Changes in language white matter tract microarchitecture associated with cognitive deficits in patients with presumed low-grade glioma

Fatih Incekara, MD,^{1,2} Djaina Satoer, PhD,² Evy Visch-Brink, PhD,² Arnaud Vincent, MD, PhD,² and Marion Smits, MD, PhD¹

Departments of ¹Radiology and Nuclear Medicine and ²Neurosurgery, Erasmus MC–University Medical Center, Rotterdam, The Netherlands

OBJECTIVE The authors conducted a study to determine whether cognitive functioning of patients with presumed low-grade glioma is associated with white matter (WM) tract changes.

METHODS The authors included 77 patients with presumed low-grade glioma who underwent awake surgery between 2005 and 2013. Diffusion tensor imaging with deterministic tractography was performed preoperatively to identify the arcuate, inferior frontooccipital, and uncinate fasciculi and to obtain the mean fractional anisotropy (FA) and mean diffusivity per tract. All patients were evaluated preoperatively using an extensive neuropsychological protocol that included assessments of the language, memory, and attention/executive function domains. Linear regression models were used to analyze each cognitive domain and each diffusion tensor imaging metric of the 3 WM tracts.

RESULTS Significant correlations (corrected for multiple testing) were found between FA of the arcuate fasciculus and results of the repetition test for the language domain ($\beta = 0.59$, $p < 0.0001$) and between FA of the inferior frontooccipital fasciculus and results of the imprinting test for the memory domain ($\beta = -0.55$, $p = 0.002$) and the attention test for the attention and executive function domain ($\beta = -0.62$, $p = 0.006$).

CONCLUSIONS In patients with glioma, language deficits in repetition of speech, imprinting, and attention deficits are associated with changes in the microarchitecture of the arcuate and inferior frontooccipital fasciculi.

<https://thejns.org/doi/abs/10.3171/2017.12.JNS171681>

KEYWORDS glioma; diffusion tensor imaging; white matter tracts; cognition; oncology

LOW-GRADE gliomas (LGGs) are WHO grade I or II, slow-growing, primary brain tumors that commonly show no or minimal contrast enhancement. Patients with LGG often present with seizures, but headache and (mild) cognitive deficits are also observed frequently.³¹ Because of the widespread representation of cognitive functions, it is important to make use of a neuropsychological protocol in patients with glioma to detect deficits.²⁴ Using a neuropsychological assessment, Satoer et al.²⁶ found

preoperative and postoperative deficits in the domains of language, memory, and the attention/executive function in a series of 45 patients with glioma. We hypothesize that such cognitive deficits can, at least partly, be attributed to changes in white matter (WM) tract microarchitecture caused by tumor effects such as edema or infiltration.

In vivo anatomical visualization of WM tracts, such as the arcuate fasciculus (AF), inferior frontooccipital fasciculus (IFOF), and uncinate fasciculus (UF), can be

ABBREVIATIONS AF = arcuate fasciculus; DTI = diffusion tensor imaging; FA = fractional anisotropy; HGG = high-grade glioma; IFOF = inferior frontooccipital fasciculus; LGG = low-grade glioma; MD = mean diffusivity; ROI = region of interest; UF = uncinate fasciculus; WM = white matter.

SUBMITTED July 11, 2017. **ACCEPTED** December 23, 2017.

INCLUDE WHEN CITING Published online June 8, 2018; DOI: 10.3171/2017.12.JNS171681.

obtained with the use of diffusion tensor imaging (DTI)-based tractography. DTI is an MRI modality in which the 3D diffusion of free water in the brain can be assessed. Because water diffuses preferentially along the direction of the WM fibers instead of perpendicular to them, measuring the direction of free-water diffusion enables an approximation of the WM fiber orientation. On a DTI-derived color-coded map, the WM tracts are conventionally represented in green for the anterior-posterior direction (e.g., optical fibers), in red for the left-right direction (e.g., corpus callosum), and in blue for the ventral-dorsal direction (e.g., corticospinal tract). To delineate the WM tracts, specific regions of interest (ROIs) are delineated manually on diffusion tensor images based on a priori anatomical knowledge. WM tracts of interest running through these ROIs are then visualized in 3 dimensions using tractography.^{5,32} The AF is an association bundle that is involved in language by connecting perisylvian language areas of the frontal, temporal, and parietal lobes.⁵ Intraoperative stimulation of the AF elicits phonemic paraphasias.⁹ The IFOF is an association bundle that connects the occipital lobe and the orbitofrontal cortex. It seems to be involved in several cognitive functions, such as language (semantics and reading),¹⁰ but also attention and visual processing abilities.^{5,7} The UF is an association bundle that connects the orbitofrontal cortex with the anterior temporal lobe and is suggested to be involved in memory and language.²⁴

Quantitative information on WM tract microarchitecture can be derived from tractography and expressed as fractional anisotropy (FA) and mean diffusivity (MD). FA is a measure of microstructural integrity and has a value between 0 and 1; 0 indicates that diffusion is the same in all directions (isotropic diffusion, such as that seen in the ventricles), and a value of close to 1 indicates that the diffusion of water is seen along a specific direction (anisotropic diffusion, such as that seen along WM tracts). A reduction of FA in a WM tract is considered to be an indication of loss of tract integrity. MD is a measure of the average water diffusion and reflects membrane density. High MD values are seen in free water (the ventricles) and low MD values in the WM. An increase of MD in the WM is considered an indication of an increase of the extracellular space, such as that seen with edema. Although derived from the same imaging sequence, FA and MD reflect different aspects of WM tract structure and thus can be used to assess the effects of tumor infiltration and edema.² Important to note is that perilesional WM tracts and edematous zones around a glioma show a reduction in FA values that suggests increased extracellular water and fiber disorganization caused by tumor infiltration.¹ Studies have found that tumor-infiltrated WM tracts such as the AF have a relationship with language impairment.^{3,15} However, to the best of our knowledge there has not been a large-scale quantitative correlation of WM tract microarchitecture with cognitive functioning in patients with LGG.

The purpose of this study was to determine whether cognitive functioning of patients with presumed LGG is associated with changes in language WM tract microarchitecture. We analyzed FA and MD values of the AF, IFOF, and UF in relation to 3 cognitive domains (language,

memory, and attention/executive function) assessed with an extensive preoperative neuropsychological assessment in patients selected for awake surgery.

Methods

Study Participants

A total of 131 patients (> 18 years old) with presumed LGG who underwent awake surgery between April 2005 and May 2013 were considered for this retrospective study. Non- to mildly contrast-enhancing tumors (i.e., presumed LGG) on preoperative MRI scans were considered. Note that to ensure that our findings would be valid for the real-life clinical situation of preoperative assessment and selection of patients when histopathology is not yet available, we kept patients with tumors even if histopathological examination after resection of their tumors displayed features of high-grade glioma (HGG). Hence, we use the term “presumed” LGG based on clinical and radiological characteristics. All these patients were native Dutch speakers. Patients with recurrent glioma ($n = 24$), without a preoperative neuropsychological assessment ($n = 3$), without sufficient DTI data ($n = 25$), or for whom the time frame between their neuropsychological and DTI assessments was longer than 6 months ($n = 2$) were excluded, which resulted in a total of 77 patients available for data analysis (Table 1). Of the 77 patients (mean age 43 years, range 20–74 years), 49 (63.6%) were male and had a mean age of 44 years (range 21–74 years); the 28 (36.4%) females had a mean age of 40 years (range 20–60 years). Although most of their tumors were localized in the left hemisphere, 15 patients with a right-sided tumor were also included in this study because they had right dominance for language, as seen on functional MRI, which was performed preoperatively. Therefore, these patients were selected for awake surgery to prevent damage to the Broca region. The study was approved by the medical ethical committee of Erasmus MC–University Medical Center, which waived the need for written informed consent from the patients because of the retrospective nature of the study and the (emotional) burden that would result from contacting the patients or their relatives to obtain consent.

Tumor Localization and Characterization

Tumor localization was determined by a neuroradiologist (who had 8 years of experience) viewing preoperative T1- and T2-weighted images. The histopathological type and grade of each tumor were determined by a neuropathologist from tissue obtained during tumor resection.

Image Acquisition and Preprocessing

Diffusion MR data were acquired using a single-shot spin-echo echo-planar imaging sequence at 1.5 T ($n = 20$) and 3.0 T ($n = 57$) (GE Healthcare) with an 8-channel head coil. In general, 25 noncollinear gradient directions at $b = 1000 \text{ sec/mm}^2$ ($n = 71$) and 3 images at $b = 0 \text{ sec/mm}^2$ were acquired ($n = 64$). In 6 patients, all imaged at 3.0 T, 31 gradient directions were acquired with 4 images at $b = 0 \text{ sec/mm}^2$. The slice thickness was 2.0–3.5 mm, and the in-plane resolution was 1.9–3.4 mm². Raw diffusion MRI data were transferred to an offline workstation.

First, all images were visually inspected for the presence of apparent artifacts. Then, MRI data were preprocessed and postprocessed using ExploreDTI.¹⁷ Motion and eddy current correction of the diffusion-weighted images was not performed to avoid interpolation errors. Instead, the acquired native data and the data-quality summary report were visually inspected in ExploreDTI. The gradient components in the x, y, and z axes were checked manually and adapted if necessary to the standard color convention (left-right, red; top-bottom, blue; front-back, green). The diffusion tensors were subsequently estimated using nonlinear least-squares regression. The following thresholds were used to perform tractography: FA termination threshold 0.2, angle threshold 45°, and step length 0.5 mm.

Tractography

Deterministic tractography was used to identify the AF, IFOF, and UF in the affected hemisphere according to standardized procedures.³⁰ From each of the reconstructed tracts, average FA and MD values were obtained. The rater was blinded to the neuropsychological test results of the patients at the time of tractography.

Arcuate Fasciculus

For the AF (Fig. 1), a coronal slice was selected at the level of the primary motor cortex, and the seed ROI was placed on the green (anterior-posterior) triangular projections of the superior longitudinal fasciculus lateral to the blue projections of the corticospinal tract in the posterior parietal lobe. For the target ROI, an axial slice was selected at the level of the genu of the corpus callosum. The blue (cranial-caudal) projections lateral to the sagittal stratum (green) in the posterior temporal lobe corresponding to the vertical portion of the AF were delineated.³⁰

Inferior Frontooccipital Fasciculus

For the IFOF (Fig. 2), the seed ROI was placed by delineating the green projections in the entire anterior part of the frontal lobe on the axial and/or coronal slices. The target ROI was placed by delineating the green projections in the entire posterior part of the occipital lobe up until the posterior crossing area between the genu of the corpus callosum (red) and the posterior part of the sagittal stratum (green) on the axial and/or coronal slices.³⁰

Uncinate Fasciculus

For the UF (Fig. 3), the seed ROI was placed in the green projections in the temporal pole/entire anterior part of the temporal lobe on the coronal slice. The target ROI was placed by delineating the green projections in the inferior part of the frontal lobe on the coronal slice.³⁰

Neuropsychological Assessment

Each patient was assessed once with a comprehensive neuropsychological test battery between the initial diagnosis (mean 9 days; SD 20 days) and surgery (mean 44 days; SD 30 days) by a clinical linguist (blinded to tractography results). As shown in Table 2,^{12,14,18,20,27,33} the performance of the patients within 3 main cognitive domains (language, memory, and attention/executive function) was

TABLE 1. Baseline patient characteristics

Characteristic	Value
Mean age in yrs (range)	43 (20–74)
Sex (male/female)	49 (63.6)/28 (36.4)
Handedness	
Right	54 (70.1)
Left	5 (6.5)
Unknown	18 (23.4)
Karnofsky Performance Scale score	
100–90	69 (90)
80–70	8 (10)
Tumor grade	
LGG	47 (61)
HGG	30 (39)
Histopathological subtype (WHO grade)	
Oligodendroglioma (II)	21 (27.3)
Astrocytoma (II)	13 (16.9)
Oligoastrocytoma (II)	11 (14.3)
Oligodendroglioma (III)	16 (20.8)
Astrocytoma (III)	12 (15.6)
Oligoastrocytoma (III)	3 (3.9)
Glioblastoma (IV)	1 (1.3)
Tumor location	
Right	15 (19.5)
Frontal	3 (3.9)
Parietal	10 (13.0)
Temporal	2 (2.6)
Occipital	0 (0)
Left	62 (80.5)
Frontal	12 (15.6)
Parietal	23 (29.9)
Temporal	26 (33.8)
Occipital	1 (1.3)
Pathological tumor growth	
Diffuse infiltrative	37 (48.1)
Circumscribed	40 (51.9)

Values are number (percentage) of patients unless otherwise stated.

examined. This combination of neuropsychological tests has been shown to be sensitive for detecting cognitive deficits and was validated in earlier studies in patients with glioma.^{24,26,31} All test results of the patients were transformed into z-scores to compare the performance of patients to a normative group and to facilitate comparisons between tests.

Statistical Analysis

Statistical analyses were performed with SPSS 21.0 statistical software (IBM Corp.). We determined whether mean patient scores according to cognitive domain and according to test differed from those of the normative group using either a 1-sample t-test with 0 (the mean score of the normal group) as the test value or the Wilcoxon signed-

FIG. 1. **A:** The first ROI is placed on the blue projections lateral to the sagittal stratum (*green*). **B:** The second ROI is placed on the green triangular projections lateral to the blue projections of the corticospinal tract in the posterior parietal lobe; the tumor is delineated in *red*. **C:** The 3D reconstruction of the AF is shown. Figure is available in color online only.

rank test. Post hoc, the mean FA and/or MD values of the 3 WM tracts and 3 cognitive domains were compared between histopathologically established LGGs and HGGs by using a 1-way ANOVA.

First, the relationships between the 3 main cognitive domains (language, memory, and attention/executive function) of the neuropsychological and FA and MD values of 3 WM tracts (AF, IFOF, and UF) were analyzed in linear regression models that included all 3 WM tracts; age and histopathological grade as regressors were of no interest. The analyses were performed separately for each main cognitive domain and each DTI metric (FA and MD). Bonferroni correction was used to adjust for multiple testing on the main cognitive domain level (6 tests); a p value of ≤ 0.008 was considered statistically significant. Then, further analyses were performed on the subtest level only within the cognitive domain(s) that was significantly correlated with a WM tract measure(s). Bonferroni correction was not used for these analyses; a p value of < 0.05 was considered significant.

Results

DTI Tractography

Successful tractography of the AF was performed for 68 (88%) patients, of the IFOF for 76 (99%) patients, and of the UF for 74 (96%) patients. In total, 13 (17%) WM tracts were not tracked because of a very large tumor volume causing extensive brain shift. These WM tracts were not included in the analysis of association with neuropsychological test results. The mean FA was 0.456 (SD 0.059) in the AF, 0.474 (SD 0.056) in the IFOF, and 0.395 (SD 0.094) in the UF. The mean FA and MD values of the 3 WM tracts were not significantly different ($p > 0.05$) between the patients with LGG ($n = 47$) and those with HGG ($n = 30$).

Patient Performance on Neuropsychological Assessments

Patients had impairments in all 3 cognitive domains (language, memory, and attention/executive function) compared to those in the normative group ($p < 0.05$), except for in 3 subtests (Table 2) (in the language domain [Aachen Aphasia Token test] and the attention/executive

function [Trail Making Tests A and B and Stroop interference tests]; $p > 0.05$). Post hoc analyses revealed that language impairments were significantly worse in patients with a histopathologically determined high-grade tumor than in those with a low-grade tumor ($p = 0.025$). Memory and attention/executive function results were not significantly different between patients in these groups ($p > 0.05$).

Relationship Between Neuropsychological Test Results and WM Tracts

The relationships between the 3 main cognitive domains and the FA and MD values of the 3 WM tracts were presented in Table 3. Significant correlations were found between the AF (FA only) and the language domain ($\beta = 0.44$; $R = 0.40$; $p = 0.003$) and between the IFOF (FA only) and the memory ($\beta = -0.48$; $R = 0.44$; $p = 0.006$) and attention/executive function ($\beta = -0.49$; $R = 0.45$; $p = 0.008$) domains. We found additional correlations between the FA and MD of the AF and IFOF and the memory and attention/executive function domains that approached significance ($0.008 < p < 0.05$). No significant correlations were found between the UF and any of the 3 cognitive domains assessed with the neuropsychological tests ($p > 0.05$).

Within the language domain, a strong significant correlation was found between the FA in the AF and the Aachen Aphasia Repetition test¹² results ($\beta = 0.59$; $R = 0.53$; $p < 0.0001$). The IFOF was correlated significantly with a subtest of the memory domain for verbal memory (i.e., the 15 Words test,¹⁸ imprinting [$\beta = -0.55$; $R = 0.48$; $p = 0.002$]) and with a subtest for selective attention within the attention/executive function domain (i.e., Stroop I [$\beta = -0.62$; $R = 0.50$; $p = 0.006$]) (Table 4).

Discussion

We performed a large-scale quantitative analysis of language WM tract microarchitecture and cognitive performance in patients with presumed LGG. Patients had deficits in all of the cognitive domains assessed (i.e., language, memory, and attention/executive function). A significant correlation was found between FA in the AF

FIG. 2. **A:** The first ROI is placed on the green projections in the anterior part of the frontal lobe. **B:** The second ROI is placed on the green projections in the posterior part of the occipital lobe; the tumor is delineated in red. **C:** The 3D reconstruction of the IFOF is shown. Figure is available in color online only.

and the language domain results, specifically with those of a repetition test, which is associated with phonological abilities. The FA in the IFOF was correlated significantly with deficits in verbal learning (imprinting) and selective attention. In this cohort of patients with tumors that radiologically appeared to be a low grade (i.e., presumed LGG), language impairments were significantly worse in patients with a tumor that was later found with histopathological examination to be a high grade.

DTI Measures Within the Language WM Tracts

We found that lower FA, but not MD, was correlated

significantly with language and verbal memory deficits in patients with presumed LGG. FA is a measure of directionality of molecular motion classically known to be sensitive to microstructural changes but not specific to the type of changes. MD is a measure of the magnitude of diffusion and is sensitive to cellularity, edema, and necrosis.² Several tumor-associated mechanisms that influence FA and MD have been described. Tumor infiltration in WM tracts and edema can cause a decrease in FA and an increase in MD, whereas compression of WM tracts caused by a tumor results in an increase in FA and a decrease in MD.¹⁵ Lee et al.¹⁶ found that purely vasogenic edema, composed purely of extracellular water (e.g., with meningiomas), causes a

FIG. 3. **Left:** The first ROI is placed on the green projections in the anterior part of the temporal lobe. The second ROI is placed on the green projections in the inferior part of the frontal lobe; the tumor is delineated in red. **Right:** The 3D reconstruction of the UF is shown. Figure is available in color online only.

TABLE 2. Neuropsychological test protocol with z-scores and p values per cognitive domain

Neuropsychological Test	No. of Pts*	Cognitive Abilities Tested	Description	Mean z-Score (SD)	p Value
Language domain				-0.78 (0.98)	0.00
Aachener Aphasia Token test ¹²	75	Language comprehension; severity of language disorder	Pointing to & manipulating geometric forms on verbal commands	-0.40 (1.97)	0.740
Aachener Aphasia Repetition test ¹²	72	Repetition	Repeating phonemes, words, & sentences	-0.11 (0.81)	0.013
Boston Naming Test ¹⁴	75	Naming (word finding)	Naming 60 pictures, presented in order of word frequency & difficulty	-1.52 (1.72)	0.00
Category fluency ²⁰	74	Flexibility of verbal semantic thought processing; working memory	Producing words of a given category (animals & processions) w/in a limited time span	-1.04 (0.84)	0.00
Letter fluency ²⁷	73	Flexibility of verbal phonological thought processing; working memory	Producing words beginning w/ a given letter (D, A, T) w/in a limited time span	-0.89 (1.19)	0.00
Memory domain				-1.49 (1.35)	0.00
15 Words test, imprinting ¹⁸	62	Verbal learning	Learning a list of 15 words	-1.82 (1.43)	0.00
15 Words test, recall ¹⁸	62	Verbal learning; immediate & delayed recall	Learning a list of 15 words, w/ 6 recall trials; 5 immediate & 1 delayed	-1.22 (1.36)	0.00
Attention/executive function				-0.57 (0.93)	0.00
Trail Making Test A ¹⁸	65	Visuomotor speed; attention	Connecting numbers placed randomly in ascending order as rapidly as possible	-0.60 (1.14)	0.00
Trail Making Test B ¹⁸	63	Mental flexibility; divided attention	Connecting alternating numbers & letters as rapidly as possible	-0.37 (1.28)	0.027
Trail Making Test BA ¹⁸	62	Visuomotor speed; attention & mental flexibility; divided attention	Time difference btwn Trail Making Tests B & A	-0.12 (1.23)	0.459
Stroop I ¹⁸	53	Mental speed; selective attention	Reading color words	-1.09 (1.39)	0.00
Stroop II ¹⁸	53	Mental speed; selective attention	Naming colors	-1.12 (1.35)	0.00
Stroop III ¹⁸	51	Mental speed; selective attention	Naming colors of printed words denoted in a different color	-0.64 (1.06)	0.00
Stroop interference ¹⁸	48	Mental speed; selective attention	Time difference btwn Stroop III & II	-0.31 (1.09)	0.056

Pts = patients.

* Number of patients assessed before surgery. In some cases, the full protocol could not be applied to all patients for several reasons. Priority was given to tests that were most relevant to the preparation of the operative procedure.

more relative increase in MD than a decrease in FA. In contrast, tumor-infiltrated edema (infiltration of tumor [e.g., glioma] cells in WM tracts) causes a more relative decrease in FA than an increase in MD. We can speculate, therefore, that our findings might reflect tumor infiltration into the WM tracts.

AF and Language Deficits

We found an association between microarchitectural changes of the AF and impaired language repetition abilities. The AF, also known as the dorsal pathway in the dual-stream model of Hickok and Poeppel,¹³ is associated with mapping sound to articulatory-based representations (e.g., phonology), which explains the functional association between microstructural changes and phonological deficits observed here. Our findings also support recent results from Sierpowska et al.,²⁹ who reported that monitoring (non)word repetition is relevant near the AF during electro(sub)cortical stimulation for the preservation of language production and, in particular, phonological performance.^{25,29}

Deficits in language repetition in combination with

relatively intact comprehension, as observed in our patient group, are “classically” known in the stroke literature as conduction aphasia. Several studies in patients with a different etiology found a link between this specific aphasia type and damage to the AF (e.g., tumor infiltration, WM tract compression).⁴ In addition, damage to the AF might be predictive of persistent language deficits^{6,22} at test level but also in relation to the quality of communication, which underlines the importance of including a repetition task when performing neuropsychological assessments.

IFOF and Cognition

Another important pathway (apart from the AF) that is reported to be related to language is the IFOF, which is part of the so-called ventral stream according to Hickok and Poeppel.¹³ The ventral stream (IFOF) is involved in mapping sound on meaning (e.g., semantics, comprehension). In our study, when compared with healthy people, the participants had no comprehension deficits as measured with the Aachener Aphasia Token test; therefore, it is not surprising that no association was found between DTI measures within the IFOF and the language domain.

TABLE 3. Relationships between 3 neuropsychological domains and FA and MD values of 3 WM tracts

Domain (no. of pts)	AF		IFOF		UF	
	FA	MD	FA	MD	FA	MD
Language (65)						
β	0.44	-0.31	-0.30	0.12	0.06	0.05
p	0.003†	0.380	0.057	0.499	0.665	0.758
R	0.40	0.28	0.40	0.28	0.40	0.28
Memory (54)						
β	0.34	-0.21	-0.48	0.45	0.32	-0.27
p	0.029*	0.172	0.006†	0.019*	0.055	0.128
R	0.44	0.37	0.44	0.37	0.44	0.37
Attention/ executive function (55)						
β	0.39	-0.33	-0.49	0.04	0.17	0.09
p	0.014*	0.036*	0.008†	0.847	0.339	0.656
R	0.45	0.32	0.45	0.32	0.45	0.32

β = standardized coefficient; R = correlation coefficient.

Linear regression models with neuropsychological test results as a dependent factor and FA or MD, histopathological grade, and age as independent factors.

* Statistically significant at a level of $p < 0.05$.

† Statistically significant at a level of $p \leq 0.008$ (see Table 4 for subtask associations).

Within the semantic level, we found impairments in category fluency, but the multidimensional background of this test (i.e., language [lexical retrieval], semantic memory, and, in part, attention/executive functioning) might be responsible for the lack of a correlation. Although it is possible that no (clear) semantic deficits in our patient population existed, this finding might also indicate a limitation in our neuropsychological test procedure, in that the applied tests for language functioning were not equivalent to the main linguistic components (i.e., semantics, syntax, and phonology). In contrast with phonology, semantics and syntax were examined more globally by using the Aachen Aphasia Token test. We therefore developed the Dutch Linguistic Intraoperative Protocol (DuLIP),⁷ a more elaborate battery for testing language functioning in patients with glioma. This tool is currently in the evaluation phase.

Besides language deficits, it has been suggested that damage to this WM tract can cause other cognitive deficits. According to a model proposed by Duffau,⁸ the IFOF could be relevant for attention and/or (working) memory. Our study revealed a correlation between FA in the IFOF and both imprinting and attention deficits, which provides additional support for previous suggestions of the involvement of the IFOF in memory.

The lack of clear cognitive deficits in other domains might be explained by neural plasticity (i.e., functional reorganization). All of our patients were presumed to have LGG (non- to mildly contrast enhancing), and in more than half of these patients, a low-grade tumor was confirmed with histopathological examination. LGG is typically associated with a relatively slow tumor growth rate, which facilitates neural plasticity. As a result, functional

TABLE 4. Association between the significant subtasks of the significant cognitive domains and FA in the AF and IFOF

Domain	Subtask	WM Tract	β	p Value	R
Language	AAT REP	AF	0.59	0.0001	0.53
Memory	15 WT IMPR	IFOF	-0.55	0.002	0.48
Attention & executive functions	Stroop I	IFOF	-0.62	0.006	0.50

AAT REP = Aachen Aphasia Repetition test; 15 WT IMPR = 15 Words test, imprinting.

Linear regression models with neuropsychological test results as a dependent factor and FA, histopathological grade, and age as independent factors.

reorganization might have taken place, which would lead to deficits that were less severe than expected from the degree of tract infiltration. Therefore, more sensitive tasks for detecting mild cognitive deficits in patients with LGG would be useful.

Tumor Grade

It should be noted that in this context a large proportion (41.6%) of non- to mildly contrast-enhancing tumors in this study were found with histopathological examination to be HGG, which could have influenced our findings if compared to those of patients purely with LGG. However, whether and how LGG influences FA and/or MD values in perilesional WM tracts differently than HGG is still under debate.^{19,23} In our study, language impairments were significantly worse in patients with histopathologically established HGG than in those with LGG, whereas no significant differences between these 2 groups in FA or MD values of the 3 WM tracts were found. The former is consistent with the more aggressive nature of these tumors and the latter with their radiological characteristics. We can speculate that the higher-grade tumors allow for less plasticity and, hence, worse deficits.

Limitations

There were some limitations to our study. Deterministic tractography was used to identify 3 WM tracts per patient by using 2 ROIs per WM tract. It is important to note that the procedure of manual anatomical seed ROI placement is subject to variability within and between raters. Subjectivity depends on the location of ROI placement and the WM tract of interest, with higher variability of tracking in cortical areas and higher variability within specific tracts (e.g., the inferior longitudinal fasciculus).^{21,28} This subjectivity is even more relevant in the context of brain tumors; Schonberg et al.²⁸ found that when WM tracts are displaced by excessive edema or shift caused by tumor compression, the variability and subjectivity of ROI placement and tractography increase significantly when compared with those of the contralateral hemisphere. We attempted to keep the intersubject variability low and success rate high by using just 1 well-trained rater who placed ROIs systematically on clearly identifiable anatomical landmarks on DTI maps using published approaches³⁰ and who visually inspected each identified WM tract in 3 dimensions. In addition, the exclusion of WM tracts of some patients that could not be

tracked in this analysis might have introduced some selection bias, because these patients potentially had a greater number of or more severe cognitive deficits. Furthermore, one could argue that the diffusion-weighted imaging acquisition, which now includes multiple b values and many more gradient directions, is not fully state of the art in the context of neuroscientific research. This study was performed within the constraints of a routine clinical context in which longer scan durations are not feasible, which might have limited our sensitivity to more subtle changes or associations, which means our negative findings need to be interpreted with care. The possibility that differences in magnet strength (1.5 vs 3.0 T) can cause a difference in FA and/or MD values in the WM tracts is another reason to interpret findings in DTI studies with care.¹¹ Such differences are likely to subsequently cause reduced strengths of associations between FA and/or MD values and cognitive outcome. However, we did not find a difference in FA and/or MD values between the 2 magnet strengths in this study, and we can state fairly confidently that the associations we did find were valid and strong.

Last, because of multiple testing, a stringent significance level was maintained. As a result, a risk of false-negative findings exists, and relevant correlations could have been obscured. However, the risk of false-positive findings was low, and correlations that passed the stringent significance level can be considered clearly positive.

Conclusions

In this clinical DTI study, we found that preoperative language deficits in repetition of speech and verbal learning and attention deficits are associated with changes in the microarchitecture of the AF and the IFOF, respectively, in patients with presumed LGG. This finding indicates that performing repetition tasks during awake surgery is especially important and should be included in the neuropsychological assessment as a standard. Verbal learning is difficult to monitor during surgery, which highlights the need for a careful preoperative assessment of the IFOF with DTI, especially in patients with decreased performance on the 15 Words test. We emphasize that, especially in patients with deficits in speech repetition or verbal learning, performing extensive tumor resection will need to be balanced carefully against preserving infiltrated WM tracts (i.e., the AF and IFOF). Further investigation is needed to assess the predictive value of preoperative FA of WM tracts, tumor genetic profile, and extent of tumor resection on postoperative cognitive outcome.

References

- Abhinav K, Yeh FC, Mansouri A, Zadeh G, Fernandez-Miranda JC: High-definition fiber tractography for the evaluation of perilesional white matter tracts in high-grade glioma surgery. **Neuro Oncol** 17:1199–1209, 2015
- Alexander AL, Hurley SA, Samsonov AA, Adluru N, Hosseinbor AP, Mossahebi P, et al: Characterization of cerebral white matter properties using quantitative magnetic resonance imaging stains. **Brain Connect** 1:423–446, 2011
- Bizzi A, Nava S, Ferrè F, Castelli G, Aquino D, Ciaraffa F, et al: Aphasia induced by gliomas growing in the ventrolateral frontal region: assessment with diffusion MR tractography, functional MR imaging and neuropsychology. **Cortex** 48:255–272, 2012
- Breier JI, Hasan KM, Zhang W, Men D, Papanicolaou AC: Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. **AJNR Am J Neuroradiol** 29:483–487, 2008
- Catani M, Thiebaut de Schotten M: A diffusion tensor imaging tractography atlas for virtual in vivo dissections. **Cortex** 44:1105–1132, 2008
- Caverzasi E, Hervey-Jumper SL, Jordan KM, Lobach IV, Li J, Panara V, et al: Identifying preoperative language tracts and predicting postoperative functional recovery using HARDI q-ball fiber tractography in patients with gliomas. **J Neurosurg** 125:33–45, 2016
- De Witte E, Satoer D, Robert E, Colle H, Verheyen S, Visch-Brink E, et al: The Dutch Linguistic Intraoperative Protocol: a valid linguistic approach to awake brain surgery. **Brain Lang** 140:35–48, 2015
- Duffau H: The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography. **Neuropsychologia** 46:927–934, 2008
- Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, et al: Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. **Brain** 125:199–214, 2002
- Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L: New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. **Brain** 128:797–810, 2005
- Fushimi Y, Miki Y, Okada T, Yamamoto A, Mori N, Hanakawa T, et al: Fractional anisotropy and mean diffusivity: comparison between 3.0-T and 1.5-T diffusion tensor imaging with parallel imaging using histogram and region of interest analysis. **NMR Biomed** 20:743–748, 2007
- Graetz S, de Blesser P, Willmes K: **Akense Afasie Test, Dutch edition**. Lisse: Swets & Zeitlinger, 1991
- Hickok G, Poeppel D: Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. **Cognition** 92:67–99, 2004
- Kaplan E, Goodglass H, Weintraub S: **Boston Naming Test**. Philadelphia: Lippincott, Williams and Wilkins, 2001
- Kinoshita M, Nakada M, Okita H, Hamada J, Hayashi Y: Predictive value of fractional anisotropy of the arcuate fasciculus for the functional recovery of language after brain tumor resection: a preliminary study. **Clin Neurol Neurosurg** 117:45–50, 2014
- Lee HY, Na DG, Song IC, Lee DH, Seo HS, Kim JH, et al: Diffusion-tensor imaging for glioma grading at 3-T magnetic resonance imaging: analysis of fractional anisotropy and mean diffusivity. **J Comput Assist Tomogr** 32:298–303, 2008
- Leemans A, Jones DK: The B-matrix must be rotated when correcting for subject motion in DTI data. **Magn Reson Med** 61:1336–1349, 2009
- Lezak MD: **Neuropsychological Assessment**. New York: Oxford University Press, 2004
- Lu S, Ahn D, Johnson G, Law M, Zagzag D, Grossman RI: Diffusion-tensor MR imaging of intracranial neoplasia and associated peritumoral edema: introduction of the tumor infiltration index. **Radiology** 232:221–228, 2004
- Luteijn F, Barelds DPF: **Groninger Intelligentie Test II (GIT II)**. Amsterdam: Pearson, 2004
- Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, et al: Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. **Cereb Cortex** 15:854–869, 2005
- Marchina S, Zhu LL, Norton A, Zipse L, Wan CY, Schlaug

- G: Impairment of speech production predicted by lesion load of the left arcuate fasciculus. **Stroke** **42**:2251–2256, 2011
23. Miloushev VZ, Chow DS, Filippi CG: Meta-analysis of diffusion metrics for the prediction of tumor grade in gliomas. **AJNR Am J Neuroradiol** **36**:302–308, 2015
 24. Papagno C, Casarotti A, Comi A, Gallucci M, Riva M, Bello L: Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). **J Neurooncol** **108**:269–275, 2012
 25. Sarubbo S, De Benedictis A, Merler S, Mandonnet E, Balbi S, Granieri E, et al: Towards a functional atlas of human white matter. **Hum Brain Mapp** **36**:3117–3136, 2015
 26. Satoer D, Visch-Brink E, Smits M, Kloet A, Looman C, Dirven C, et al: Long-term evaluation of cognition after glioma surgery in eloquent areas. **J Neurooncol** **116**:153–160, 2014
 27. Schmand B, Groenink SC, Van den Dungen M: Letterfluency: psychometrische eigenschappen en Nederlandse normen. **Tijdschr Gerontol Geriatr** **39**:65–77, 2008
 28. Schonberg T, Pianka P, Hendler T, Pasternak O, Assaf Y: Characterization of displaced white matter by brain tumors using combined DTI and fMRI. **Neuroimage** **30**:1100–1111, 2006
 29. Sierpowska J, Gabarrós A, Fernandez-Coello A, Camins À, Castañer S, Juncadella M, et al: Words are not enough: non-word repetition as an indicator of arcuate fasciculus integrity during brain tumor resection. **J Neurosurg** **126**:435–445, 2017
 30. Smits M, Jiskoot LC, Papma JM: White matter tracts of speech and language. **Semin Ultrasound CT MR** **35**:504–516, 2014
 31. Talacchi A, d'Avella D, Denaro L, Santini B, Meneghelli P, Savazzi S, et al: Cognitive outcome as part and parcel of clinical outcome in brain tumor surgery. **J Neurooncol** **108**:327–332, 2012
 32. Thiebaut de Schotten M, Ffytche DH, Bizzi A, Dell'Acqua F, Allin M, Walshe M, et al: Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. **Neuroimage** **54**:49–59, 2011
 33. Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J: Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. **J Int Neuropsychol Soc** **11**:290–302, 2005

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Incekara. Statistical analysis: all authors. Administrative/technical/material support: all authors. Study supervision: Vincent, Smits.

Supplemental Information

Previous Presentations

This work was presented in abstract form at the 11th meeting of the European Low Grade Glioma Network held in Graz, Austria, on June 3, 2016, and the European Society for Magnetic Resonance in Medicine and Biology 2016 Congress held in Vienna, Austria, on September 30, 2016.

Correspondence

Fatih Incekara: Erasmus MC–University Medical Center, Rotterdam, The Netherlands. f.incekara@erasmusmc.nl.