Supplementary Materials

The longitudinal relation between executive functioning and multilayer network topology in glioma patients

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Methods

Patients

Part of this data has been reported on previously (Belgers et al., 2020; Carbo et al., 2017; Derks et al., 2018, 2019, 2021; Douw et al., 2008; van Dellen et al., 2012a, 2012b).

Because we applied the WHO tumor classification of 2021 (Louis et al., 2021) to a historical sample (diagnosed between 2010-2019), we re-interpreted the classification for some patients. We reassigned oligoastrocytomas that were IDH-mutant, 1p/19q-codeleted to oligodendrogliomas and IDH-mutant non-codeleted oligoastrocytomas to astrocytomas. If the IDH status or 1p/19q codeletion was not tested (n = 11), the molecular subtype was deduced from the clinical course (i.e. (progression free) survival) and histology. If available, we verified our classification based on their newest pathology rapport in case of a re-resection after T2.

Neuropsychological assessment

As this is the first study to relate EF to multilayer FPN integration in glioma, multiple domains of executive functioning were assessed by three different tests. The relation with multilayer FPN integration was analyzed for each test separately since we may find test-specific outcomes, as was the case for the shifting EF domain and FPN connectivity in a study in healthy subjects (Reineberg et al., 2018).

The goal of the Categoric Word Fluency Test (WFT (Mulder et al., 2006)) is for the participant to list, within 60 seconds, as many words as they can in a particular category. In the present study, we used the category ‘animals’. This semantic fluency test is widely used to assess updating aspects of executive functioning as well as working memory, inhibition and strategy (Henry & Crawford, 2004; Shao et al., 2014), although it also depends on a language component (Whiteside et al., 2016; Zigiotto et al., 2022).

The Concept Shifting Test (CST (Van der Elst et al., 2006)), an improved version of the Trail Making Test (TMT), comprises 16 small circles all of which contain a digit (part A), a letter (part B), or a letter or a digit (part C). The small circles are grouped into a larger circle. The goal of the test is for the participant to cross out the circles as fast as possible without making errors, in ascending (part A), alphabetical (part B), or alternating order (digit-letter; part C). Condition A and B require visual recognition and scanning, attention, long-term and working memory (to monitor the progress of the sequence). In condition C, the participant also needs to switch between the two sets (digits and letters) and must inhibit the response to continue within the same set (Van der Elst et al., 2006). To correct for motor speed, the participant additionally performs a dummy condition thrice, with empty circles.

The Stroop Color-Word Test (SCWT (Hammes, 1978)) consists of three cards that have to be read aloud by the participant. The first card contains the names of four colors (red, green, yellow, and blue) printed in black ink. The second card contains rectangles printed in these same colors. The third card contains the names of the four colors from the first card, but printed in an inconsistent color ink (e.g., the word 'blue' is printed in red ink) and the participant is told to ignore the word and list the color of the ink. All cards have to be read as fast as possible, without making mistakes.

Scoring

For the WFT, the total number of correct animals listed in 1 minute was used as the final score for the WFT. For the CST, the average time to complete the motor condition was subtracted from the time in condition A, B and C. The final outcome measure was the time in seconds on condition C, minus the average of condition A + B (after correcting for motor speed), to isolate the concept-shifting performance. Moreover, higher pre and postsurgical percentages of EF impairment have been reported for the TMT B-A score (the subtracted condition C score's equivalent) than for the TMT_B score in a study including 157 glioma patients (Lemaitre et al., 2021). For the SCWT, the interference score was calculated by subtracting the time in seconds of card 2 from the time on card 3, to isolate inhibition performance.

Raw scores for each subtest were then adjusted for sex, age, and education (classified according to the Dutch Verhage system (Verhage, 1964), which ranges from level 1 [less than six years of primary education] to level 7 [university degree]) by transforming them into Z-scores relative to population norms (Schmand et al., 2012; Van der Elst et al., 2006), yielding three EF Z-scores per patient. Since Z-score calculation may lead to uninterpretable outliers, especially when a patient is particularly slow, negative Z-scores were capped at Z = -3.0.

Magnetoencephalography

To aid visual inspection of the data, the cross-validation Signal Space Separation (SSS; (van Klink et al., 2017)) was applied, after which we (SDK, LD, LCB, MLMZ) removed at most 12 noisy channels. We used the temporal extension of SSS (Taulu & Simola, 2006) in MaxFilter (version 2.2.15) for further noise removal. Patients' head position was recorded continuously with head position coils, which were digitized together with the scalp shape using a 3D digitizer (Fastrak, Polhemus; Colchester, VT, USA). Anatomical MRI (GE Discovery 3T magnet, Milwaukee, USA; voxel size 1mm x 0.5mm x 0.5mm) was used for co-registration with the digitized scalp surface using a surface matching approach (estimated accuracy 4 mm (Whalen et al., 2008)). A single best-fitting sphere was fitted to the scalp outline and used as a volume-conductor model for the beamformer approach described below. We normalized the co-registered MRI to a template and, following inverse-normalization, labeled the voxels in the co-registered MRI according to the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Coregistration accuracy of the overlays of the atlas with native brains were visually inspected in each patient, excluding the presence of large artifacts related to altered anatomy and mass effects. Broadband time series of neuronal activity were then reconstructed for each region's centroid (Hillebrand et al., 2016) using a scalar beamformer approach (Hillebrand et al., 2012). The normalized (Cheyne et al., 2007) beamformer weights were based on the lead fields for dipolar sources, broadband (0.5-48Hz) data covariance, and unity noise covariance (for the estimation of the optimum orientation (Sekihara et al., 2004)). Anatomical MRI (T1-

weighted images with and without contrast injection and T2 or FLAIR) was used to segment the tumor for each individual patient, which was then coregistered to the Montreal Neurological Institute (MNI) template brain to create a lesion map (Supplementary Figure 1).

Supplementary Table 1. Regions of the frontoparietal network within the atlas

Regions of the frontoparietal network	X	Y	Z
Inferior frontal gyrus, orbital part, L	-35.98	30.71	-12.11
Inferior frontal gyrus, orbital part, R	41.22	32.23	-11.91
Superior frontal gyrus, L	-18.45	34.81	42.20
Superior frontal gyrus, R	21.90	31.12	43.82
Middle frontal gyrus, L	-33.43	32.73	35.46
Middle frontal gyrus, R	37.59	33.06	34.04
Superior parietal gyrus, L	-23.45	-59.56	58.96
Superior parietal gyrus, R	26.11	-59.18	62.06
Inferior parietal gyrus, L	-42.80	-45.82	46.74
Inferior parietal gyrus, R	46.46	-46.29	49.54
Middle cingulate gyrus, L	-5.48	-14.92	41.57
Middle cingulate gyrus, R	8.02	-8.83	39.79

Legend. L = left hemisphere, R = right hemisphere

Supplementary Table 2. Case summary of individual executive functioning corrected Z-scores at T1, T2 and over time (Δ).

Patients with (n = 7) and without (n = 30) progression before T2 are shown.

	T1 CST	T2 CST	Δ CST	T1 WFT	T2 WFT	Δ WFT	T1 SCWT	T2 SCWT	Δ SCWT
Progression									
1	-1.20	-1.20	0.00	-0.80	-1.30	-0.50	0.40	-0.80	-1.20
2	0.63	-1.74	-2.37	-1.00	-1.30	-0.30	0.90	-0.80	-1.70
3	0.37	0.30	-0.07	1.30	0.80	-0.50	-0.30	0.00	0.30
4	-0.11	-0.09	0.02	0.80	1.00	0.20	-0.50	1.10	1.60
5	-0.60	-0.24	0.36	-0.40	-1.90	-1.50	-0.40	2.00	2.40
6	-0.17	-1.80	-1.63	-0.80	-2.70	-1.90	-0.80	-	-
7	-1.75	-1.81	-0.06	-1.70	-2.30	-0.60	-0.80	-	-
N	7	7	7	7	7	7	7	5	5
Mean	-0.40	-0.94	-0.54	-0.37	-1.10	-0.73	-0.21	0.30	0.28
Min.	-1.75	-1.81	-2.37	-1.70	-2.70	-1.90	-0.80	-0.80	-1.70
Max.	0.63	0.30	0.36	1.30	1.00	0.20	0.90	2.00	2.40
SD	0.84	0.91	1.03	1.06	1.46	0.72	0.64	1.23	1.76
No progression									
1	-0.30	0.68	0.99	1.50	-1.00	-2.50	1.80	-2.40	-4.20
2	-1.78	0.64	2.42	-2.50	-2.90	-0.40	0.30	-1.20	-1.50
3	-	0.01	-	-0.60	-0.40	0.20	0.40	-0.80	-1.20
4	-0.83	0.69	1.52	-0.80	0.60	1.40	-0.50	-0.40	0.10
5	-1.76	-1.80	-0.04	-0.60	-0.80	-0.20	0.50	-0.30	-0.80
6	1.01	0.66	-0.35	0.40	-1.30	-1.70	1.10	-0.30	-1.40
7	-0.78	1.50	2.28	0.20	-1.70	-1.90	1.20	-0.30	-1.50
8	-1.60	-1.28	0.32	0.40	-0.40	-0.80	0.90	-0.10	-1.00
9	1.36	0.80	-0.56	1.00	0.00	-1.00	1.00	0.00	-1.00
10	1.35	1.35	0.00	-0.60	-1.00	-0.40	0.30	0.10	-0.20
11	-1.75	-1.82	-0.07	-0.40	0.60	1.00	0.40	0.20	-0.20
12	-0.20	-0.96	-0.75	-1.00	-1.00	0.00	0.70	0.20	-0.50
13	-0.08	-0.88	-0.80	3.10	0.40	-2.70	0.10	0.30	0.20
14	-1.74	-0.92	0.82	-1.00	-1.00	0.00	0.30	0.40	0.10

15	0.38	1.06	0.68	1.90	1.10	-0.80	1.10	0.40	-0.70
16	0.55	1.43	0.87	0.00	-1.00	-1.00	1.20	0.40	-0.80
17	-	0.30	-	0.40	-0.40	-0.80	1.30	0.40	-0.90
18	0.80	1.49	0.69	1.10	1.10	0.00	0.30	0.60	0.30
19	0.40	-0.31	-0.71	0.60	-1.10	-1.70	0.50	0.60	0.10
20	0.19	0.69	0.50	1.90	-0.20	-2.10	1.10	0.80	-0.30
21	-0.98	-1.75	-0.77	-0.60	-1.30	-0.70	1.30	0.90	-0.40
22	-0.12	-0.54	-0.42	-0.60	-0.80	-0.20	2.10	0.90	-1.20
23	-0.42	0.59	1.01	-1.30	0.40	1.70	0.90	1.10	0.20
24	-0.08	-0.93	-0.85	-1.00	0.60	1.60	1.40	1.10	-0.30
25	-1.40	-0.21	1.19	0.80	-	-	1.00	1.20	0.20
26	-1.08	0.15	1.23	1.10	0.40	-0.70	0.60	1.30	0.70
27	-1.75	-0.46	1.28	0.80	-1.00	-1.80	1.00	1.30	0.30
28	0.99	-1.21	-2.20	-0.20	0.00	0.20	0.80	1.70	0.90
29	-1.16	-0.80	0.37	1.60	1.50	-0.10	1.60	2.20	0.60
30	-1.77	-1.74	0.03	-0.40	-1.50	-1.10	1.00	-	-
N	28	30	28	30	29	29	30	29	29
Mean	-0.45	-0.12	0.31	0.17	-0.42	-0.57	0.86	0.36	-0.50
Min.	-1.78	-1.82	-2.20	-2.50	-2.90	-2.70	-0.50	-2.40	-4.20
Max.	1.36	1.50	2.42	3.10	1.50	1.70	2.10	2.20	0.90
SD	1.05	1.06	1.03	1.18	0.98	1.14	0.54	0.91	0.98

CST = Concept Shifting Test, WFT = Word Fluency Test, SCWT = Stroop Color-Word Test, SD = standard deviation.

Supplementary Table 3. Overview of longitudinal cognitive Z-score changes of (-)1 or more.

	All patients		Patients without progression	
	1 ≥ Δ Z-score ↑	-1 ≤ Δ Z-score ↓	1 ≥ Δ Z-score ↑	-1 ≤ Δ Z-score ↓
Fluency n (%)	4 (11.1%)	12 (33.3%)	4 (13.8%)	10 (34.5%)
Set shifting n (%)	7 (20.0%)	3 (8.6%)	7 (25.0%)	1 (3.6%)
Inhibition n (%)	2 (5.9%)	10 (29.4%)	0 (0%)	8 (27.6%)

Supplementary Table 4. Non-significant results concerning multilayer integration

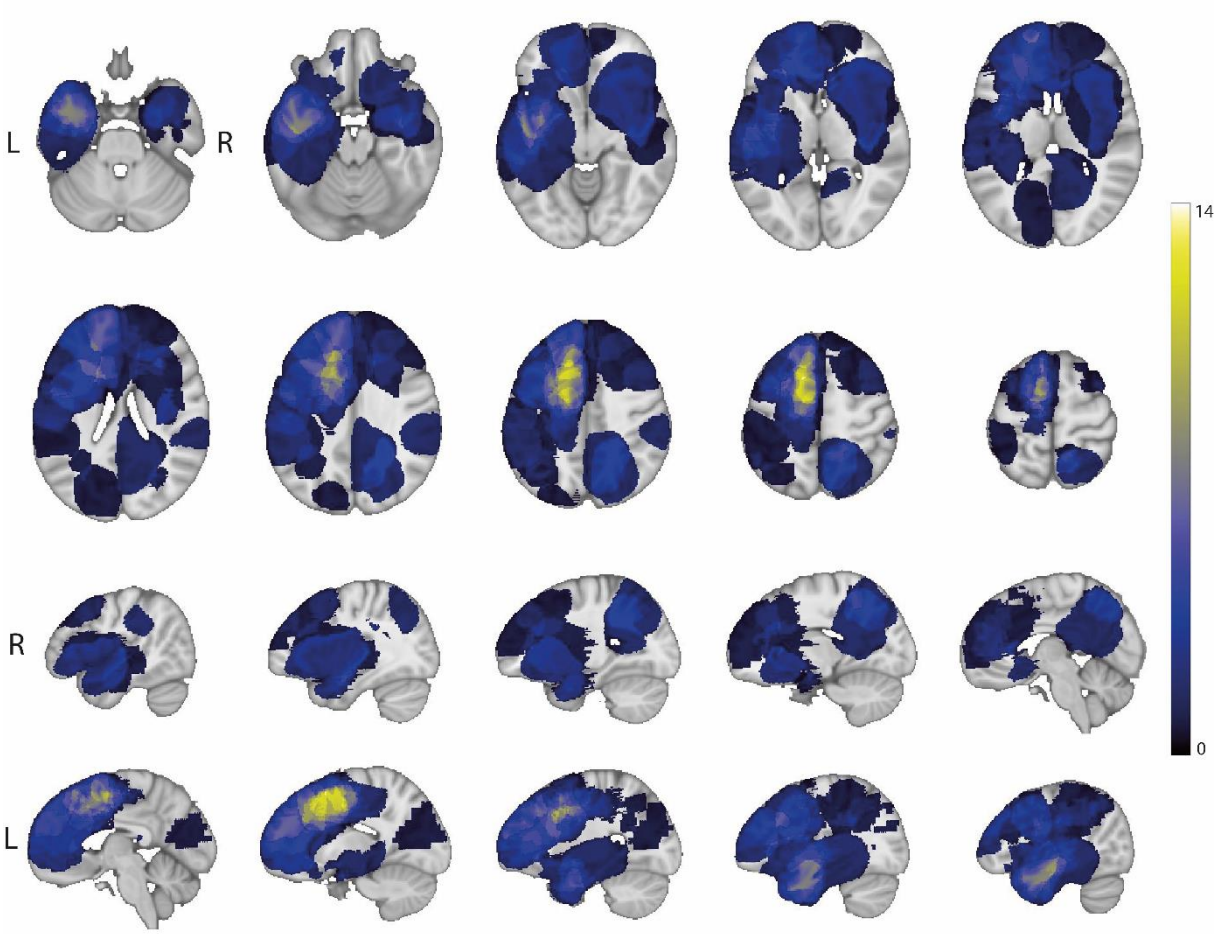
Dependent	adj. R^2	F (df)	*p*-value	Included predictors	B (stand.)	*p*-value	Excluded variables	*p*-value
T1 Word fluency	0.135	3.73 (2,33)	0.035	IDH-wildtype (ref = IDH-mutant, 1p/19q-codeleted)	-0.430	0.015	T1 multilayer EC	0.451
				IDH-mutant, non-codeleted	-0.305	0.079	Non-frontal tumor (ref = frontal)	0.126
T1 Inhibition	0.060	3.25 (1,34)	0.080	IDH-wildtype	-0.295	0.080	Non-frontal tumor	0.709
							IDH-mutant, non-codeleted	0.575
							T1 multilayer EC	0.533
Δ Word fluency	0.396	9.84 (2,25)	<0.001*	IDH-wildtype	0.482	0.005	Δ multilayer EC	0.827
				IDH-mutant, non-codeleted	0.626	0.001	RT and XT	0.519
Δ Inhibition	-0.013	0.652 (1,27)	0.426	RT (ref = no treatment)	-0.154	0.426	Δ multilayer EC	0.885
							RT and XT	0.645
Δ Word fluency	0.617	15.5 (3,24)	<0.001*	T1 Word fluency	-0.498	0.001	T1 multilayer EC	0.743
				IDH-wildtype	0.327	0.020	RT	0.946
				IDH-mutant, non-codeleted	0.491	0.001	RT and XT	0.195
Δ Inhibition	0.197	4.44 (2,26)	0.022	T1 Inhibition	-0.452	0.014	T1 multilayer EC	0.812

				Age	-0.309	0.084	RT and XT	0.599
							RT	0.167
Δ Set shifting	0.223	4.88 (2,25)	0.016*	T1 Set shifting	-0.340	0.069	T1 multilayer EC	0.766
				Active treatment at T2 (ref	0.341	0.091	Interval resection - NPA	0.660
				= no treatment)				

*significant p-value (<.0167) after Bonferroni correction. EC = eigenvector centrality, Δ = change score (T2-T1), RT = radiotherapy, XT = chemotherapy, NPA = neuropsychological assessment. In case of dummy-coded variables, the reference category (ref) is indicated at first mention only.

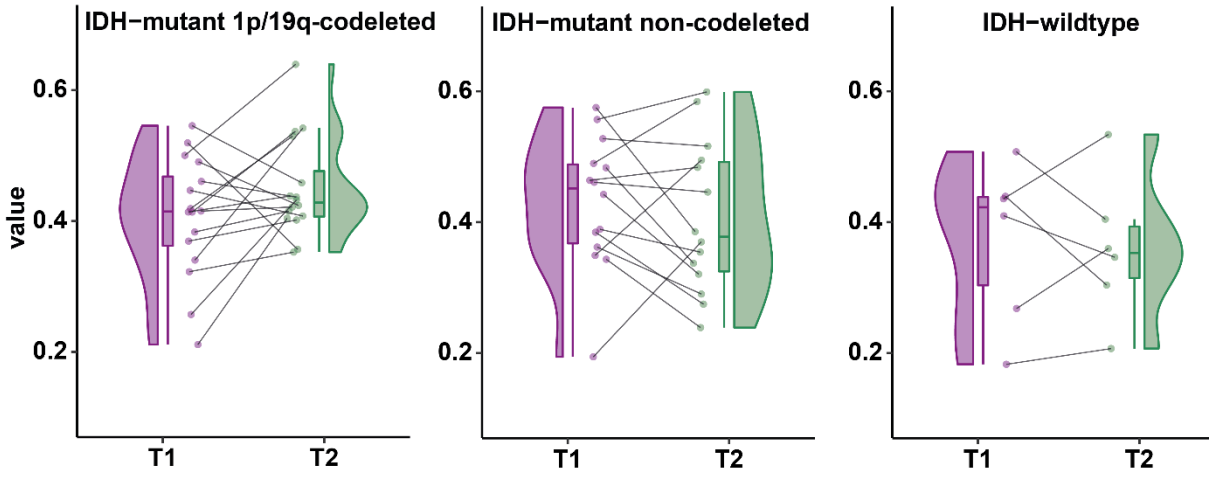
Supplementary Table 5. Selection of relevant literature on cognition in glioma before and after resective surgery

	References	Type
Presurgical cognitive functioning	(Caramanna et al., 2021)	Research article
	(van Kessel et al., 2017)	Systematic review
	(Wefel et al., 2016)	Research article
	(Zhang et al., 2020)	Research article
Pre- and postsurgical cognitive functioning	(Cochereau et al., 2020)	Research article
	(Klein et al., 2004)	Research article
	(Klein et al., 2012)	Review
	(Lemaitre et al., 2021)	Research article
	(Ng et al., 2019)	Meta-analysis
	(Sinha et al., 2020)	Systematic review
	(Tabor et al., 2021)	Review
	(Tanzilli et al., 2022)	Research article



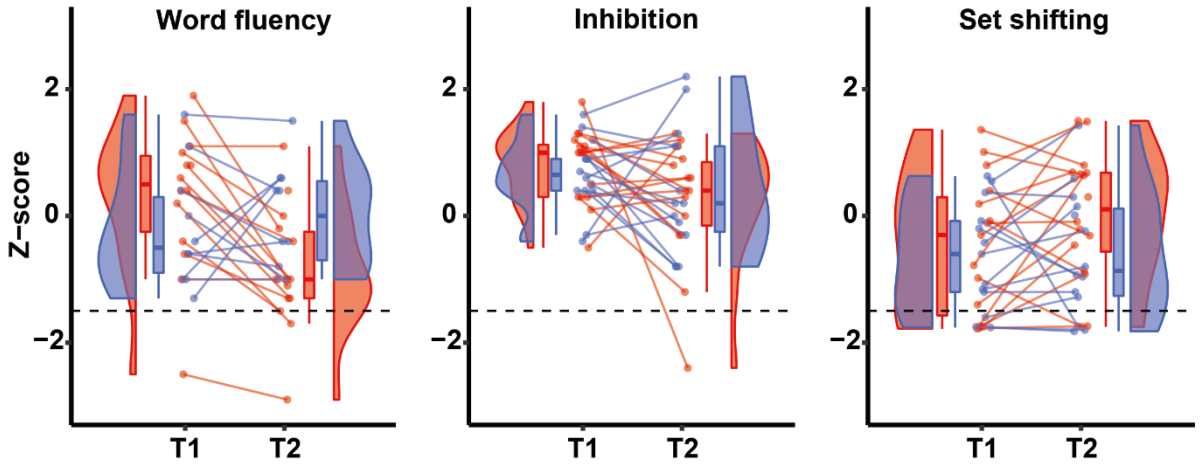
Supplementary Figure 1. Lesion map

Low tumor occurrence is indicated with blue colors and high occurrence with yellow colors (maximum is n = 14 patients). A preference for the left hemisphere is observed.



Supplementary Figure 2. Individual changes in multilayer integration per glioma subtype

Each panel shows multilayer eigenvector centrality of the frontoparietal network in patients with IDH-mutant 1p/19q-codeleted, IDH-mutant non-codeleted, and IDH-wildtype gliomas at both time points.



Supplementary Figure 3. Individual changes in executive functioning at both time points

The raincloud plots with clouds, raindrops and lines represent the IDH-mutant non-codeleted (blue) and IDH-mutant 1p/19q-codeleted (red) glioma subgroup. Scores below the dashed line at -1.5 indicate clinically relevant cognitive deficits.

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