression analysis.
[b]$P < .05$.

pathways in SVZ-invaded gliomas. Moreover, exploring the impact of different treatment modalities on cognitive outcomes in patients with SVZ-invaded glioma would enhance our understanding and management of these complex cases.

CONCLUSION

In conclusion, SVZ invasion contributes to domain-specific neurocognitive impairment, independent of tumor laterality or

TABLE 3. Analysis of Factors Associated With Cognitive Dysfunction: Defective Domain ≥4 vs 0-3[a]

	Crude (univariable)		Adjusted (multivariable)	
Factors	**OR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**
Age (y)	1.04 (1.01, 1.06)	.004[b]	1.03 (1.01, 1.06)	.012[b]
Education (y)	0.96 (0.89, 1.04)	.324		
SVZ invasion	2.87 (1.40, 5.89)	.004[b]	1.84 (0.79, 4.30)	.160
Location: parietal	3.11 (0.77, 12.62)	.112		
Location: paracentral	0.20 (0.04, 0.92)	.037[b]		
Speech eloquent	2.45 (1.13, 5.33)	.022[b]		
T1 C+ volume (mL)	1.02 (1.01, 1.04)	.004[b]		
T2 volume (mL)	1.01 (1.01, 1.02)	<.001[b]	1.01 (1.00, 1.02)	.008[b]
WHO (Grade 2 = ref)		.002[b]		
Grade 3	2.18 (0.84, 5.69)	.11		
Grade 4	4.90 (2.01, 11.93)	<.001[b]		

aOR, adjusted odds ratio; SVZ, subventricular zone; WHO, World Health Organization.
[a]Univariate factors with $P < .05$ were selected into multivariable logistic regression analysis.
[b]$P<.05$.

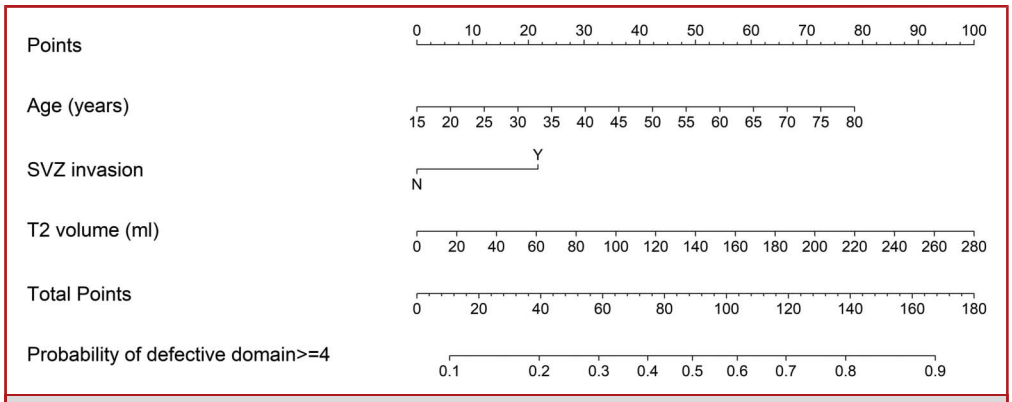

FIGURE 3. *Probability nomogram using age, T2 volume, and SVZ invasion to predict the number of defective cognitive domains (≥4). SVZ, subventricular zone.*

grade, emphasizing the importance of precise SVZ-based tumor mapping and individualized strategies to preserve cognitive function in patients with glioma.

BRIEF KEY POINTS

1. SVZ invasion affects cognitive function independent of tumor laterality and grade.
2. Distinct cognitive decline patterns were linked to tumor grading, laterality, and location of SVZ invasion.
3. The model using age, T2 volume, and SVZ invasion had moderate predictive accuracy for cognitive impairment.

IMPORTANCE OF THE STUDY

The study evaluated the influence of SVZ invasion on neurocognitive dysfunction in 129 patients with diffuse glioma, an analysis that had not been performed before. SVZ invasion (SVZ+) was identified in 64 patients, correlating with a higher risk of cognitive deficits compared with noninvading cases (SVZ−). Distinct patterns of cognitive decline were identified between low-grade and high-grade gliomas, as well as between left-sided and right-sided tumors. In addition, SVZ invasion in the frontal horn was linked to working memory decline, whereas invasion in the body part was associated with emotional deficits. SVZ+ was an independent predictor of cognitive decline, alongside age, T2 volume, and WHO grade. A model and nomogram combining age, T2 volume, and SVZ invasion demonstrated moderate predictive accuracy for cognitive impairment. These findings suggest future implications for more precise tumor mapping and tailored interventions aimed at optimizing the oncofunctional balance in patients with glioma at the individual level.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental digital content *is available for this article at neurosurgery-online.com.*

Supplemental Digital Content 1. **Figure 1**. Predictive model composed of age, T2 volume, and SVZ invasion for predicting the risk of having ≥4 defective domains (AUC 0.749).

Supplemental Digital Content 1. **Table 1**. Comprehensive list of neuropsychological assessments.

Supplemental Digital Content 1. **Table 2**. Subgroup analysis of patients with LGG and HGG with and without SVZ invasion.

Supplemental Digital Content 1. **Table 3**. The clinical characteristics and NPA performance between SVZ+ and SVZ− groups in patients with left hemispheric treatment-naïve glioma.

Supplemental Digital Content 1. **Table 4**. The clinical characteristics and NPA performance between SVZ+ and SVZ− groups in patients with right hemispheric treatment-naïve glioma.

Supplemental Digital Content 1. **Table 5**. Subregion of ventricular invasion among patients with SVZ+ treatment-naïve glioma.

COMMENTS

Cognitive performance after diffuse glioma surgery depends on many tumor factors such as molecular and oncobiological characteristics,[1a] invasion of specific eloquent domains, and technical issues during the resection. Impaired memory, psychomotor function, and language deficits are major concerns postoperatively even after a gross total resection or/and a satisfactory radiological picture. From the other side, SVZ involvement in gliomas was associated with poorer outcomes.[2a] The present study introduced us an important hypothesis about a linkage between the aforementioned factors which were clearly but separately associated with worse prognosis. There are 2 groups of 65 and 64 patients categorized as SVZ + and SVZ -. Patients with SVZ+ gliomas exhibited an increased number of cognitive deficits and more impairments in language, auditory learning, and visual learning. Specific invaded regions have different patterns of cognitive decline and difference was noted also between 2 hemispheres, underscoring the need for tailored therapy depending on tumor laterality. The initial hypothesis about SVZ invasion and cognitive impairment enables interestingly not only a high possible linkage but also a different specialization of involved networks in cognitive function between regions of the same hemisphere and between the

left and right hemisphere. SVZ invasion in gliomas is suggested that affects circuits and neurogenesis even the need for more studies to clear the biological mechanisms. Aiming to fill an important gap in literature, the present article opened a new era of estimating the role of disruption of eloquent connections and pathways according to cognitive impairment and surely to worse outcomes in diffuse glioma patients.

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1a. van Kessel E, Berendsen S, Baumfalk AE, et al. Tumor-related molecular determinants of neurocognitive deficits in patients with diffuse glioma. *Neuro Oncol.* 2022;24(10):1660-1670.
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The neurogenic niche in the subventricular zone (SVZ) is known to harbor neural stem cells in the mammalian brain, and aside from its potential role in gliomagenesis,[1b] iatrogenic or disease related disruption of the SVZ is associated with poor outcomes.[2b,3b] The authors present a single institution retrospective study analyzing the role SVZ invasion plays in neurocognitive dysfunction in a single institution series of glioma patients who underwent awake craniotomy (n = 129). This is an interesting study as it links SVZ involvement with specific functional impairments. The authors hypothesized that glioma patients with SVZ involvement had worse cognitive function than those without, measured through systematic neuropsychological assessments of a cohort of treatment naive patients from their awake craniotomy database. Although the cohort itself is a selected patient population, it still provides an interesting dataset for analysis, and this limitation was acknowledged in this study. The authors found that SVZ invasion was correlated with higher risk of cognitive deficits with distinct patterns of cognitive decline noted between LGG and HGG; SVZ involvement was also an independent predictor of cognitive decline, and a predictive model was also developed to evaluate the risk of cognitive decline. Since the size of tumor can be a confounding factor in the interpretation of these findings, the authors also performed a subgroup analysis of the smaller tumors and noted a statistically significant difference in multiple cognitive domains in patients with SVZ involvement, further supporting the idea that SVZ involvement is an independent risk factor for neurocognitive impairment. This work is therefore a welcome addition to the literature, reinforcing the concept that glioma infiltration of SVZ is linked to poor outcomes, and this study builds on this by highlighting some of the specific neurocognitive consequences of this infiltration.

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Compliments to you and your team on your significantly improved final manuscript, as your clearer efforts are greatly appreciated in addressing the concerns raised in the original review. This will make a valuable contribution as there is not a large body of existing literature in the subject area of subventricular zone invasion with regard to resultant clinical outcomes.

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