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Research Report

Executive functioning following surgery near the frontal aslant tract in low-grade glioma patients: A patient-specific tractography study

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ABSTRACT

Background: The Frontal Aslant Tract (FAT) has been associated with executive functions (EF), but it remains unclear what role the FAT plays in EF, and whether preoperative dysfunction of the FAT is associated to long-lasting postsurgical executive impairments.

Methods: In this study, we examined the course of EF from pre-surgery ($n = 75$) to 3 ($n = 61$) and 12 ($n = 25$) months after surgery in patients with frontal and parietal low-grade gliomas (LGGs), to establish the degree to which long-term EF deficits exist. Secondly, we used patient-specific tractography to investigate the extent to which overlap of the tumor with the FAT, as well as integrity of the FAT, presurgery were related to EF on the short and longer term after surgery.

Results: LGG patients performed worse than healthy controls on all EF tests before and 3 months postsurgery. Whereas performances on three out of the four tests had normalized 1 year postsurgery ($n = 26$), performance on the cognitive flexibility test remained significantly worse than in healthy controls. Patients in whom the tumor overlapped with the core of the right FAT performed worse presurgery on three of the EF tests compared to those in whom the tumor did not overlap with the right FAT. Presurgical right FAT integrity was not related to presurgical EF, but only to postsurgical EF (from pre-to 3 months postsurgery). Longitudinal analyses demonstrated that patients with right (but not left) FAT core overlap performed on average worse over the pre- and postsurgical timepoints on the cognitive flexibility test.

Conclusions: We emphasized that LGG patients perform worse than healthy controls on the EF tests, which normalizes 1-year postsurgery except for cognitive flexibility. Importantly, in patients with right hemispheric tumors, tumor involvement of the FAT was associated with worse pre- and 3- months postsurgical performance, specifically concerning cognitive flexibility.

Abbreviations: FAT, frontal aslant tract; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; DW-MRI, diffusion weighted magnetic resonance imaging; SLF, superior longitudinal fasciculus; FA, fractional anisotropy; MD, mean diffusivity; CSD, Constrained Spherical Deconvolution; LGG, low-grade glioma; HGG, high-grade glioma; EF, executive function.

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1. Introduction

In glioma surgery, it is of paramount importance to understand the functional role of peritumoral areas in order to optimize the resection while limiting postoperative neurological, cognitive and emotional disturbances. Although treatment advances have significantly improved median survival of low-grade glioma patients (LGG) (IDH-mutated oligodendrogliomas and astrocytomas) towards 9–17 years (Molinaro, Taylor, Wiencke, & Wrensch, 2019), many patients suffer from cognitive disturbances even years after treatment (IJzerman-Korevaar, Snijders, de Graeff, Teunissen, & de Vos, 2018) negatively affecting daily life (Teng et al., 2021; van Kessel, Baumfalk, van Zandvoort, Robe, & Snijders, 2017). One of the most common cognitive disturbances are impairments in executive functions (EF) (Ng et al., 2019). EFs are general-purpose control mechanisms that regulate the dynamics of daily human cognition and action, such as inhibitory control and cognitive flexibility (Diamond, 2013; Friedman, Miyake, Robinson, & Hewitt, 2011; Miyake et al., 2000; Miyake & Friedman, 2012). Various daily activities require different EFs, and even neuropsychological tests that are traditionally viewed as non-EF measures appear to tap into EFs to some degree (Davis & Pierson, 2012).

Neuroscientific and clinical studies have demonstrated that damage to specific white matter pathways leads to persistent deficits in motor, language and visual functions (Bates et al., 2003; Catani, 2007; De Benedictis & Duffau, 2011; Lawes et al., 2008; Lus, Angelini, de Schotten, Mandonnet, & Duffau, 2011; Maier-Hein et al., 2017; Rutten & Ramsey, 2010). As a consequence, preoperative and intraoperative tools have been developed to identify and preserve these pathways in order to prevent postoperative deficits (Hamer, Robles, Zwinderman, Duffau, & Berger, 2012). EFs, however, have not (yet) been clearly linked to specific white matter pathways, and EF outcomes are only seldom taken into account during surgical decision making and planning (Duffau, 2016; Rijnen et al., 2019). Still, certain pathways appear indispensable for executive functioning given the high prevalence of executive dysfunctions after LGG resections most likely caused by structural disconnections (Cochereau et al., 2020; Ng et al., 2019; Rijnen et al., 2019).

A relatively newly discovered white matter pathway that has been associated with EFs is the frontal aslant tract (FAT). The FAT was first described in 2007 and named ‘aslant’ several years later because of its oblique course connecting pars opercularis and pars triangularis of the inferior frontal gyrus to the pre-Supplementary Motor Area (pre-SMA) and the Supplementary Motor Area (SMA) of the superior frontal gyrus (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Catani et al., 2012; Dick, Bernal, & Tremblay, 2014; Dick, Garic, Graziano, & Tremblay, 2019). The connectivity of the FAT can be visualized with diffusion-weighted magnetic resonance imaging (DW-MRI) and has been verified in anatomical post-mortem studies (Bozkurt et al., 2016; Catani et al., 2013; Dick et al., 2019; Mandelli et al., 2014; Vergani et al., 2014).

Functionally, the right FAT in particular has been linked to EFs (Burkhardt, Kinoshita, & Herbet, 2021; Dick et al., 2019), whereas the left FAT has been mostly associated with (initiation of) motor-speech (Corrivetti et al., 2019; Rutten, 2015; Szelényi et al., 2010; Vassal, Boutet, Lemaire, & Nuti, 2014) and verbal fluency (Kinoshita et al., 2015). Most of the evidence that suggests involvement of the right FAT in EF is indirect, that is, derived from studies that investigated the areas connected by the FAT (Aron, Robbins, & Poldrack, 2014; Erika-Florence, Leech, & Hampshire, 2014; Varriano, Pascual-Diaz, & Prats-Galino, 2018), but not the FAT itself (Landers, Sitskoorn, Rutten, Mandonnet, & De Baene, 2022). In a previous quantitative tractography study, we studied the integrity as well as the proximity of the FAT to the tumor in a sample of LGG and high-grade glioma (HGG) patients (Landers, Meesters, van Zandvoort, De Baene, & Rutten, 2020). An association was found between preoperative proximity to/integrity of the right FAT and preoperative performances on tests assessing cognitive flexibility and verbal fluency, suggesting involvement of the right FAT in aspects of EF.

Results from a recent study assessing the postoperative course indicated that surgically-related disruption of the FAT leads to specific EF impairments (inhibition and cognitive flexibility) at least three months after surgery in LGGs (Cochereau et al., 2020). Furthermore, the superior longitudinal fasciculus (SLF) II and SLF III, two fasciculi of which anterior parts run in close vicinity of the FAT, were also associated with EF impairments (in verbal inhibition and verbal fluency). It is important to note that a standardized white matter atlas was used to approximate the anatomical position of the FAT. This approach does not take into account normal individual anatomical variances and possible displacement of tracts by the tumor. DWI-tractography methods more accurately assess the anatomical position of a tract, as tracts are generated for each individual patient.

Currently, it remains unclear what role the FAT plays in different EFs, and whether preoperative dysfunction of the FAT (via mass effect or infiltration by the tumor) is associated to long-lasting postsurgical executive impairments in patients with LGG (Duffau, Gatignol, Mandonnet, Capelle, & Taillandier, 2008; Jellison et al., 2004; Mormina et al., 2015). Cognitive problems are one of the main priorities reported by brain tumor patients and carers, and this should be taken into account in treatment (Armstrong et al., 2012; Tucha, Smely, Preier, & Lange, 2000). Having a better understanding of the relevance of preoperative FAT measures/integrity for EF can aid treatment planning, more targeted monitoring of patients at risk for adverse cognitive outcome, and patient informing. In addition, due to the anatomical position of the (anterior parts of) long-range frontoparietal pathways (SLF II and III) and their possible role in EF deficits in patients with LGG

(Koshiyama et al., 2020; Mandonnet et al., 2017), these pathways should be taken into account when investigating the role of the FAT.

In this study, we first examined the course of performances on tests tapping into EF from pre-surgery up to one year after surgery in patients with frontal and parietal IDH-1 mutated LGGs, to establish the degree to which deficits exist and persist. Secondly, we used patient-specific tractography to investigate the extent to which overlap of the tumor with the FAT, as well as integrity of the FAT, prior to surgery were related to performances on these tests on the short and longer term after surgery, while controlling for nearby tracts.

2. Methods

In the following section we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Study design and patient sample

We retrospectively analyzed data from adult patients with newly diagnosed unilateral frontal or parietal LGGs, grade II and grade III IDH mutated, from whom DW-MRI was acquired between 4 and 1 days prior to surgery, according to the standard presurgical functional imaging protocol of the Elisabeth-TweeSteden hospital (Tilburg, the Netherlands). These patients underwent glioma resection from November 2010 to Augustus 2021and were eligible for the current study if they had completed a neuropsychological screening in the week prior to surgery (see section Neuropsychological assessment). Exclusion criteria were age below 18 years, previous craniotomy, impaired testability (e.g., severe aphasia or motor dysfunction), a recent history of other major medical illnesses in the past year before surgery, severe neurological or psychiatric disorders in the past two years and lack of Dutch language skills. Patients did not undergo neoadjuvant treatment before surgery. A positive advice for this study was provided by the local ethics committee (NW2020-32, METC Brabant, The Netherlands) and all patients gave written informed consent to participate. No part of the study procedures or analysis plans was preregistered prior to the research being conducted. The data is stored in an institutional repository and not publicly available due to hospital legislation and medical ethical objections. Metadata is available upon request if the ethical committee Brabant (METC Brabant) approves and if the data sharing agreement is undersigned by both a demanding and providing party.

2.2. Measures and procedure

2.2.1. DWI tractography by means of constrained spherical deconvolution (CSD)

All DWI scans were acquired using a Philips Achieva 3T MRI-scanner ($b = 1500$, 50 diffusion weighting directions, 6 $b = 0$ images, 2 mm isotropic voxel size). Probabilistic tractography was performed to generate tractograms of the FAT and the SLF II and III using a pipeline for subject-specific automatic reconstruction of white-matter pathways (Meesters, Landers, Rutten, & Florack, 2023 (Submitted)). This automated pipeline uses the MRtrix software package for the constrained spherical deconvolution-based iFOD2 method with *tckgen* (Tournier, Calamante, & Connelly, 2012). All generated patient-specific regions of interest (ROIs) and tractograms were verified by at least two medical professionals. A lesion overlap map is included as supplementary material (Supplementary Fig. 1), as well as illustrations of the used ROIs (Supplementary Fig. 2).

2.2.2. Tumor segmentation

Semi-automatic tumor segmentations were conducted to obtain volumetric data using active tumor contours available in ITK-SNAP (Yushkevich et al., 2006). This program involves some manual assistance to set tumor margins and then automatically segments the tumor. FLAIR images were used to delineate tissue. All segmentations were verified by at least two medical professionals.

2.2.3. Coregistration

All images (T1/FLAIR, DWI, tractograms and tumor segmentations) were transferred into the same diffusion-weighted MRI space using NiftyReg affine coregistration for further data processing (Clayden, Modat, Presles, Anthopoulos, & Daga, 2019).

2.2.4. Tumor overlap with the core of the FAT

To assess whether the tumor overlapped with the core of the FAT, the proximity of the tumor to the FAT was calculated first. An algorithm was used that generated the shortest distance between any fiber of the tract and the nearest tumor voxel (Wolfram Research, 2019). In case this value was zero, we considered the tumor to be contiguous with the FAT and these cases were visually classified by at least two medical professionals to determine whether the tumor overlapped with the *core* of the FAT (yes/no), which was defined as the white matter in between the frontal operculum (pars triangularis, pars opercularis) and (pre)SMA. Cases were not classified to overlap if the tumor was contiguous with the FAT but did not overlap with the core of the FAT. Two examples are included, one example of a patient in which the tumor overlapped with the core of the FAT and one of a patient in which the tumor did not overlap with the core of the FAT (Supplementary Fig. 3).

2.2.5. Structural integrity

Fractional anisotropy (FA) and mean diffusivity (MD) are both well-known measures of structural integrity (Mormina et al., 2015). FA is a measure that reflects the coherent directionality of water diffusion, or anisotropy, caused by the constriction of water molecules across the walls of axons. MD is an isotropic measure that reflects water diffusion in each direction, being the inverse of membrane density. FA and MD are mutually correlated but FA has a skewed distribution in white matter, whereas MD is more normally distributed in white matter. We used MD as a measure of structural integrity in this study, as it is a more robust marker for pathological processes than the anisotropic measure and increases due to any disease process that affects barriers (Alexander, Lee, Lazar, & Field, 2007). MD was calculated using *tcksample* to investigate structural integrity of the FAT, SLF II and SLF III, after calculating tensors with the MRtrix method *dwi2tensor*. The calculated values for each voxel of the tract were averaged, which resulted in an average MD.

2.2.6. *Neuropsychological assessment*

Neuropsychological screening was performed between 4 and 1 days prior to surgery (T0), 3 months after (T3) and 12 months after surgery (T12) and administered as part of standard clinical care. See Supplementary Table 1 for an overview and detailed description of the included tests and cognitive domains.

The Dutch version of CNS Vital Signs was used, which is a computerized neuropsychological test battery (Rijnen et al., 2020), and a pen-and-paper task. From the computerized battery we selected three test measures based on involvement of EF, the shifting attention test, the interference measure of the Stroop test (i.e., the difference in reaction time on Stroop task 3 − Stroop task 2), which are tests traditionally viewed as EF tests. We also included the symbol digit coding test, as this test is consistently predicted by cognitive flexibility alongside (psycho-)motor speed and visual scanning (Crowe et al., 1999; Davis & Pierson, 2012). Z-scores were calculated to adjust for age, sex and education level based on a Dutch normative control sample (Rijnen et al., 2017), and additionally for practice effects for T3 and T12 scores. Scores were reversed for Stroop interference so that for all tests higher z-scores indicate better performance.

Letter fluency was assessed using a (non-computerized) Dutch version of the Controlled Oral Word Association Test (COWAT) (Schmand, Groenink, & Van den Dungen, 2008). Z-scores for the letter fluency test were adjusted for education level only, as age and sex were not found to significantly influence test performance in healthy individuals (Schmand et al., 2008). Legal copyright restrictions prevent public archiving of all used neuropsychological tests which can be obtained from the copyright holders in the cited references.

2.3. *Statistical analysis*

Statistical analyses were performed using SPSS 27.0 (Corp., 2016) and Rstudio v4.1.0.

2.3.1. *Sample*

Descriptive statistics were calculated for the following participant characteristics at baseline: age, sex, level of education, affected hemisphere, tumor volume and MD. To inspect potential bias in our T12 follow up sample with regard to patient characteristics and level of baseline cognitive function, we statistically compared the baseline characteristics as well as test performances between patients with T0 and T12 assessment versus those with only T0 and no T12 follow up assessment with independent samples *t*-tests or Mann–Whitney *U* tests (continuous variables, depending on data distribution) and Chi-square tests (categorical variables), with significance level of .05. The number of patients who received additional therapy was added for the T12 follow up sample.

2.3.2. *Relationship between integrity and overlap*

We ran point-biserial correlations to determine the relationship (and possible multicollinearity for the prediction analyses) between presence of overlap of the tumor with the core of the FAT and structural integrity as measured with MD. Data analyses were separately performed for left and right according to affected hemisphere.

2.3.3. *Presurgical cognitive function*

2.3.3.1. DEGREE OF DYSFUNCTION. The extent to which mean performances on group level (z-scores) deviated from healthy controls was analyzed with one-sample z-tests with $M = 0$ and $SD = 1$. The numbers of patients displaying performances at a low ($-1.5 < Z < -1$) or impaired ($Z < -1.50$) level were counted to gain insight into the prevalence of clinically relevant dysfunction (Lezak, Howieson, Bigler, & Tranel, 2012).

2.3.3.2. PRESURGICAL COGNITIVE FUNCTION IN RELATION TO FAT INTEGRITY AND CORE OVERLAP.. To assess whether core overlap and MD were explanatory factors for T0 performance on the different EF tests, multivariable linear regressions were run. For both measures assumptions for linear regression were evaluated. Tumor volume, SLF II integrity and SLF III integrity were included in a base model, and the FAT overlap measure and FAT structural integrity measure (MD) were added subsequently to investigate their added value. Data analyses were separately performed for affected hemisphere (left and right).

2.3.4. *Cognitive performances over time*

2.3.4.1. DEGREE OF DYSFUNCTION. To investigate whether patients' performances at the follow-up timepoints (T3, T12) deviated from healthy controls, we used z-tests in a similar manner as described above.

2.3.4.2. CHANGES IN COGNITIVE PERFORMANCES. To assess changes in performances on the EF tests over time, we performed longitudinal mixed models (LMM, one model per cognitive test). Here, Time (T0–T3–T12) was the level 1 measure that was nested in the patients at level 2. A linear effect of Time was specified for all models, as the study design comprised only three timepoints. We added random slopes if model fit significantly improved (likelihood ratio test, $\alpha = .05$). Different correlation structures were compared based on the Akaike Information Criterion (AIC) value. The correlation structure providing the best fit (i.e., lowest AIC) for the majority of the models was adopted uniformly. We specified additional models with Time as factor (instead of continuous variable) in order to investigate whether changes occurred a specific interval (from T0 to T3 or from T3 to T12).

The LMM procedure described was adopted for 3 models that are described below. The restricted maximum likelihood (REML) algorithm was adopted to estimate model parameters.

Model 1: The course of EF performances over time

To describe patients' performances on the EF tests from the pre-to 3 and 12 months postsurgical time points in the entire sample, irrespective of tumor characteristics, we adopted Time as the only predictor in Model 1.

Model 2: Changes in test performances over time for frontal versus parietal tumor location

In order to assess whether patients with frontal versus parietal tumors showed differences in cognitive performances over time, we added an interaction between time*location (parietal – as reference-*vs* frontal). We chose to include parietal tumors given that it is unclear whether or not the long-range frontoparietal pathways (SLF II and III) may account for deficits in EF when impaired by a glioma. The models were performed for right and left hemispheric tumors separately.

Model 3: Changes in test performances over time in relation to FAT integrity and core overlap

Overlap of the tumor with the FAT core and MD of the FAT were predictors of interest. In all models, we specified tumor volume, SLF II integrity and SLF III integrity (both measured with MD) as covariates. We specified LMM (one per cognitive test) with interaction effects between Time and each variable of interest (overlap, MD of the FAT, SLF II and SLFII and tumor volume) to assess their relationship with changes in cognitive function over time. The models were performed for right and left hemispheric tumors separately.

3. Results

3.1. *Descriptive statistics*

See Table 1 for sociodemographic and clinical sample characteristics. The FAT was readily identifiable in all patients. Neuropsychological data were available for 75 patients at T0, 61 at T3 and 26 at T12. Comparison of the characteristics of the sample with T0 only versus the sample with T0 and T12 assessment demonstrated a significant difference for sex with a lower proportion of females in the group with both T0 and T12 ($p < .017$). The groups did not differ significantly on any other patient characteristics nor on baseline cognitive performances. From the 26 patients who underwent neuropsychological assessment at T12, 11 patients received additional treatment of which 4 patients underwent radiotherapy and 7 patients underwent chemoradiation therapy and 15 did not get additional treatment.

3.2. *Relationship between integrity and overlap*

The point-biserial correlation demonstrated a positive correlation between FAT core overlap and FAT MD in right- and left-sided tumors, indicating that structural integrity of the FAT was significantly lower in case of tumor overlap compared to no overlap (right $r_{pb} = .568$, $n = 36$, $p < .001$; left $r_{pb} = .605$, $n = 39$, $p < .001$).

3.3. *Presurgical cognitive function*

3.3.1. *Degree of dysfunction*

Table 2 shows patients' mean scores on the EF tests. *Z*-tests showed that the patient sample demonstrated significant lower mean performance than the normative sample on the symbol digit coding, shifting attention and letter fluency tests before surgery (p's $< .05$). At T0, the prevalence of low performance ranged from 19% (shifting attention) to 31% (letter fluency) and of impaired performances from 13% (Stroop interference) to 19% (letter fluency).

3.3.2. *Presurgical cognitive function in relation to FAT integrity and core overlap*

Preliminary analyses including visual inspection of scatterplots demonstrated linearity for the structural integrity measure and all EF tests. The residues showed homoscedasticity and normality. The results of the linear regression analyses are presented in Table 3. In right-sided tumors, only tumor overlap with the FAT core (and not FAT integrity) was associated with presurgical performance on the Stroop interference measure ($p < .01$, $\beta = -.519$), shifting attention ($p < .01$, $\beta = -.473$) and symbol digit coding ($p < .01$, $\beta = -.495$) tests. In left-sided tumors, neither tumor overlap with the FAT core nor FAT integrity showed statistically significant associations with preoperative performance.

3.4. *Cognitive performances over time*

3.4.1. *Degree of dysfunction at each timepoint*

Z-tests showed that patients' mean performances were significantly lower compared to normative controls for all tests at T3. At T12, only patients' performance on the shifting attention test remained lower than controls (p's $< .05$). At T3 the prevalence of low performance ranged from 26% (letter fluency) to 29% (shifting attention) and of impaired from 14% (Stroop interference) to 20% (shifting attention). At T12 the prevalence of low ranged from 15% (symbol digit coding) to 38.5% (shifting attention) and of impaired from 0% (symbol digit coding) to 22% (letter fluency).

Results of the longitudinal mixed models (LMM) concerning change in EF performances over time are shown in Table 4 (Model 1 – Time only, Model 2 – frontal *vs* parietal involvement, Model 3 – FAT). The results of the LMM that investigated effects within each interval (Time as factor; T0–T3 and T3–T12) are presented in Supplementary Table 2.

Model 1 – EF performances over time

Fig. 1 shows individual trajectories of scores on each cognitive test over time. The LMM indicated no statistically significant coefficients of Time as predictor (p's $> .05$), except for the symbol digit coding test. For this measure, the LMM showed an improvement on performance in the T3-T12 interval specifically ($b = .56$, SE $= .19$, $p < .01$).

Model 2 – EF performances over time in relation to frontal and parietal involvement

Frontal tumor location (versus parietal location) was not a significant predictor of performance on any of the tests over time (p's $> .05$).

Model 3 – EF performances over time in relation to FAT integrity and FAT core overlap

Table 1 – Baseline characteristics of patients with T0 assessment only and patients with both T0 and T12 assessment T0 only (*n* = 75) T0 and T12 (*n* = 26).

		T0 only (n = 75)		T0 and T12 (n = 26)	
Age M (SD; range) in years		41.0 (11.8; 19–67)		40.2 (11.7; 23–66)	
Sex (*n*)	Male	44 58.7%		20 76.9%	
Level of education (*n*)[a]	Low	14 18.7%		3 11.5%	
	Middle	26 33.6%		11 42.3%	
	High	35 46.7%		12 46.2%	
Affected hemisphere (*n*)	Right	36 48.0%		9 65.4%	
	Left	39 52.0%		17 34.6%	
Tumor volume median (Q1; Q3)[b] in cm^3	Right	28.7 (3.0; 141.4)		38.8 (4.1; 141.4)	
	Left	35.0 (7.4; 189.6)		46.8 (7.4; 183.1)	
Location	Frontal	64 82.1%		23 88.5%	
	Parietal	14 17.9%		4 15.4%	
FAT core overlap		Yes	No	Yes	No
	Right	8 22.2%	28 77.8%	2 22.2%	7 77.8%
	Left	9 23.1%	30 76.9%	3 17.6%	14 82.4%
Hemisphere		Affected	Non affected	Affected	Non affected
FAT Mean diffusivity$^{1\times10e-3}$ mean (SD)	Right	.76 (.10)	.71 (.08)	.79 (.08)	.74 (.07)
	Left	.81 (.13)	.74 (.06)	.82 (.1)	.74 (.05)
Baseline cognitive performances M (SD)					
Symbol digit coding		−.48 (1.07)		−.18 (1.05)	
Shifting attention		−.31 (1.20)		−.34 (1.11)	
Stroop interference		−.24 (1.40)		−.02 (1.14)	
Letter fluency		−.24 (1.31)		−.40 (1.24)	

*$p < .05$.

[a] Education classified according to Dutch coding system of Verhage, Low: Verhage 1–4, Middle: Verhage 5 and High: Verhage 6–7 (Verhage, 1964).

[b] Quartile 1, median of the lower half of the dataset; Quartile 3, median of the upper half of the dataset.

Fig. 2 depicts performances over time according to overlap of the tumor with the FAT core, separated for left (2A) and right FAT (2B). We found no significant interaction between Time (continuous effect) and FAT integrity or tumor overlap with the FAT (*vs* no overlap), indicating that patients' performances over time from T0 to T12 did not differ as a function of FAT integrity or whether the tumor overlapped with the right or the left FAT core. We found a significant main effect of tumor overlap with the FAT in the right hemisphere for performances on the shifting attention test ($b = -1.2$, SE = .4, $p = .02$) and for the symbol digit coding test ($b = -1.2$, SE = .5, $p = .02$), indicating that patients in whom the tumor overlapped with the right FAT core performed worse overall over the timepoints as compared to patients in whom the tumor

Table 2 – Group-level performances on cognitive tests at all timepoints.

	Timepoint		
	T0	T3	T12
Symbol digit coding N	75	61	26
Mean (SD)	−.37 (1.07)**	−.58 (1.13)**	.15 (1.39)
Low performance N (%)	17 (22.7)	17 (27.9)	4 (15.4)
Impaired N (%)	11 (14.7)	10 (16.4)	0 (.0)
Shifting attention N	73	59	26
Mean (SD)	−.32 (1.16)**	−.50 (1.20)**	−.54 (.80)*
Low performance N (%)	16 (21.9)	15 (29.4)	10 (38.5)
Impaired N (%)	12 (16.4)	12 (20.3)	4 (15.4)
Stroop interference N	72	57	25
Mean (SD)	−.14 (1.31)	−.38 (1.56)**	−.22 (1.43)
Low performance N (%)	14 (19.4)	16 (28.1)	7 (28.0)
Impaired N (%)	9 (12.5)	8 (14.0)	5 (20.0)
Letter fluency N	64	50	23
Mean (SD)	−.29 (1.28)*	−.30 (1.18)*	−.39 (1.30)
Low performance N (%)	20 (31.3)	13 (26.0)	8 (34.8)
Impaired N (%)	12 (18.8)	9 (18.0)	5 (21.7)

**$p < .01$; *$p < .05$, z-tests comparing patient to controls (M = 0 with SD = 1).

Table 3 – Linear regression analyses T0.

		Stroop interference	Shifting attention	Symbol digit coding	Letter fluency
RIGHT	Base model[a]	*F*(3, 31) = 1.305, *p* = .291, R^2 = .112	*F*(3, 32) = .964, *p* = .421, R^2 = .083	*F*(3, 32) = .858, *p* = .473, R^2 = .074	*F*(3, 27) = 1.418, *p* = .259, R^2 = .136
Volume	B (SE)	1.108e-5 (.000)	−5.635e-6 (.000)	−7.204e-6 (.000)	−1.954e-5 (.000)
	Beta	.208	−.153	−.216	−.346
SLF II MD	B (SE)	−6461.810 (6126.976)	−5292.409 (3804.501)	3778.681 (3468.916)	−2287.937 (5013.433)
	Beta	−.315	−.383	.301	−.131
SLF III MD	B (SE)	5385.904 (3806.744)	3028.592 (2411.459)	−1636.360 (2198.750)	1067.059 (2980.123)
	Beta	.423	.346	−.206	.358
	Model[b]	*F* change (2, 29) = **4.787*** R^2 change = **.220***	*F* change (3, 30) = 2.950 R^2 change = .151	*F* change (2, 30) = 3.468 R^2 change = .248	*F* change (2, 25) = .736 R^2 change = .048
FAT core overlap	B (SE)	**−1.972 (.729)***	**−1.235 (.530)***	**−1.173 (.476)***	−.399 (.731)
	Beta	**−.519***	**−.473***	**−.495***	−.131
FAT MD	B (SE)	269.845 (4237.202)	1788.860 (3031.426)	1199.254 (2725.006)	−2959.782 (3858.332)
	Beta	.017	.172	.127	−.224
LEFT	Base model[a]	*F*(3, 33) = .998, *p* = .406 R^2 = .083	*F*(3, 33) = 4.045, *p* = .015, R^2 = .269	*F*(3, 35) = 2.220, *p* = .103, R^2 = .160	***F*(3, 29) = 3.714, *p* = .022*, R^2 = .278**
Volume	B (SE)	−2.335e-6 (.000)	−8.006e-6 (.000)	−6.845e-6 (.000)	**−1.480e-5 (.000)***
	Beta	−.105	−.288	−.265	**−.416***
SLF II MD	B (SE)	4669.033 (2844.576)	**9919.640 (3208.051)****	**6323.405 (2875.301)***	9990.483 (5183.782)
	Beta	.459	**.787****	**.523***	.680
SLF III MD	B (SE)	−3870.960 (2391.233)	**−9045.366 (2735.855)****	**−4718.341(2278.812)***	−7945.626 (4775.068)
	Beta	−.430	**−.797****	**−.472***	−.591
	Model[b]	*F* change (2, 31) = .268 R^2 change = .016	*F* change (2, 31) = .124 R^2 change = .006	*F* change (2, 33) = 1.265 R^2 change = .060	*F* change (3, 29) = 3.714 R^2 change = .017
FAT core overlap	B (SE)	−.423 (.584)	−.168 (.657)	.905 (.626)	.504 (.762)
	Beta	−.187	−.059	.348	.163
FAT MD	B (SE)	633.179 (1548.930)	−502.886 (1784.544)	−2001.158 (1661.053)	69.017 (2181.404)
	Beta	.088	−.054	−.238	.007

** meaning $p < .01$, * meaning $p < .05$.

[a] Base model including structural integrity SLF II, structural integrity SLF III, and tumor volume, without overlap core and structural integrity as prognostic factors.

[b] Multivariable model, added value for each independent variable (overlap and structural integrity).

Table 4 – Results of the longitudinal mixed model.

		Symbol digit coding	Shifting attention	Stroop interference	Fluency
M1 time	Model AIC	554	458	480	406
Time	b(SE)	−.03(.02)	−.02(.02)	.01(.02)	−.01(.02)
	p	.06	.22	.64	.80
		Symbol digit coding	Shifting attention	Stroop interference	Fluency
M2 (frontal vs parietal)	Model AIC	481	467	547	298
Frontal*time	b(SE)	.03(.05)	−.05(.05)	.12(.07)	.07(.05)
	p	.49	.28	.10	.16
Frontal	b(SE)	.19(.35)	.11(.36)	−.22	−.62(.37)
	p	.59	.76	.60	.10
		Symbol Digit Coding	Shifting attention	Stroop interference	Fluency[a]
M3 (FAT) – right hemisphere	Model AIC	204	212	277	184
MD FAT*time	b(SE)	106.67(359.27)	−627.42(394.79)	571.60(800.55)	4718.15(3220.53)
	p	.76	.12	.48	.16
FAT core overlap*Time	b(SE)	.00(.62)	.10(.07)	.12(.14)	−.52(.55)
	p	.99	.19	.40	.35
MD SLF II*time	b(SE)	−418.14(544.65)	905.31(591.85)	−222.50(1217.05)	−1875.42(4903.98)
	p	.45	.14	.85	.71
MD SLF III*time	b(SE)	189.32(476.84)	−403.90(517.50)	−1099.28(1061.15)	−127.12(2736.19)
	p	.69	.44	.31	.96
Main effects					
MD FAT	b(SE)	378.52(2599.35)	377.90(2527.12)	−3125.27(3653.68)	−8466.40(5628.61)
	p	.86	.89	.40	.14
FAT core overlap	b(SE)	**−1.15(.46)**	**−1.22(.49)**	−1.31(.64)	.25(1.00)
	p	**.02**	**.02**	.05	.81
MD SLF II	b(SE)	4861.40(3979.24)	−5783.32(4193.24)	−2535.50(5612.55)	2805.35(8529)
	p	.23	.18	.65	.75
MD SLF III	b(SE)	−1149.91(2025.77)	366124(2135.26)	5305.37(3086.54)	13382.78(4592.81)
	p	.57	.10	.10	.77
Volume (mm^3)	b(SE)	.00(.00)	.00(.00)	.00(.00)	.00(.00)
	p	.05	.76	.34	.09
Model 3 (FAT) – left hemisphere	Model AIC	280	248	287	177
MD FAT*time	b(SE)	427.5(321)	190.1(280)	495.7(374)	597.11(2444.87)
	p	.19	.50	.19	.84
FAT core overlap*time	b(SE)	−.06(.09)	−.02(.08)	−.04(.12)	.15(.68)
	p	.55	.84	.70	.82
MD SLF II*time	b(SE)	−966.9(489)	−592.3(430)	307.1(578)	3265.24(4643.01)
	p	.05	.17	.60	.49
MD SLF III*time	b(SE)	928.9(472)	394.3(420)	−209.8(562)	−2269.37(4785.45)
	p	.06	.35	.71	.64
Main effects					

(continued on next page)

Table 4 – (continued)

		Symbol digit coding	Shifting attention	Stroop interference	Fluency
MD FAT	b(SE)	−2654.7(1680)	−937.8(1512)	−1527.8(2021)	−944.57(3710.06)
	p	.05	.54	.46	.80
FAT core overlap	b(SE)	.6(.6)	−.3(.5)	.2(.7)	.37(1.15)
	p	.33	.60	.78	.74
MD SLF II	b(SE)	6288.8(3020)	**9256.4(2758)**	5135.5(3891)	5240.57(8631.61)
	p	.05	**<.01**	.20	.55
MD SLF III	b(SE)	−455.7(2351)	**−9008.3(2226)**	−4047.8(3260)	−3428.67(8502.54)
	p	.06	**<.01**	.22	.69
Volume (mm^3)	b(SE)	.00(.00)	.00(.00)	.00(.00)	**−.00(.00)**
	p	.13	.21	.32	**.02**

Bold font = $p < .05$.

[a] Fluency test was analyzed from T0 to T3 only (sample size at T12 too low for this LMM due to number of predictors).

did not overlap the right FAT core. Furthermore, we found a significant main effect of left SLF II and III MD on the shifting attention test ($b = 9256$, SE $= 2758$, $p < .01$; $b = 9008$, SE $= 2226$, $p < .01$).

Analysis of the Time intervals showed a significant negative interaction between Time*right FAT MD for performance on the shifting attention test, indicating a decline in performance from T0 to T3 with higher MD values (i.e., lower integrity) ($b = -7073$, SE $= 2971$, $p = .02$). From T3 to T12, we found a significant positive interaction between time*left FAT MD for the stroop test, indicating an improvement in performance with higher MD values (i.e., decreasing integrity) in this interval ($b = 13814$, SE $= 4336$, $p < .01$).

4. Discussion

4.1. Summary of results

This study demonstrates that LGG patients perform worse than healthy controls on tests measuring different facets of EF before and 3 months after surgery. Whereas group performances on three out of the four tests had normalized 1 year after surgery, performance on a test of cognitive flexibility (shifting attention test) remained significantly worse than in healthy controls.

Before surgery, patients with a tumor overlapping the core of the right FAT performed worse on three of the EF tests compared to patients with a tumor not overlapping the right FAT, whereas its integrity was not related to EF performances. Patients with tumors showing overlap with the right (but not left) FAT core performed worse on average over the presurgical and 3 and 12 months postsurgical timepoints on measures that tap into cognitive flexibility to different degrees (shifting attention test and the symbol digit coding test). Finally, lower right FAT integrity was related to decline in cognitive flexibility performance from pre-to 3 months postsurgical assessment only. Our findings regarding the right FAT were independent of tumor volume, as well as integrity of long-range frontoparietal pathways (SLF II and III) that partly run in close vicinity of the FAT and have also been associated with EF.

4.2. Postsurgical course of executive functioning in LGG patients

In general, the results are in line with previous studies demonstrating that patients who undergo surgery for LGG have postsurgical EF impairments (Cochereau et al., 2020; Ng et al., 2019; Rijnen et al., 2019). A recent meta-analysis also observed a sustained impaired performance in tests for cognitive flexibility and inhibition 3-months postsurgery in LGG and HGG patients, despite the test used for measuring cognitive flexibility (TMT) was different (Ng et al., 2019). Furthermore, a recent network-behavior mapping study also found impairments on several EF tests, although these were not significant at group level (Cochereau et al., 2020). The authors described long-lasting EF impairments (between 3 and 78 months postsurgery with a mean of 6.5 months postsurgery) for the TMT, Stroop test and phonemic fluency test

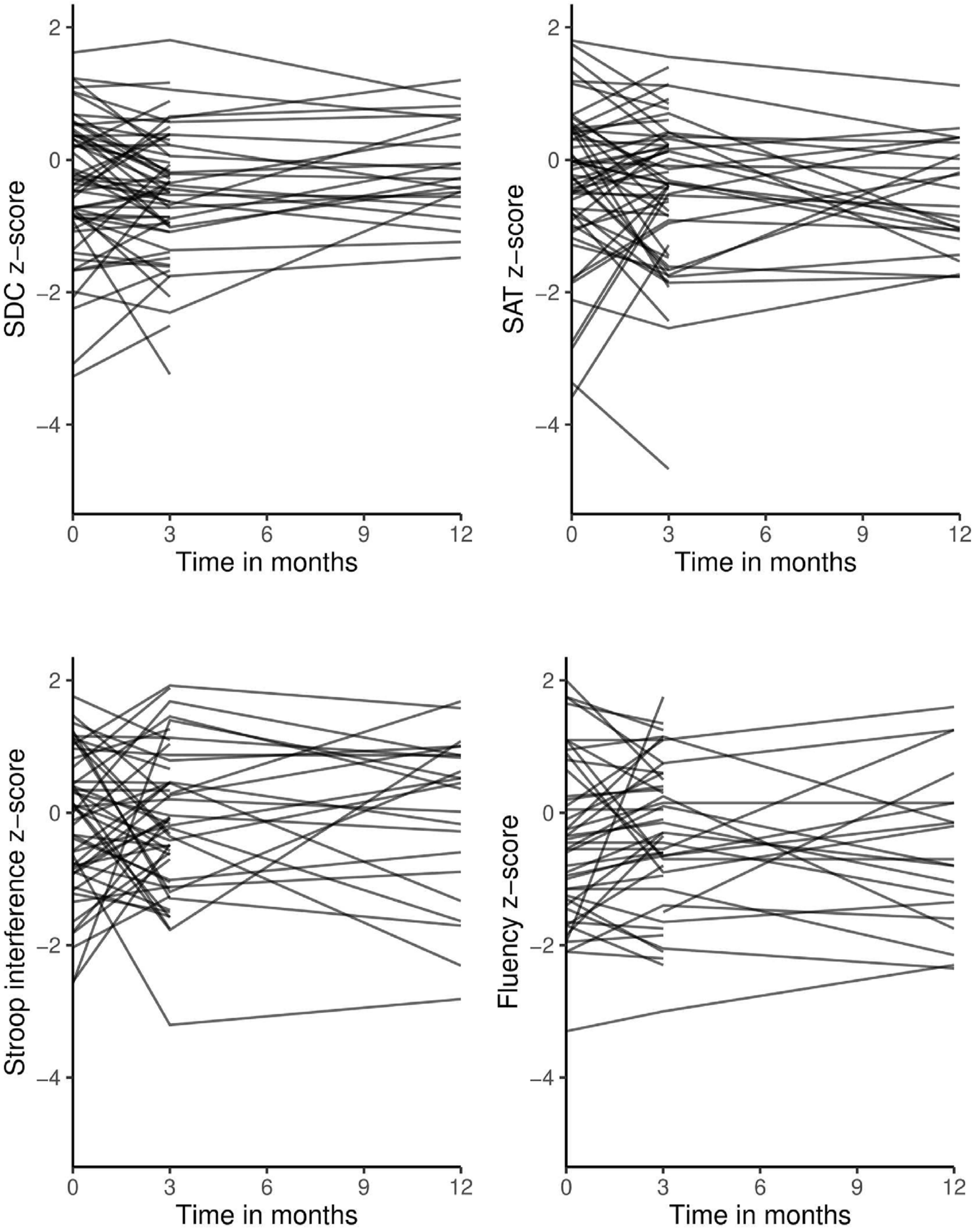

Fig. 1 – Trajectories of performances (Z-scores, Y-axis) on each test over time (in months, X-axis), with lines representing individuals.

with 10–15% being impaired ($z < -1.65$), which are largely comparable to the 14%–22% level of impairment ($z < -1.5$) for the postsurgical prevalences found in our study. In conclusion, these consistent findings demonstrate that (modest) dysfunction in LGG patients remains at least on the short term after surgery.

4.3. *The frontal aslant tract and presurgical and postsurgical EF*

Our findings mostly support previous work demonstrating that brain tumors that involve the right FAT are related to poorer presurgical EF, whereas this does not account for the left FAT (Burkhardt, Kinoshita, & Herbet, 2021; Dick et al., 2019; Landers et al., 2020). We previously demonstrated that spatial proximity of the tumor to and lower structural integrity of the right FAT were related to worse presurgical performance on the shifting attention and letter fluency test but not to non-EF-test performances in LGG and HGG patients (Landers et al., 2020). The current finding, that right FAT tumor overlap was related to worse cognitive flexibility, supports the presumption that the right FAT plays an important role in the fronto-parietal network, responsible for top-down executive control processes that are needed to shift attention (i.e., cognitive

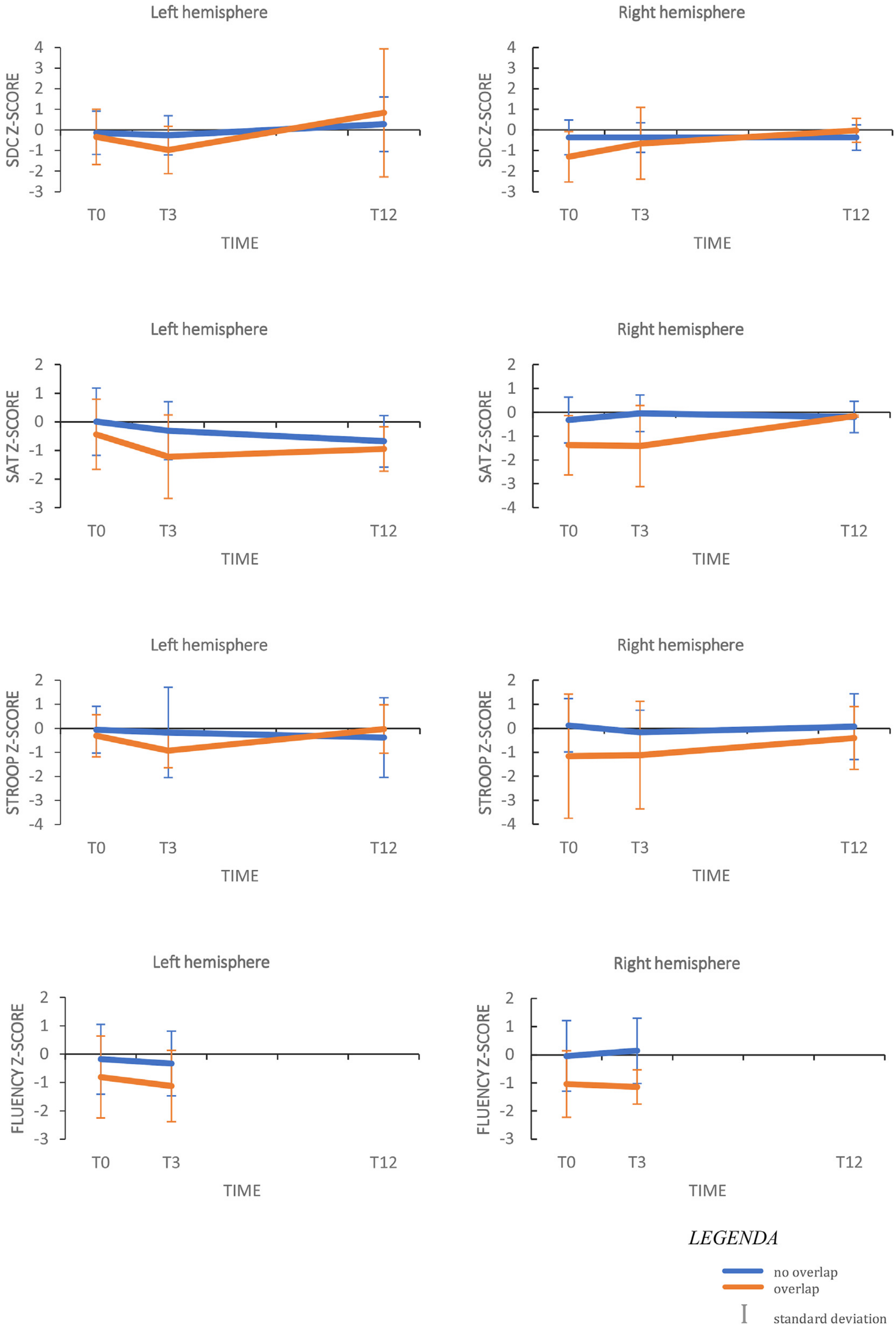

Fig. 2 – Mean performances at each time point for patients with (orange) and LEGENDA without (blue) tumor overlap with the FAT core per hemisphere. Time is indicated on the x-axis and mean z-scores on the y-axis.

flexibility, see previous work for detailed explanation (Landers et al., 2020)). Notably we did not find presurgical FAT integrity (as measured with MD) to be related to presurgical EF performance. Our previous sample also included HGGs which potentially either have a more devastating effect on white matter tracts and/or cause (more) edema which both may have a strong influence on the structural integrity measures (Alexander et al., 2007; Sternberg, Lipton, & Burns, 2014). This might explain why we did not find any significant effects for MD as it might not be sensitive enough to detect differences in LGG patients.

In the current study, performance for presurgical letter fluency, which relies partly on similar top-down networks as needed for shifting attention (Landers et al., 2020), was not significantly lower when the tumor overlapped with the right FAT. We think that this is potentially caused by power related issues. The letter fluency test was the final test in the assessment protocol, and due to time restrictions on the assessment day (e.g., other clinical appointments) the first test to be left out, thus leading to a smaller sample. As previously mentioned, this did not lead to attrition bias as the group with presurgical and 12 months postsurgical assessment versus no 12 months postsurgical follow up assessment did not differ significantly on patient characteristics (apart from sex) nor on baseline level of cognitive function.

With regard to the postsurgical course, patients with right FAT core overlap (compared to no overlap) performed worse on average on cognitive flexibility across the timepoints. This seems to be predominantly attributed to the presurgical and 3-months postsurgical timepoints. Patients' mean cognitive flexibility 1-year postsurgery was still significantly lower than healthy controls' performance. We should note that the results from the 3–12 months postsurgical interval can only be interpreted with caution given the small sample size 12 months postsurgery. Our findings regarding the right FAT cannot be compared with the findings from the previously mentioned network-behavior mapping study (Cochereau et al., 2020), Cochereau et al., 2020 as their tractwise conclusions only concern the left hemisphere. For left-hemispheric tumors, the authors observed significant negative correlations between FAT damage (residual tumor infiltration volume) and postsurgical performance on inhibition and phonemic fluency. In our study, the only effect we observed for left FAT integrity was its relationship to improvements between the 3–12 months postsurgical interval on inhibition (Stroop interference measure). We do note that our study used a more direct method of tractography to assess presurgical structural disconnection (i.e., patient-specific tractography instead of atlas-based tractography) that more accurately assesses the morphological and pathological variations of subcortical tracts in vicinity of brain tumors and may therefore be a more sensitive method to detect true anatomico-functional relationships (Silvestri et al., 2022).

In our study, we have taken MD as a proxy for the microstructural integrity of the fiber tracts. It appears that measures of integrity of the tract and overlap with a tract have differential predictive values for cognition in LGG patients. Right FAT integrity was not related to any of the presurgical EF performances, but was related to postsurgical cognitive flexibility performance, whereas right FAT core overlap was related to both presurgical performance and postsurgical performance. One explanation for the lack of predictive value of structural integrity measures for presurgical EF could be that some (but not all) of the tracts that run in the periphery of a LGG are still functional, whereas their integrity measures have already been affected due to the diseased tissue. Very few studies investigated a one-to-one relation between integrity values of glioma-infiltrated pathways and their functionality (Kinoshita, Nakada, Okita, Hamada, & Hayashi, 2014). It is, however, a well-known finding from brain mapping studies and clinical experience in awake brain surgery that glioma-infiltrated white matter pathways can still be part of a normal functioning brain network (Duffau, 2005; Teunissen, Verheul, & Rutten, 2017). Our findings demonstrate that for the FAT specifically, the more the FAT is affected (in terms of microstructural integrity) prior to surgery, the worse the patients will perform in the postoperative course. This could perhaps also be explained in terms of distance, given that the worse the structural integrity is, the more likely that the FAT lies closely to or even overlaps with the tumor, and the more likely there is a surgically-related disruption of the FAT, in turn leading to postsurgical disturbances of cognitive function.

4.4. *Limitations and recommendations for future research*

An important limitation of this study concerns power-related statistical issues for the 1-year follow-up, mainly for the fluency tests. Although there was substantial drop-out, the 1-year postsurgical sample did not differ significantly from the group without 1-year postsurgical assessment on patient characteristics (except for sex) and baseline EF test performance. Therefore, we conclude that our long-term findings were not biased to a different patient sample, but given the small sample size still should be interpreted with caution.

Tractography studies can provide valuable information to learn more about the correlation between tract and function. However, a subcortical tract is clearly part of one or more networks that together underlie cognitive functions. As we research tracts in relation to cognitive function from a neurosurgical perspective, we should be cautious to attribute (changes in) a cognitive function solely to a single tract, while most likely more tracts within or between networks are important as well. For example, besides the FAT, the superior longitudinal fasciculi are also part of the frontoparietal network and potentially involved in EFs (Nakajima, Kinoshita, Shinohara, & Nakada, 2019). Still, we were able to demonstrate involvement in particular EFs for the right FAT that was at least independent of the major pathways of the superior longitudinal system (SLF II and III).

We recognize methodological considerations regarding our tractography method and its corresponding measures. A well-known problem with tractography in brain tumor patients is that infiltrated white matter pathways may not be trackable (i.e., false-negatives). However, in the current study we chose to use CSD, which is known to generate more accurate tractography results in tumor regions and regions of crossing fibers when compared to the generally used DTI method (Farquharson et al., 2013). In the current study the FAT was readily identifiable in all patients., Even though the CSD-method has improved tractography substantially by the ability to better resolve regions of crossing fibers, accurate tractography near tumor tissue is still challenging as is research validating measures to reflect a tract's structural integrity and linking its corresponding measures to functional outcomes (Jones, Knösche, & Turner, 2013). Moreover, in the current study we chose to use MD as a measure of structural integrity because we learned from previous studies that FA, but not MD, is influenced by both compression and infiltration, whereby compression was shown to often increase, instead of to lower FA (Jellison et al., 2004; Landers et al., 2020). These inconsistencies are generally not observed and MD was therefore concluded to be a more accurate measure to specifically represent the structural integrity of a subcortical pathway in brain tumor patients, than FA. Other measures, such as the number of streamlines, were not considered because previous research has demonstrated that the streamline count does not necessarily reflect the quality of a tract and is modulated by tract length, curvature and branching which results in even more challenging problems for interpretation of results (Jones et al., 2013).

This exploratory study provided us with valuable information regarding the course of EF in LGG patients that undergo surgery and indicates that the FAT plays an important role in this. Given the lack of postsurgical DWI imaging we have no information about the postsurgical condition of the FAT. We acknowledge that in case of deep lying tumors, the surgical technique and approach (e.g., transopercular approach) may have led to FAT damage. As postsurgical performances of patients with deeply located tumors that were transcortically approached (6 cases in total) were either higher than in the other cases and/or were higher than their presurgical scores, the overall results are likely not mistakenly confounded by surgical factors that were not taken into account. Recommendations for future research would be to also include postsurgical tractography to quantify the FAT damage postsurgically, besides presurgical tractography and pre- and postsurgical neuropsychological assessment up to at least one year after surgery to investigate if postsurgical disconnection of the FAT causes permanent EF deficits. Moreover, we recommend neurosurgical practice to administer these neuropsychological and imaging assessments in every LGG patient and collaborate in multicenter studies to increase the number of patients to study. This would allow us to study the FAT (and its interactions with other subcortical tracts such as SLF II, III, frontostriatal tract and cingulum) in relation with the different EFs with higher statistical power and help us to determine if this pathway is truly indispensable for long-term normal EF and therefore relevant for neurosurgical practice.

5. Conclusion

The current study emphasizes that LGG patients perform worse than healthy controls on the EF tests, which normalizes 1-year postsurgery except for cognitive flexibility. Importantly, in patients with right hemispheric tumors, tumor involvement of the FAT was associated with worse pre- and 3-months postsurgical performance, specifically concerning cognitive flexibility. The value of pre- and postsurgical patient-specific tractography for the prediction of long-term EF outcomes should be further explored.

Ethics approval

The local ethics committee (METC Brabant, The Netherlands) gave a positive advice for this study.

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Author's contributions

Author contributions included conception and study design (MJL, EB), data collection and analyses (MJL, EB), interpretation of results (MJL, EB, KG, WDB, GJR), writing first draft of manuscript (MJL), revising draft manuscript (MJL, EB, KG, WDB, GJR) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (all authors).

Consent to participate

Informed consent was obtained from all patients.

Consent for publication

Informed consent was obtained from all patients.

Availability of data and material

The data is stored in an institutional repository and not publicly available due to hospital legislation and medical ethical objections. Metadata is available upon request if the ethical committee Brabant (METC Brabant) approves and if the data sharing agreement is undersigned by both a demanding and providing party. This can be requested via the corresponding author.

Code availability

Available upon request through corresponding author.

Declaration of competing interest

None declared.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2023.05.019.

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