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Clinical Article

Brain tumour surgery in the vicinity of short-term memory representation – results of neuronavigation using fMRI images

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Summary

Objective. Functional information concerning the surrounding brain is mandatory for a good clinical outcome in brain tumour surgery. The value of fMRI to detect the motorcortex and Broca's area is widely accepted. If an appropriate paradigm is used, short-term memory areas can be visualized as well. We report our first experiences with the direct integration of short-term memory fMRI into cranial neuronavigation.

Method. From January 2001 to March 2002 14 patients with an intracranial tumour were operated on using short-term memory fMRI imaging, using the ''two-back-paradigm''. Both pre- and postoperatively, the short-term memory of all patients was tested by a standardized test battery including 16 different verbal and visuo-spatial items.

Results. In all 14 patients the general level of working memory capacity was preserved after surgery. The visuo-spatial performance was kept unchanged or deteriorated slightly, the alertness slightly worsened as well, but we found an improvement in verbal test items.

Conclusion. The two-back paradigm is able to visualize verbal memory tasks in fMRI. For visuo-spatial items, a new paradigm has been designed. In contrast to deep seated brain lesions, focal cortical impairments do not lead to obvious and serious memory deficits. Therefore, the aim of gross total tumour removal has to be balanced against the aim of preservation of short-term memory fields. Nevertheless, the knowledge of the localization of cortical short-term memory fields during navigated brain tumour surgery, may lead to a longer and better quality of life.

Keywords: Functional neuronavigation; intracranial gliomas; short-term memory.

Introduction

In 1986 Roberts [18] presented the first surgical microscope with an integrated frameless stereotactic positioning system. With the increasing capacity of modern computer workstations neuronavigation became the sextant of the neurosurgeon [6]. For functional preservation of the cortical areas, monitoring techniques must be used. Unfortunately cortical SSEP or cortical stimulation can be used only in motorcortex or speech area.

The correct anatomical localization of the motorcortex and Broca's area was recently verified by electrophysiological methods [3, 7, 12, 22].

Belliveau *et al*. introduced functional MRI in 1991 [2], which offers a wide new field for the neurosurgeon. Functional images, based on the so-called BOLD effect (blood oxygen level dependent), can be integrated into neuronavigation for clinical use. In 1995 Bellemann *et al.* [1] demonstrated that with fMRI it is also possible to detect cortical short-term memory fields.

We report a prospective clinical pilot study of the direct integration of working memory fMRI images into cranial neuronavigation in patients with a frontal or precentral glioma. The aim was to assess the value of fMRI in surgery in these areas. The aim of ''gross total tumour'' was deemed superior to ''preservation of the short-term memory field''.

Methods

From January 2001 to March 2002 14 (7 female and 7 male) patients were operated on for intracerebral frontal or precentral glioma in our department, using direct integration of short-term memory fMRI images into cranial neuronavigation. In 7 patients the glioma was newly diagnosed, the other 7 patients had a recurrent tumour.

For fMRI examination a 1.5 tesla Magnetom Vision (Siemens Co., Erlangen, Germany) was used. Using turbo spin-echo sequences (TR 3072 ms, TE 99 ms, flip angle 180 degree, matrix 256×256, FOV 230 mm) 16 anatomical base slices, each 5 mm thick, were scanned.

Afterwards fMRI data were acquired using echoplanar T2*-sequences (TR 0.96 ms, TE 66 ms, flip 90 degree, matrix 128×128, FOV 230 mm). The so-called two-back-test served as paradigm for the working memory: In this, the patient is shown 2 different figures on a computer screen for 3 seconds. After a short break, another figure appears and the patient has to decide if this new figure is positioned in the same place as one of the figures presented previously.

The paradigm was transferred to the patient by videogoggles (Resonance Technology, California). Data analysis was mainly done by Kolmogorov-Smirnov-tests to detect areas with significant MRI signal increase due to the BOLD effect. Only pixels reaching significance of $p < 0.000001$ were counted as activated. In some cases additional statistical tests like cross correlation, fast Fourier transformation or Wilcoxon's test were used. Artifacts due to head movements could be levelled out by a self-developed program. fMRI images were integrated into neuronavigation by image fusion with standard gadolinium enhanced thin-sliced T1 weighted images.

The pre- and postoperative working memory status was tested by standardized items, explained in the following. The general level of the working memory capacity was determined by the mini-mental state examination and a performance test with 40 tasks to be solved within 10 minutes. The visuo-spatial short-term memory was tested by 5 items [11, 20]. We started with the modified clock-drawing-test [21], followed by the trail-making-tests [17], the block span test forward and backward [19] and the visuo-spatial memory test VSMT. In this the patient is shown 2 different Figs. on a computer screen for 3 seconds, after a short break, another figure appears and the patient had to decide if the new figure is positioned in the same place as one of the Figs. presented previously. The verbal working memory was tested by the Wechsler Memory Scale-Revised test [4] and the so-called verbal fluency test: for a given word category (f.e. animals) the patient furthermore had to name as many species as possible within 1 minute. 4 test items were used to measure the alertness of the patient [16]. First, the patient had to click a button as fast as possible if a cross had appeared on the computer screen. In the second part of the test he received a warning signal before, but the interval between the signal and the appearance of the cross was accidental. During the dual-task item the patient was offered two different stimuli simultaneously. He received optical and acoustic stimuli and had to click on a button, if the optic or acoustic stimulus was presented in a distinct manner. The Go/NoGo-test scrutinized the ability to suppress inappropriate reactions. In arbitrary sequences, the patient was presented an "x" or a "+" on the computer screen and had to click the button only in case of an "x". The capacity to solve complex combined visuo-spatial and verbal tasks was tested by the Wisconsin Card Sortening Test (WCST) and the Rule Alternation Test (or Odd man out test) [13].

The patient is shown 4 cards with 4 different symbols in 4 different numbers and colours. Afterwards a new card is presented and the patient has to decide which stack this card should be assigned. This defined sorting strategy had to be kept up subsequently.

In all 14 patients the above-mentioned tests could be performed postoperatively, in 12/14 short-term-memory fMRI was repeated during the regular tumour control MRI. Our local Ethics Committee had approved the study, the patient's consent was always obtained. Statistical analysis was performed using the t-test and the Wilcoxon test, respectively.

The aim of our prospective pilot study was as follows. Is fMRI able to detect short term memory fields? Is short-term memory capacity of the patient preserved after brain tumour surgery, if the fMRI-detected cortical representation is spared during surgery? As the value of fMRI concerning these fields was not known so far, the aim of our pilot study was to analyze this aspect. Therefore the aim of "gross total tumour removal" was deemed superior to "preservation of the short-term memory field" in the presented first 14 cases.

Results

The mean age of our patients was 38.7 ± 7.7 years, ranging from 26 to 51 years. All surgically removed tumours were classified as gliomas, the detailed histological classification is shown in Table 1. Preoperative fMRI always showed a close relationship between tumour and short-term memory representation detected by the two-back paradigm (in maximum 1.5 cm space in between them). 3 patients had to be treated by additional irradiation, 4 received chemotherapy and 3 were given a combined postoperative regime. In each of these 10 patients, the postoperative working memory test was performed after this additional treatment and the results of these patients will be discussed separately.

In April 2005, 12 patients were alive, the average follow-up period was 37.3 months. 8 patients did not

Table 1. *Histological classification of the tumours*

	WHO °II	WHO °III	WHO °IV
Astrocytoma	1	4	
Oligoastrocytoma	1	3	
Oligodendrglioma	1	1	
Glioblastoma			3

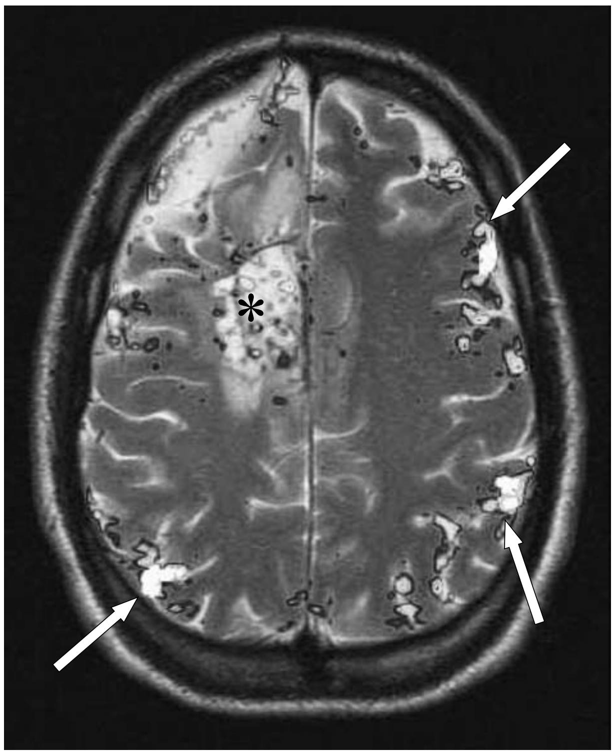
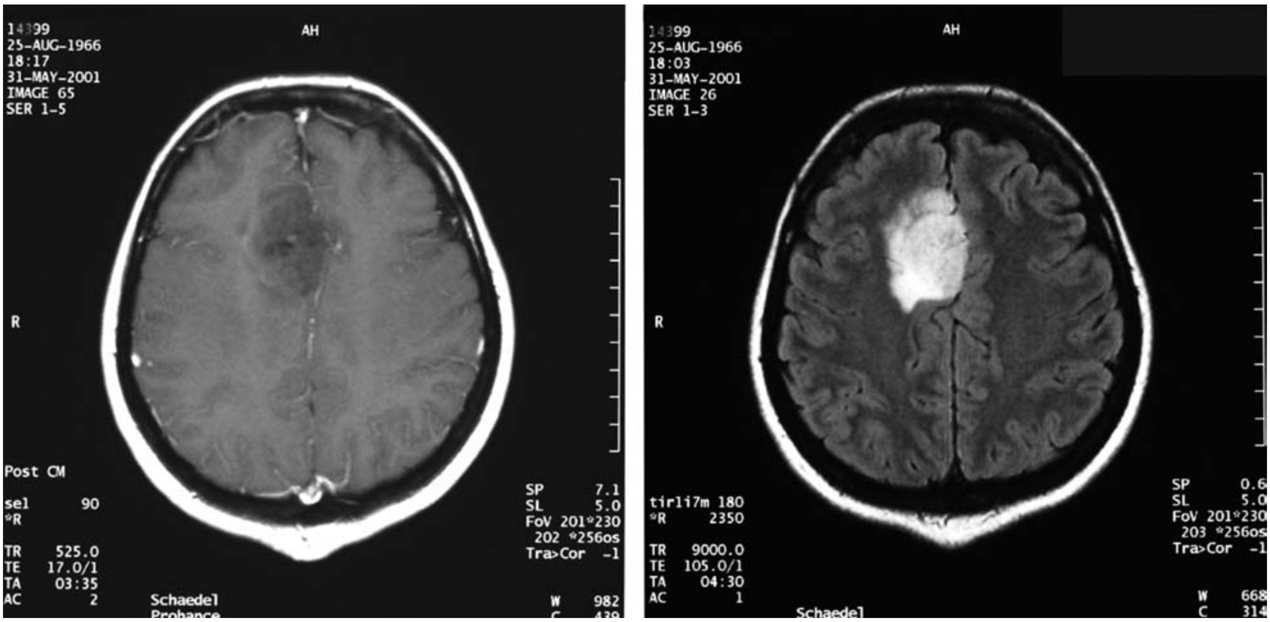


Fig. 1. fMRT basing on the two-back-paradigm: the arrows mark the activated areas, activity is missing arround the tumour (astrocytoma WHO °II, asterisk)

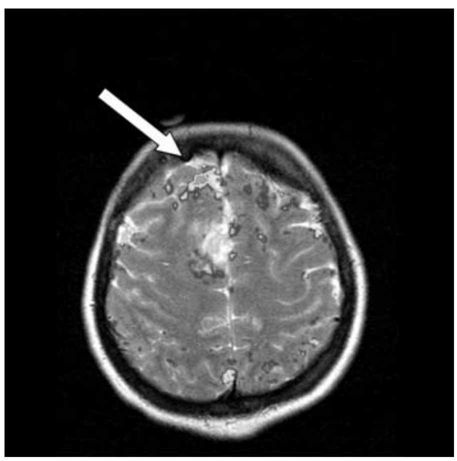
show any sign of tumour recurrence, their tumours had been classified as oligodendroglioma °II (n = 1), oligodendroglioma °III (n = 1), astrocytoma °II (n = 1), oligo-astrocytoma °II (n = 1), oligo-astrocytoma °III (n = 3) and glioblastoma multiforme (n = 1). 5 patients were undergoing an operation for tumour recurrence.

In 6 patients (4 astrocytoma °III, and 2 glioblastoma multiforme) tumour recurrence was obvious, meanwhile 2 patients had died, 1 patient was reoperated on and 3 others received further treatment (chemotherapy).

Functional MRI based on the two-back-paradigm typically showed a bilateral activity in the frontal and parietal lobe (Fig. 1). In the postoperative fMRI control study (12 patients so far) the BOLD effect was unchanged in 11, and missing in the area of tumour in 1 patient. This patient had a malignant oligo-astrocytoma WHO °III (Fig. 2a). The preoperative short-term memory fMRI showed activity next to the tumour (Fig. 2b). As mentioned above, gross total tumour removal was the major goal of the operation was performed in July 2001. The patient received chemotherapy afterwards but declined irradiation. In April 2005, MRI did not show any sign of tumour recurrence (Fig. 2c), but no more activity could be seen in the postoperative short-term memory fMRI



a



b

Fig. 2. (a) preoperative MRI (T1 and T2 weighted images with Gd) of a patient with a malignant oligodendroglioma WHO ° III. (b) Preoperative short-term memory fMRI: activation adjacent to the tumour (arrow) (c) MRI (T1 and T2 weighted images with Gd) 4 years after surgery. (d) postoperative short-term memory fMRI: the primarily seen activation adjacent to the tumour is missing postoperatively

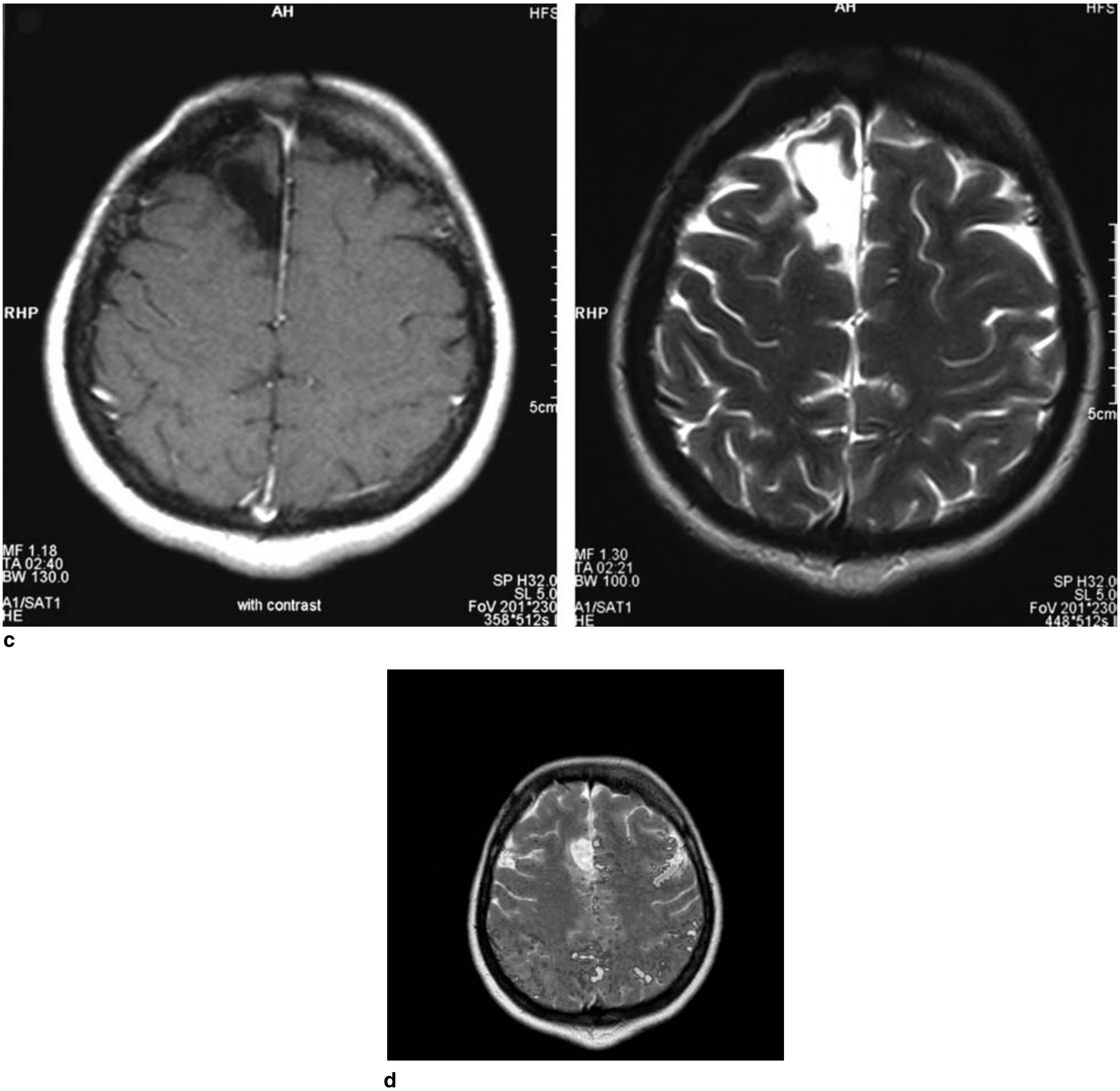


Fig. 2 (*continued*)

adjacent to the resection zone (Fig. 2d). Interestingly, this patient deteriorated markedly in the postoperative working memory tests, especially in verbal test items.

Table 2 presents the results of the tests of memory comparing the pre- and postoperative performance. Overall, the general level of working memory capacity was preserved (mini-mental state examination and performance test). The results of the visuo-spatial short-term memory are not uniform. Whereas patients slightly worsened in the clock and block span tests, they were unchanged in the VSMT and even improved in the trail-making-tests. The tests concerning verbal memory showed an encouraging result. 7 patients improved in the verbal fluency test. Even more promising were the results of the Wechsler Memory Scale-Revised test part I (forward test): 11 improved or at least kept unchanged. In contrast, the level of alertness showed a tendency to decrease. Tests with and without a warning signal showed a prolongation of the reaction time. Finally tests concerning complex items combining verbal and visuo-spatial memory tasks showed an improvement in reaction time and a reduction of faults, but increasing problems for the

Table 2. *Results of the different memory tests*

Test	Improved (no. of pat.)	Unchanged (no. of pat.)	Deteriorated (no. of pat.)	Average pre-op	Average post-op
General level of the working memory capacity					
Mini mental	7	4	3	28.9 ± 1.1 points	29.3 ± 1.3 points
Performance	5	2	7	31.5 ± 4.1 points	30.9 ± 5.7 points
Clock drawing	1	11	2	1.36 ± 0.5 points	1.43 ± 0.5 points
Trail making	9		5	90.7 ± 27.2 sec	92.5 ± 39.8 sec
Block span forward	2	3	9	7.4 ± 2.0 points	6.3 ± 1.7 points
Block span backward	4	1	9	6.8 ± 2.1 points	5.9 ± 2.4 points
VSMT				1270.0 ± 370.5 msec	1266.1 ± 381.5 msec
Visuo-spatial short-term memory					
Verbal fluency	7	1	6	19.2 ± 5.4 No. of words	19.5 ± 5.8 No. of words
WMSR I	8	3	3	7.8 ± 1.3 points	8.3 ± 0.9 points
WMSR II				5.6. ± 1.1 points	5.5 ± 1.8 points
Verbal memory					
Alertness with signal	4	2	8	234.5 ± 44.9 msec	244.2 ± 46.5 msec
Alertness without signal	5	1	8	238.3 ± 29.2 msec	241.2 ± 66.2 msec
Dual task	7	–	7	663.3 ± 94.2 msec	692.9 ± 94.2 msec
Go/No go	6	–	8	353.1 ± 29.4 msec	374.9 ± 61.4 msec
Complex items combining verbal and visuo-spatial memory tasks					
WCST 13 patients	10	–	3	38.0 ± 34.8 sec	21.6 ± 12.1 sec
WCST (change of strategy)	3	–	10	59.6 ± 26.4 sec	86.7 ± 61.6 sec
Odd man out	10	–	4	2663.6 ± 1137.0 msec	2076.6 ± 752.7 msec

patients in items necessitating the change of strategies, resulting in prolonged reaction times for this task.

As mentioned before, 6 patients received radiotherapy immediately after surgery. Comparing the results of this subgroup with the non-irradiated patients, only one significant difference was obvious. In the visuo-spatial memory test, the mean reaction time was statistically significantly worse in the irradiation group ($p = 0.02$) with 1506.2 msec compared with only 1086.0 msec, the number of mistakes also was statistically significantly higher ($p = 0.02$) with a mean of 8.0 ± 2.9 compared with 3.3 ± 2.9. All the other tests showed no statistically significant difference, although a trend to a deterioration in the irradiation group was obvious.

Discussion

Dorward [6] named neuronavigation, introduced by Roberts *et al.* [18], the sextant of the neurosurgeon. However, intra-operative inaccuracies – commonly summarized as brain shift – may occur due to CSF loss and deformation of the brain anatomy by self-retaining retractors and tumor reduction. Brain shift can be minimized using appropriate surgical techniques described and refined by Kelly *et al.* [10]. Nevertheless, this technique only offered anatomical information. For functional preservation, intra-operative monitoring was still essential.

Recently different groups of investigators showed that fMRI is able to localize the motorcortex and Broca area, provided that appropriate paradigms are used [3, 7, 12, 22]. By integration of fMRI images into cranial neuronavigation functional preservation of eloquent cortical areas is possible. So far higher cortical functions (like working memory capacity) have been beyond the ability of electrophysiological monitoring. In 1995 Bellemann *et al.* [1] demonstrated, that fMRI can detect cortical short-term memory fields.

In contrast to the motorcortex and speech areas, short-term memory fields are not situated in one single centre, but in wide-spread cortical areas. Furthermore, short-term memory capacity is not based on a single task, it is composed of a wide variety of visual, spatial or verbal items. Therefore, no standardized tests are available yet to define working memory capacities. Almost every group of investigators concerned with this problem have developed their own test battery. Cacace and coworkers [5] used non-verbal visual and auditory stimuli, Wiegersma *et al.* and Goldstein *et al.* relied on rows of numbers in different modalities and presentations [8, 23]. But each of these three studies only used a small selection out of the wide field of working memory test items. Markowitsch and coworkers [15], as well as Luria [14], demonstrated that different working memory capacities may be disturbed over an extremely wide range. Focal cortical lesions do not lead to obvious and serious memory deficits. In the majority of cases, these lesions only produce partial defects, which can only be detected by detailed test batteries.

The 14 patients included in the present study had superficially seated cortical and subcortical tumours in the frontal, or precentral area. Short-term memory may have been endangered by neurosurgical tumour removal. Therefore our study included a wide range of memory tests both pre- and postoperatively, in order to detect even slight working memory deficits.

This very complex test battery, lasting for 2 hours, cannot be transferred exactly into a functional MRI paradigm. The results of the Department of Psychiatry of our university with the two-back-paradigm for anatomical localisation of short-term memory areas encouraged us to use this paradigm for our study. It was clear, that these paradigm target primarily verbal memory capacity, visuo-spatial working fields are considered to be activated less. Furthermore a majority of our patients received irradiation and/or chemotherapy post operatively before the postoperative memory tests could be performed. It is well known, that irradiation may affect memory capacities [9].

As reported by Goldstein *et al.* [8], Luria *et al.* [14] and Markowitsch *et al.* [15], we did not find serious disturbances of the general intelligence level, and the results in the mini-mental state examination and the performance test remained almost unchanged. Irradiation does not significantly influence these tests.

In 2003 Goldstein *et al*. published their study about the influence of brain tumour surgery on alertness and working memory. In 55 patients they found a slight deterioration of alertness. In contrast to our study, they were able to perform their postoperative tests before chemotherapy or irradiation. In our series, we noticed a slight impairment as well, and all our measured reaction times showed a prolongation. Therefore brain surgery for frontal or precentral tumours has a risk of adversely affecting the patient's alertness. The two-back-paradigm seems to be insufficient for a preservation of this working memory item.

Wiegersma and coworkers found a significant postoperative disturbance of verbal memory capacities in patients with frontal tumours [23]. The localization of the tumours in their series and in our study corresponded. Furthermore, our two-back-paradigms was especially aimed at verbal tasks; an improvement of our patients could have been expected. Indeed our patients performed much better than Wiegersma's. We found an improvement in verbal fluency and the Wechsler Memory Scale-Revised test. Therefore the integration of functional MRI images based on the two-back paradigm into cranial neuronavigation offers an advantage in patients with frontal and precentral tumours. A better outcome in verbal working memory capacity can be expected. Interestingly irradiation did not have a significant influence on this feature.

In contrast, visuo-spatial performance did not respond equally. Whereas patients slightly worsened in the clock and block span tests, they were unchanged in the VSMT and even improved in the trail-making-tests. We, therefore, plan a new fMRI paradigm, targeted specially on visuo-spatial short-term memory capacity.

Finally, our tests concerning complex items, combining verbal and visuo-spatial memory tasks, showed an improvement in reaction time and a reduction of faults, but an increase in the problems of patients for whom it was necessary to change strategies, resulting in prolonged reaction times for this tasks. This might have been expected, because the two-back-paradigm reflects only parts of the working memory capacity which must be used to solve these test items. In future we expect an improvement combining our new visuo-spatial short-term memory fMRI paradigm with the two-back-paradigm used in this study.

Conclusion

Functional fMRI based on a paradigm for short-term memory tasks can improve the outcome after resection of cortical and subcortical brain tumours localized in the frontal and precentral area. The two-back paradigm, in combination with our newly developed visuo-spatial paradigm mainly visualizes verbal memory areas. We expect an improvement of the outcome of visuo-spatial and complex-combined capacities even though irradiation may lower this capacity. In contrast to deep seated brain lesions, focal cortical impairments do not lead to obvious and serious memory deficits. Therefore, the aim of gross total tumour removal has to be balanced against the aim of preservation of short-term memory fields. The deterioration demonstrated in verbal memory capacity in our patient treated for malignant oligoastrocytoma WHO °III caused some impairment in her daily life, but was tolerated as the prize of tumour control. Nevertheless, the knowledge of the localization of cortical short-term memory fields during navigated brain tumour surgery, may offset the patient a better quality, and a longer span of life.

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