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Significant improvement in neuropsychological functions after awake craniotomy in a patient with Oligodendroglioma: A case report

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ABSTRACT

Objective: The goal of awake craniotomy in glioma patients is sparing of cognitive function. Previous investigations suggest that patients in the postoperative state may reach their preoperative level regarding domain-based criteria. Data on significant postoperative improvement beyond the preoperative level is sparse. This article examines the prospective neuropsychological assessment of a glioma patient who underwent awake craniotomy and has shown functional improvement exceeding preoperative levels.

Methods: A 34-year-old patient with high premorbid cognitive function level who underwent awake craniotomy for left frontal oligodendroglioma was neuropsychologically assessed and took part in a fMRI-examination at 3 different time points.

Results: Preoperative examination revealed severe isolated impairment of working memory, long-term narrative memory in free recall and recognition, and alertness with intact language production and comprehension. After transient global aphasia in the postoperative state, the follow-up examination showed significant improvement in memory and attention exceeding the preoperative level.

Conclusions: Tumor location is an important factor in terms of surgical procedures. Cognitive impairment is, however, not always associated with a specific location. Mechanical pressure of the tumor might have led to the isolated consolidation deficit which fully recovered after tumor removal. Psychological disorders should be taken into account regarding prodromal symptoms of neurooncological diseases.

1. Introduction

Gross total tumor resection without functional deficit is the goal of glioma surgery. In many cases, complete resection of the tumor however results in temporary postoperative deficits, which may recover to presurgical levels over the course of several months [1]. Resolution of postsurgical oedema as well as reorganization processes are thought to be the main drivers of such functional recovery. Postoperative improvement of function beyond the preoperative level is however rare [2] and cannot be explained by the same mechanisms. Instead, lingering functional deterioration may be caused by interaction of the tumor with neighboring cortex and fiber tracts, either by direct mechanical compression, changes of the surrounding micro-environment or functional interference with nearby networks. If this interaction is largely non-destructive, removal of the tumor then abolishes the inhibitory factors, allowing for recovery not only to a preoperative but potentially to a "pre-tumoral" level. It is noteworthy, though, that age and higher education levels can play an important role in cognitive restitution [3].

Across the last few years, there is increasing interest in neuropsychological performance changes in neurooncological patients due to

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neurosurgical procedures. Most work in this area has focused on functional integrity. Preserving intact neuropsychological function is a main goal in treatment of gliomas. Data on significant postoperative improvement beyond the immediate preoperative level is, however, sparse. Studies suggest that up to 24% of patients without preoperative impairments improve their postoperative performance regarding domain-based criteria, whereas those improvements rarely reach statistical significance [2,4,5]. In this report, we present a case of functional improvement exceeding preoperative levels after surgery of low-grade glioma.

2. Case report

A 34-year-old male patient was presented to our department due to a first-time generalised seizure. Clinically, we saw a patient without apparent focal neurological deficit.. His medical history revealed panic disorder; however, at the time of tumor diagnosis, he had fully recovered from this. MRI showed a left frontal hyperintense mass on T2-weighted sequences without contrast uptake. Anatomical MRI and Diffusion Tensor Imaging (DTI)revealed a close relationship to Broca's area and the arcuate fasciculus (Fig. 1). Under anticonvulsant therapy with levetiracetam, the patient had no recurrence of seizures.

The Edinburgh-Handedness-Inventory (EHI) indicated right-handedness (LQ = 100).

The patient underwent preoperative (2 days before awake craniotomy), postoperative (10 days neuropsychology, respectively 19 days (fMRI)) and follow up (6 months after surgery) neuropsychological assessment, intensive language testing, and fMRI examination.

To identify significant changes in neuropsychological performance, critical differences were calculated for preoperative and follow-up assessment using the following equation: $D_{crit} = z^{*}SD + \sqrt{2(1 - r_{tt})}$). Each session of fMRI included different language paradigms. We only report the design and results for a general language localizer task. Protocols and task design can be found in the appendix. Activation maps for intact > degraded language during each of the three sessions are shown in Fig. 2.

2.1. Preoperative examinations

The preoperative neuropsychological examination (Table 1) showed an estimated premorbid IQ of 134 and revealed severe impairment of long-term narrative memory in free recall and recognition (Logical Memory II). However, memory span and working memory (digit span), as well as free recall and recognition of a word list (California Verbal Learning Test – short version), were intact. The patient performed above average for visuoconstruction and visual memory tasks (Rey Complex Figure Test) and showed no deficits in processing speed (Trail Making Test-A), cognitive flexibility (Trail Making Test-B), perceptual speed, and visual scanning (Symbol Digits Modalities Test) and impulsivity

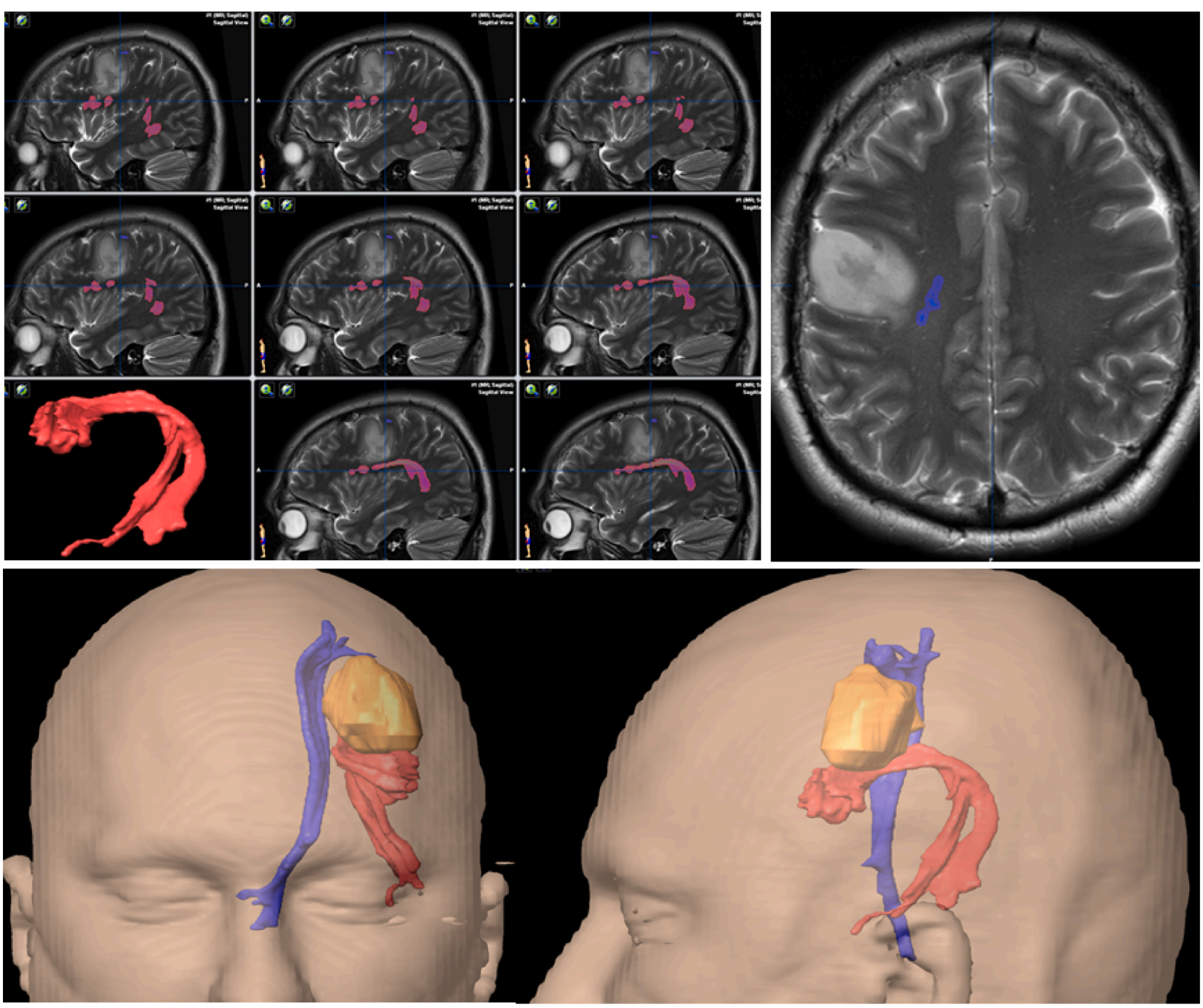

Fig. 1. Preoperative Imaging. 3D-Reconstruction is shown in the lower half (Tumor: Yellow; arcuate fasciculus: Red; pyramidal tract: Blue). In the upper half, T2-imaging is shown with sagittal slices (left) and axial slices (right); the tracts have the same respective clour as in the below reconstructions. The axial slice is formatted according to radiological convention ("left is right").

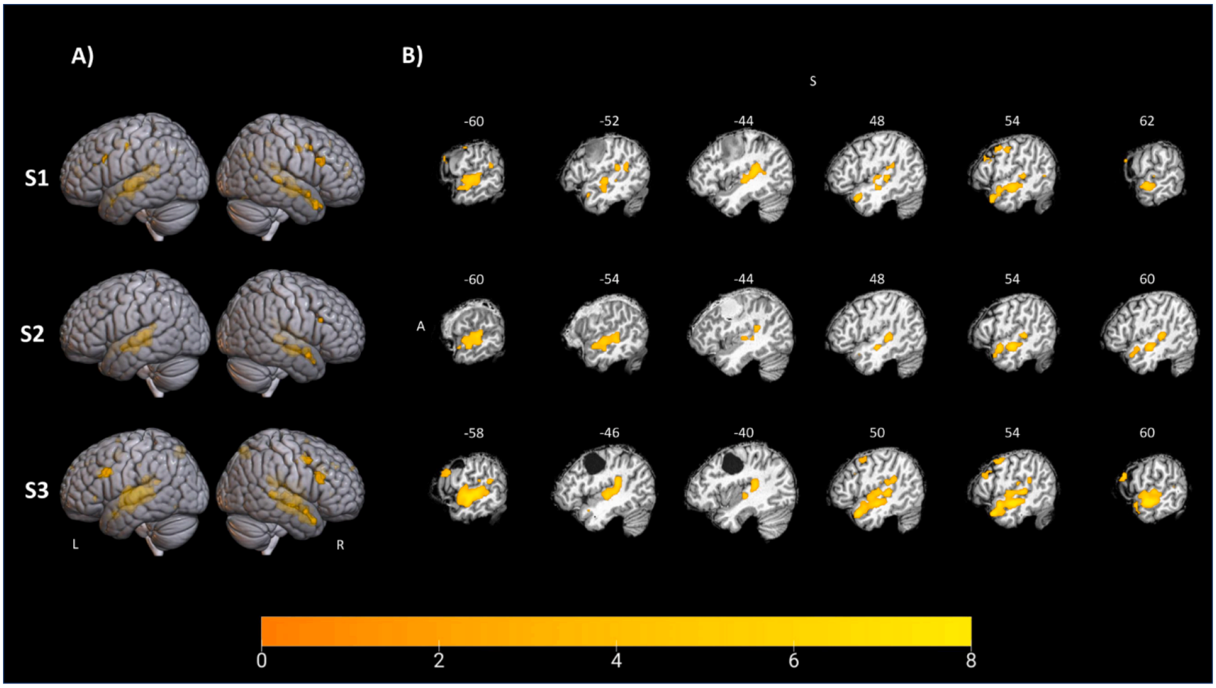

Fig. 2. Activation maps of the Localizer Task for the contrast intact > degraded language. A) Whole brain activation maps on the standardized mni125 brain template; B) Selected slices of the patient's brain (normalized to MNI standard space; sagittal view) which show activation clusters. P value < 0.001 uncorrected. Abbreviations: S1: Session 1 (preoperative); S2: Session 2 (19 days postoperatively); S3: Session3 (6 months postoperatively). L: Left hemishere; R: Right hemisphere; A: Anterior; S: Superior.

(Testbatterie zur Aufmerksamkeitsprüfung Version 2.3.1). The patient showed below-average response speed for tonic and phasic alertness but performed above-average for the subset of visual stimuli in a task for divided attention. The results are consistent with an isolated deficit in consolidation for verbal material most likely due to impaired auditory attention processing.

Additionally, the patient underwent an extensive preoperative language assessment (Table 1). In the Aachener Aphasia Test (AAT), he achieved the best possible scores in all conducted subtests. However, the patient showed reduced verbal fluency, as measured by the "Regensburger Wortflüssigkeits-Test" (RWT). The patient performed well in lexical tasks" (LEMO). In the fMRI examination, the patient showed activation within a bilateral fronto-temporal network, including the inferior frontal gyrus (IFG), the anterior temporal lobe (ATL), the angular gyrus (AG) as well as superior and middle temporal regions of both hemispheres.

2.2. Surgery and further treatment

Due to the vicinity of highly eloquent structures, awake craniotomy was performed under neurophysiological monitoring. Initial language mapping by monopolar 50 Hz-stimulation confirmed the location of Brocás area in the pars opercularis as suspected by DTI. The tumor was located within in the face-representation of the precentral gyrus itself. Beginning with the first maneuvers of tumor resection, the patient developed massive deterioration of verbal fluency; spontaneous speech was severely impaired, while language comprehension seemed to be mostly unaffected. Dysarthria, which we had anticipated as a direct result from our surgical manipulation due to the tumoŕs location in the precentral gyrus, was not confirmed. The patieńs drive to speak seemed to be affected primarily. During the further course of resection, the patient showed rapidly progressing signs of fatigue, gradually impairing formal testing. Thus, parts of the tumor closest to the arcuate fascicle were resected quickly as long as testing was still feasible, and for the rest of surgery, we had to continue mainly guided by neuronavigation.

Postoperatively, the patient was initially globally aphasic, but this symptomatology improved significantly during his stay in the hospital.

Postoperative resection control by MRI revealed gross total resection. The histopathology report revealed an oligodendroglioma CNS WHO grade 2 (WHO classification of 2021). After rehab, adjuvant radiotherapy (1,8 Gy ad 54 Gy) and chemotherapy according to the PCV regimen (procarbazine, lomustine and vincristine) followed as indicated by the histopathological result and according to the decision of our interdisciplinary tumor board.

2.3. Postoperative examinations

The neuropsychological screening after surgery showed severe deficits in all cognitive domains tested (verbal memory, processing and perceptual speed, cognitive flexibility). At the time of language assessment (Table 1), the patient had already significantly recovered from his initial postoperative global aphasia. Nevertheless, dysphasic symptoms were still present in all language tests. In the postoperative fMRI session, language-related activation was overall reduced, bilateral activation was found in the superior and middle temporal gyrus and the right IFG.

A neuropsychological follow-up test of 6 months later showed statistically significant improvement for certain cognitive domains, even compared to the preoperative level. These improvements included the following areas: word list learning, working memory, long-term narrative memory in free recall, response speed for tonic and phasic alertness tasks and auditive divided attention. A descriptive improvement occurred in the lexical decision task and AAT values (Table 1). The results in the semantic-categorical fluency tasks were still below his preoperative performance. Language activation (fMRI) seemed to have normalized again. Notably, bilateral language activity was even slightly stronger than in the preoperative session. The patient reported almost no limitations in everyday life.

Table 1
Pre-, post- and follow up-test scores and z-scores in the neuropsychological assessment.

	T-scores			
test/examination	preoperative	postoperative	follow-up	D_{crit}
CVLT-K				
total score	50	20	56	5.68*
delayed recall	50	20	50	–
recognition	50	20	50	–
Wechsler Memory Scale-IV				
digit span				
forward	57	50	53	12.08
backward	40	20	53	13.00*
sequence	47	40	43	13.00
Wechsler Memory Scale-IV Logical memory				
I	20	–	50	9.99*
II	20	–	57	9.19*
recognition	30	–	66	–
TMT-A	53	20	58	–
TMT-B	55	20	53	–
SDMT	45	20	43	12.40
RCFT				
copy	50	50	50	16.63
immediate	64	47	68	13.40
delay	64	51	62	9.28
AAT				
Token test	80	57	69	–
written language	80	66	80	–
language comprehension	80	62	78	–
RWT				
formal lexical verbal fluency	40	20	40	–
formal lexical category changes	34	33	39	–
semantic-categorical verbal fluency	43	20	38	–
semantic category changes	50	30	42	–
LEMO				
lexical decision	ER: 0 (guess value: 40)	ER: 4 (guess value: 40)	ER: 2 (guess value: 40)	–
Synonym decision	Accuracy: 36/40	Accuracy: 38/40	Accuracy: 37/40	–
Alertness - tonic	38	–	50	21.81*
Alertness - phasic	37	–	49	24.40*
divided attention - auditive	45	–	52	73.17*
divided attention - visual	64	–	60	40.82
Go/NoGo	44	–	47	56.04

Abbrevations: CVLT-K: California Verbal Learning Test Kurzversion,TMT: Trail Making Test, SDMT: Symbol Digit Modalities Test, RCFT: Rey Complex Figure Test, AAT: Aachener Aphasie Test; ER: Error rate; LEMO: Lexikon modellorientiert;; RWT: Regensburger Wortflüssigkeits-Test, TAP: Testbatterie zur Aufmerksamkeitsprüfung.
* $p < 0.05$.

3. Discussion

In the presented case, we saw an improvement in performance for working memory, alertness and especially long-term narrative memory that even exceeded the preoperative level at six months after surgery. As the fMRI language localizer implied, language comprehension was not confounded with the ability to perform verbal tasks in the neuropsychological examination. While restitution is often observed in patients with traumatic brain injury through intense specific training [6], this patient reported no significant changes in behavior regarding his preoperative everyday life. The restitution of the consolidation impairment with respect to complex verbal information may have been supported by a high level of premorbid cognitive functioning or cognitive reserve as suggested by the “*Sozialformel*”.

As tumor location is not always associated with a specific cognitive impairment [7], the initial neuropsychological deficits might have been caused by mechanical pressure by the tumor. While this seemed to have no noticeable effects on language related activity in Broca’s area, it most likely affected frontal structures resulting in a consolidation deficit. Pressure on the ascending pathway of the alerting network including the hippocampus may also be a potential explanation for impairment, especially in phasic alertness. It is also possible that the tumor interfered with cortical structures of the norepinephrine pathway. This might have caused a transmission disruption in the projection to the hippocampus which then led to the consolidation impairment. Norepinephrine is also known to be associated with panic disorders, which is noteworthy, as the patiente's medical history revealed psychotherapeutical and medical treatment (Escitalopram 10 mg, 1–0-0) for panic disorder and compulsions. The first panic attack occurred in the patient‘s late twenties.

Especially compulsions develop early on in adolescence or the early twenties [8]. Psychiatric symptoms are common in patients with glioma [9]. The patient harbored a very slow-growing tumor which might have been present for years before the initial seizure. Therefore, it is possible that changes in orbitofrontal metabolism due to the tumor may have contributed to compulsive behavior as prodromal symptoms that also caused neuropsychological deficits.

A limitation of the study is that practice effects in neuropsychological assessment cannot be completely ruled out. Especially with respect to the subtests digital span, as there was no parallel version available and sequences have been the same on all time points of the assessment. However, the used subtests of TAP were shown to be resistant to practice effects in previous studies [10]. With respect to long-term narrative memory, it is rather unlikely that the scores in the follow-up assessment result from practice effects as there has only been a single presentation within the 6 months-interval. Also, there was no MRI scan from the onset of the psychiatric symptoms available. Psychiatric anamnesis was solely based on the information the patient gave us.

4. Conclusions

In this case report, we present a patient with oligodendroglioma who underwent awake craniotomy and was able to significantly surpass premorbid neuropsychological performance to an above average degree in a six-month follow-up. This implies that the removal of the tumor may have allowed a complete restitution, which resulted in significantly better performance in the follow-up examination. Future research in awake craniotomy will have to shed light on neuropsychological functions beyond speech. Mental disorders should be considered as possible prodromal symptoms of neurooncological diseases.

5. Statement of ethics

This case is part of a study conducted by the Department of Neurosurgery at University Hospital Halle.

This study protocol was reviewed and approved by the ethics committee of University Hospital Halle, approval number Reg. Nr. 2020–073.

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

CRediT authorship contribution statement

Mareike Thomas: Data curation, Formal analysis, Investigation, Software, Writing – original draft. **Maximilian Scheer:** Writing – review & editing, Investigation, Data curation, Formal analysis. **Kai Spindler:** Investigation. **Laura Nieberlein:** Writing – review & editing, Validation, Software. **Gesa Hartwigsen:** Conceptualization, Software, Formal analysis. **Alexander Gussew:** Visualization, Software, Formal analysis. **Stefan Schob:** Visualization, Software, Formal analysis. **Julian Prell:** Methodology, Project administration, Formal analysis. **Christian Strauss:** Supervision, Writing – review & editing. **Stefan Rampp:** Methodology, Project administration, Formal analysis.

Data Availability Statement

As the main study is still on-going and not published yet, data for fMRI analysis is only available per request. For neuropsychological assessments, all data generated or analysed during this study are included in this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We acknowledge the financial support within the funding programme Open Access Publishing by the German Research Foundation (DFG). G Hartwigsen was supported by the Lisener excellence program of the Max Planck Society.

Appendix

1.1. fMRI Protocols

Structural and functional MRI measurements were performed using a Siemens Skyra 3-Tesla Scanner (Siemens, Erlangen, Germany). First, a high resolution T1-weigted anatomical image was acquired with an MPRage (magnetization-prepared rapid acquisition gradient echo) sequence in sagittal orientation (voxel size = $1 \times 1 \times 1$ mm; TR = 2530 ms; TE = 2.67 ms). Then, fMRI data were collected using a gradient echoplanar (EPI) imaging sequence with blood oxygenation level dependent (BOLD) contrast for the acquisition of T2*-weighted images. The block design used the following parameters: TR/TE = 2000 ms/30 ms; flip angle 90°; distance factor = 33%; matrix: 64×64 pixel; voxel size: $3 \times 3 \times 3$ mm; field of view 192 mm. A total of 141 images consisting of 36 slices were acquired continuously in descending order during each session.

1.2. fMRI task design

To identify the patient's language network, a functional localizer paradigm was used [11]. During this task, excerpts from the story "Alice in Wonderland" were presented via headphones. Six passages were presented in intact, comprehensible German language and six passages in degraded speech as a control condition, interleaved with rest blocks [11].

1.3. Statistical analyses

The fMRI data were processed using the SPM12 toolbox (Wellcome Department of Cognitive Neurology, University College London, UK, Centre for Neuroimaging; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in Matlab (The Mathworks Inc., Natick, MA, USA) [12]. Preprocessing: Motion correction (realignment and unwarping)[13], slice timing correction, coregistration of the T1 and mean EPI images, segmentation, normalization into standard stereotactic space (Montreal Neuro- logical Institute (MNI) template), and spatial smoothing with a Gaussian kernel of 6 mm. Statistical first-level analysis of fMRI data was performed using the general linear model (GLM) in a flexible factorial design. For the localizer task, intact language and degraded language was modelled as separate regressors. A regressor representing the temporal onsets of stimulus presentation and presentation duration was convolved with the canonical hemodynamic response function (HRF) to produce the predicted hemodynamic response for each condition. Voxel-wise regression coefficients were estimated using the least squares method within SPM12, and statistical parametric maps of the t-statistic (SPM t) were generated from each condition. The significance level of the results was set to a threshold of $p < 0.05$.

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