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A functional MRI study of presurgical cognitive deficits in glioma patients

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Abstract

Background. The main goal of this functional MRI (fMRI) study was to examine whether cognitive deficits in glioma patients prior to treatment are associated with abnormal brain activity in either the central executive network (CEN) or default mode network (DMN).

Methods. Forty-six glioma patients, and 23 group-matched healthy controls (HCs) participated in this fMRI experiment, performing an N-back task. Additionally, cognitive profiles of patients were evaluated outside the scanner. A region of interest–based analysis was used to compare brain activity in CEN and DMN between groups. Post hoc analyses were performed to evaluate differences between low-grade glioma (LGG) and high-grade glioma (HGG) patients.

Results. In-scanner performance was lower in glioma patients compared to HCs. Neuropsychological testing indicated cognitive impairment in LGG as well as HGG patients. fMRI results revealed normal CEN activation in glioma patients, whereas patients showed reduced DMN deactivation compared to HCs. Brain activity levels did not differ between LGG and HGG patients.

Conclusions. Our study suggests that cognitive deficits in glioma patients prior to treatment are associated with reduced responsiveness of the DMN, but not with abnormal CEN activation. These results suggest that cognitive deficits in glioma patients reflect a reduced capacity to achieve a brain state necessary for normal cognitive performance, rather than abnormal functioning of executive brain regions. Solely focusing on increases in brain activity may well be insufficient if we want to understand the underlying brain mechanism of cognitive impairments in patients, as our results indicate the importance of assessing deactivation.

Keywords

central executive network | cognitive deficits | default mode network | functional MRI | glioma

In his landmark paper from 1990, Mesulam proposed that brain functions are subserved by large-scale networks, and that the relationship between function and structure is dynamic, as well as both localized and distributed.[1] This network approach offered an alternative for the traditional clinical view of a modular and fixed organization of the brain. It paved the way toward more efficient and safer brain tumor surgery. Our improved understanding of the complex architecture of the motor and language network, combined with the use of intraoperative mapping techniques, has increased resectability and reduced the amount of late severe neurological deficits.[2,3]

In contrast, brain regions or networks that underlie cognitive deficits in glioma patients remain largely elusive. That is unfortunate, because results from neuropsychological assessments in brain tumor patients have indicated that cognitive deficits occur frequently[4–7] and may have a large negative impact on normal socio-professional functioning and quality

of life.[8,9] These deficits occur across different cognitive domains and across different types, grading, and location of the brain tumor.[4–7] Therefore, it is more likely that an overarching mechanism is responsible for these deficits than dysfunction of a specific peritumoral region, in line with the large-scale network view. A better understanding of the neural correlates of cognitive deficits in glioma patients will be a necessary first step toward preventing cognitive deficits after (surgical) treatment, and developing specific rehabilitation methods.

A number of large-scale networks have been associated with cognitive performance, whereby involved brain areas either increase or decrease their activity during goal-oriented behavior.[10–14] The central executive network (CEN) is engaged during a range of cognitive tasks and shows a typical pattern of increased brain activity as compared to rest.[10–12] The default mode network (DMN) also shows changes in activity during a variety of cognitive tasks, but brain activity within this network decreases compared to rest.[13,14] Deactivation of DMN regions is therefore often interpreted as a necessary inhibition of brain processes that may interfere with cognitive task performance,[15] whereas CEN activation is typically associated with execution of the task itself.[10–12] Conversely, abnormal functioning of either of these 2 networks may underlie cognitive impairments in brain tumor patients.

To test this hypothesis, we performed a functional MRI (fMRI) experiment and studied glioma patients (prior to treatment) as well as healthy controls (HCs) during cognitive task performance. Brain activity levels within the CEN and DMN network in glioma patients were compared to brain activity levels in HCs. Because cognitive functions are more often impaired in high-grade glioma (HGG) patients than in low-grade glioma (LGG) patients[16], we performed post hoc analyses to investigate possible differences in cognitive performance or brain activity levels between these subgroups.

Methods

Study Population

All newly diagnosed patients with a presumed diffuse glioma undergoing surgical tumor resection at the Elisabeth-TweeSteden Hospital in Tilburg (the Netherlands) between July 2016 and February 2019 were invited to participate in this prospective, 3T fMRI study. Exclusion criteria included 1) age younger than 18 years and older than 75 years, 2) history of intracranial surgery, 3) history of cranial radiotherapy, 4) history of neurological or psychiatric disorders, 5) lack of basic proficiency in Dutch, 6) inability to undergo fMRI scan session because of severe visual, motor, or cognitive problems or poor general health, and 7) contraindications for the MRI scan (such as magnetic elements in the body or claustrophobia).

To be able to investigate possible differences between LGG and HGG patients in post hoc analyses, patients were divided into 2 groups based on a combination of histopathological and molecular tumor characteristics. Patients with a World Health Organization (WHO) grade II tumor with an isocitrate dehydrogenase (*IDH*)1 mutation (*IDH*1+, astrocytoma as well as oligodendroglioma [with 1p19q codeletion]) were classified as LGG. Patients with a WHO grade II tumor with *IDH*1 wild-type (*IDH*1–), WHO grade III tumor (*IDH*1+ or *IDH*1–), or a WHO grade IV tumor were classified as HGG.[17] One patient had a WHO grade I dysembryoplastic neuroepithelial tumor and was excluded from further analyses to increase the study homogeneity in terms of participants, considering the less-infiltrative nature of this tumor.

Because of technical problems, 3 LGG and 2 HGG patients had incomplete fMRI task data and were therefore excluded from our analyses. Ultimately, 46 glioma patients (21 LGG and 25 HGG patients) were included in this study. Patients were scanned 1 to 5 days prior to surgery. Because of postponement of the surgery, 1 LGG patient and 1 HGG patient were scanned 20 days and 37 days prior to surgery, respectively.

Furthermore, 37 healthy volunteers were recruited through online advertisement as a control group. Exclusion criteria included 1) age younger than 18 years and older than 75 years, 2) previously diagnosed neurological or psychiatric disorders, 3) severe concussion of the brain with loss of consciousness in the past, or 4) contraindications for the MRI scan (such as pregnancy, magnetic elements in the body, and claustrophobia).

To minimize the effect of age on task performance as well as brain activity, HCs were matched on a group level with the glioma group so the mean age and range in age did not significantly differ between the glioma patient group and the HC group. From the initial 37 HCs, ultimately 23 group-matched HCs were included for further analyses.

Detailed sociodemographic characteristics of the HC and glioma group and clinical patient characteristics of the glioma group can be found in Table 1. Additionally, sociodemographic and clinical characteristics are presented for LGG and HGG patients separately to further specify both groups that are used in post hoc analyses. The distribution of tumor localization can be found in Figure 1 for LGG and HGG patients separately.

All participants gave written informed consent prior to the scan session. This study was approved by the independent medical ethical committee (protocol number: NL51147.028.14).

Neuropsychological Assessment

As part of clinical care, patients were neuropsychologically evaluated prior to surgery. Cognitive performance was examined using the formal Dutch translation of the computerized neuropsychological battery Central Nervous System Vital Signs (CNS VS).[18] To obtain a cognitive profile of both patient groups, test results of the 7 neuropsychological tests that are examined in this battery were used: verbal memory, visual memory, symbol digit coding, finger-tapping, Stroop III, shifting attention, and a continuous performance test[19].

In-Scanner Task Design

To examine brain activity during cognitive performance, HCs as well as glioma patients performed a 2-back working memory (WM) task (2B) inside the scanner.[20] As baseline, we included a 0-back task (0B) to exclude activation associated with motor and visual processes. Stimuli were identical for both conditions as participants paid attention to a sequence of consonants that was presented in the center of the screen. Because of different instructions, task difficulty varied between conditions. For 0B, participants needed to respond to the target consonant "X." For 2B, participants needed to respond if a stimulus was equal to a stimulus that was presented 2 trials before (Figure 2).

The task was presented in blocks of 30 seconds and rest blocks of 15 seconds. The experiment also comprised

Table 1. Sociodemographic and Clinical Characteristics

Variable	HCs (N = 23)	Glioma (N = 46)	LGG (N = 21)	HGG (N = 25)
Age, y, mean ± SD (range)	43.5 ± 16.2 (18-69)	46.7 ± 14.1 (18-71)	39.9 ± 12.5 (19-67)	52.3 ± 13.0 (18-71)
Sex, male/female	8 (35)/15 (65)	29 (63)/17 (37)	14 (67)/7 (33)	15 (60)/10 (40)
Handedness, left/right	2 (9)/21 (91)	6 (13)/40 (87)	2 (10)/19 (90)	4 (16)/21 (84)
Histopathological diagnosis				
WHO grade II				
*IDH*1+, astrocytoma		13 (28)	13 (59)	–
*IDH*1+, oligodendroglioma		8 (17)	8 (36)	–
*IDH*1−		2 (4)	–	2 (8)
WHO grade III				
*IDH*1+		4 (9)	–	4 (16)
*IDH*1−		–	–	–
WHO grade IV		19 (41)	–	19 (76)
Tumor hemisphere, left/right/both		23 (50)/22 (48)/1 (2)	10 (48)/10 (48)/1 (4)	13 (52)/12 (48)/–
Tumor volume, cm^3, mean (range)		64.79 (5.13-233.99)	61.09 (5.13-233.99)	67.90 (5.24-189.64)
Antiepileptic medication		27 (59)	14 (67)	13 (52)

Abbreviations: HCs, healthy controls; HGG, high-grade glioma; *IDH*, isocitrate dehydrogenase; LGG, low-grade glioma; WHO, World Health Organization.
Sociodemographic characteristics are presented for HCs. For glioma patients, sociodemographic and clinical patient characteristics are presented. Additionally, sociodemographic and clinical characteristics are presented for LGG and HGG patients separately, as these groups are compared in post hoc analyses. Values are indicated as number of participants (%) unless indicated otherwise.
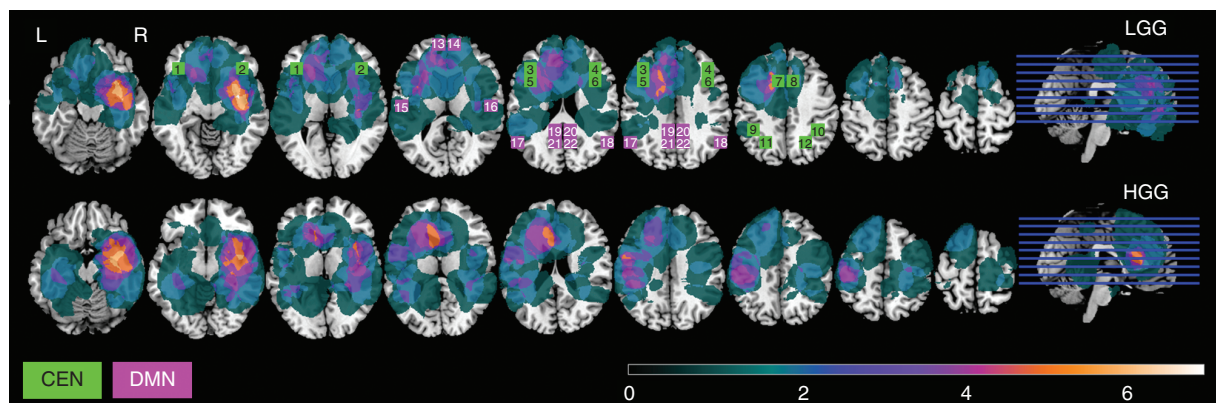

Figure 1. The distribution of tumor localization is presented here for low-grade glioma (LGG, upper panel, n = 21) and high-grade glioma (HGG, lower panel, n = 25) patients separately. The color scale shows minimal overlap (dark green) to maximal overlap (white). Additionally, selected regions of interest (ROIs) are illustrated. ROIs belonging to the central executive network (CEN, in purple) and the default mode network (DMN, in green) are superimposed on the tumor distribution to indicate the ROI location with respect to tumor location. The numbers correspond to the numbers indicated in Table 2, where further characteristics of the individual ROIs can be found.

conditions that were unrelated to this article. 2B as well as 0B consisted of 2 blocks and the number of targets was equal for both conditions (12 targets per block). Stimuli were presented for 400 ms with an interstimulus interval of 1 second (Figure 2). Instructions for each condition were presented for 4 seconds prior to the relevant task block. The participants responded to a target by pushing a button on a button box with their right hand.

Prior to the fMRI scanning session, the N-back WM task was practiced on a laptop outside the scanner to make participants familiar with the task and to reduce possible practice effects during the fMRI scanning session.

Image Acquisition

Scans were performed on a 3T Philips Achieva scanner (Philips Medical Systems) using a 32-channel head coil. A 3-dimensional (3D) T1-weighted structural image was acquired for anatomical registration purposes (scan parameters: repetition time [TR]/echo time [TE]: 8.4/3.8 ms, field of view [FOV]: $254 \times 254 \times 158$ mm^3, flip angle: 8°, voxel size 1 mm isotropic, 158 slices [sagittal orientation]). fMRI images were obtained using an echo-planar imaging pulse sequence (scan parameters: TR/TE: 2000/28 ms, FOV: $240 \times 240 \times 111$ mm, voxel size: $3 \times 3 \times 3$ mm, 219 volumes). Each run also included other conditions and tasks unrelated to this paper.

fMRI Preprocessing

fMRI data were preprocessed and analyzed using SPM12. All scans were registered to the first scan to correct for participant movement during the experiment and slice-timing correction was applied. Subsequently, the images were coregistered to the anatomical image and spatially normalized to standard Montreal Neurological Institute (MNI) space using parameters derived from the spatial normalization of the anatomical image. Individual scans were spatially smoothed with a 3D Gaussian filter (full-width at half-maximum: 12 mm) to minimize effects of functional anatomical differences between participants.

fMRI Analysis

For the evaluation of the fMRI data, we performed a blocked generalized linear model regression analysis with separate regressors for the 0B and 2B condition. The generalized linear model was designed such that the beta value represented a percentage signal change. Signal changes were calculated compared to rest for 0B and 2B separately.

A region of interest (ROI) analysis was performed for the evaluation of signal changes, using a systematic system of equal-sized ROIs.[21,22] Furthermore, this ROI-based analysis provides high statistical power thanks to the larger regions and strongly reduced need for correction for multiple tests.[23] Additionally, the use of systematically designed ROIs allows for comparison of signal changes between networks and regions, as well as quantitative replication of the findings of this study[23,24].

Region of Interest Selection

For our fMRI analysis, we focused on the brain activity within the CEN and the DMN, because these networks have been shown to be consistently involved in cognitive processes.[10–14] We based our ROI selection on brain activity clusters that have been previously reported[10,25–27] to avoid circular analysis.[28] We selected cube-shaped ROIs with dimensions of $15 \times 15 \times 15$ mm from a predefined grid in MNI space[21,22] so they overlapped with the previously reported peak coordinates. By using a predefined shape and size for the ROIs, we further minimized the effect of circularity because the borders were not influenced by noise.[28] All ROIs were placed symmetrically for both hemispheres. The location and other characteristics of the selected ROIs are presented in Figure 1 and Table 2. Ultimately, the CEN consisted of regions within the dorsal- and ventral lateral prefrontal cortex, the premotor cortex, the anterior cingulate, and regions along the intraparietal sulcus.[10] The DMN consisted of brain regions within the medial prefrontal cortex,[25] posterior cingulate,[26] angular gyrus,[26] precuneus,[27] and medial temporal cortex. Brain activity was averaged over all ROIs within the CEN and DMN respectively for further analyses.

Statistical Analyses

To obtain a better cognitive profile of the glioma patient group, raw neuropsychological test scores of patients were converted into sociodemographically adjusted z-scores based on a Dutch normative sample.[19] Individual patient test scores were considered impaired if the z-score was less than or equal to 1.5.[29] Subsequently, we calculated the percentage of patients with an impaired score for each test separately and determined the percentage of patients with an impaired score for one or more tests in the glioma group, as well as in LGG and HGG patients separately.

To evaluate the in-scanner task performance of HCs as well as glioma patients, we determined the number of missed targets and the number of false alarms separately for 0B and 2B in each group. Subsequently, we calculated the increase in percentage of incorrect responses between 2B and 0B (combining false alarms and missed targets), analogous to the fMRI analyses. Finally, we used these results to conduct separate analyses of covariance (ANCOVAs) to test for group differences between glioma patients and HCs. Age (in years) was included as a covariate to minimize the effect of this factor on task performance in each group. Post hoc analyses included separate ANCOVAs with age as a covariate to test for possible differences between LGG and HGG patients.

To identify brain activity specifically associated with cognitive performance, brain activity during 0B was subtracted from brain activity during 2B in both networks. Subsequently, we conducted separate ANCOVAs for activity averaged over all ROIs included in the CEN and all ROIs included in the DMN, comparing activity in these 2 networks between glioma patients and HCs. Age was included as a covariate to control for effects of this factor on activity in each group. Again, post hoc analyses included separate ANCOVAs with age as a covariate to test for

Table 2. Description of Selected Regions of Interest

ROI	ROI full name	BA	MNI$_x$	MNI$_y$	MNI$_z$
	Central executive network				
1	Left ventrolateral prefrontal cortex	47	–39	30	0
2	Right ventrolateral prefrontal cortex	47	39	30	0
3	Left dorsolateral prefrontal cortex	48	–39	30	30
4	Right dorsolateral prefrontal cortex	48	39	30	30
5	Left premotor cortex	44	–39	15	30
6	Right premotor cortex	44	39	15	30
7	Left anterior cingulate	32	–9	15	45
8	Right anterior cingulate	32	9	15	45
9	Left intraparietal sulcus lateral anterior part	40	–39	–45	45
10	Right intraparietal sulcus lateral anterior part	40	39	–45	45
11	Left intraparietal sulcus medial posterior part	7	–24	–60	45
12	Right intraparietal sulcus medial posterior part	7	24	–60	45
	Default mode network				
13	Left medial prefrontal cortex	10	–9	60	15
14	Right medial prefrontal cortex	10	9	60	15
15	Left medial temporal cortex	48	–54	–15	15
16	Right medial temporal cortex	48	54	–15	15
17	Left angular gyrus	39	–54	–60	30
18	Right angular gyrus	39	54	–60	30
19	Left posterior cingulate	23	–9	–45	30
20	Right posterior cingulate	23	9	–45	30
21	Left precuneus	0	–9	–60	30
22	Right precuneus	0	9	–60	30

Abbreviations: BA, Brodmann area; MNI$_{xyz}$, Montreal Neurological Institute coordinates; ROI, region of interest.
The numbers of individual ROIs correspond to the ROIs presented in Figure 1. MNI coordinates represent the center point of the 15 × 15 × 15 mm cube-shaped ROIs.

possible differences between LGG and HGG patients. All statistical analyses were performed using SPSS 24.

Results

Neuropsychological Assessment

Forty-four out of 46 glioma patients (21 LGG patients and 23 HGG patients) underwent neuropsychological assessment prior to surgery. Percentages of patients with impaired scores ranged over tests from 11% to 30%, whereas in a normative sample 7% of impaired scores is expected for each test. Post hoc analyses showed that percentages of patients with impaired scores ranged over tests from 5% to 24% in the LGG group and from 9% to 45% in the HGG group. In total, 57% of the LGG patients had an impaired score for 1 test, and 19% had an impaired score for 2 or more tests. In the HGG group, 17% had an impaired score for 1 test, whereas 61% of the patients had an impaired score for 2 or more tests.
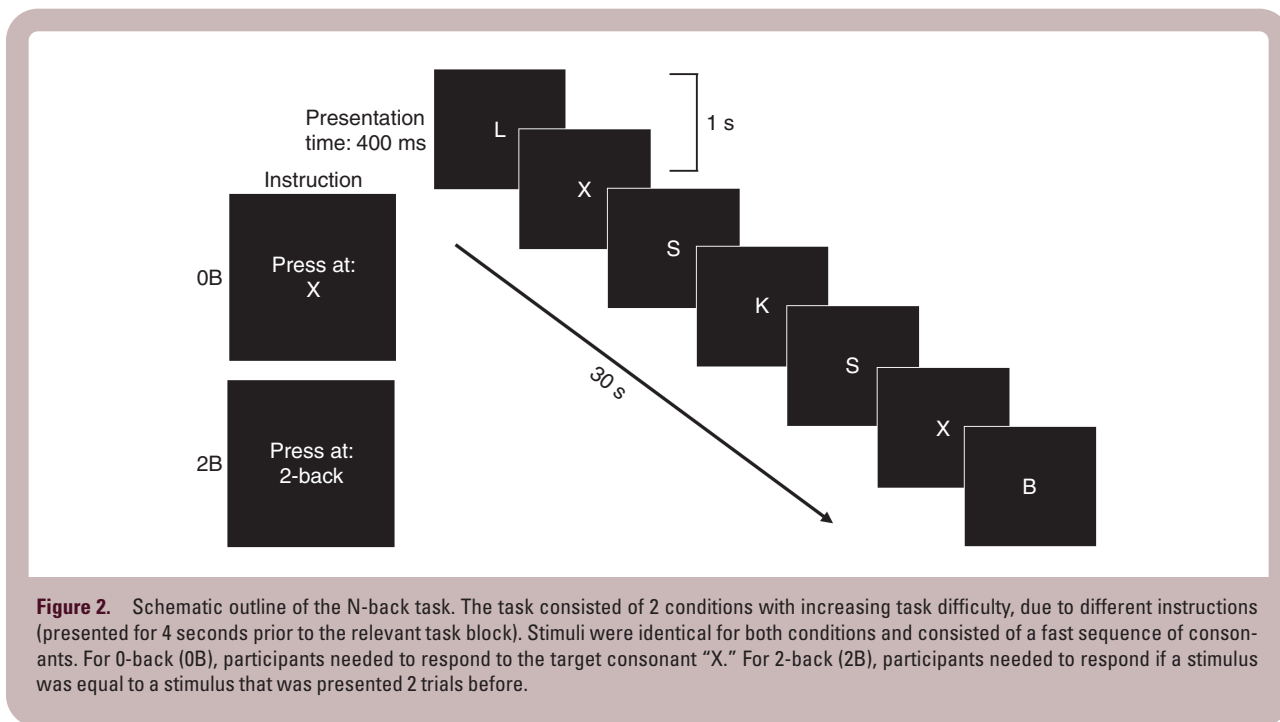
In-Scanner Task Performance

As expected, the percentage of incorrect responses (mean ± SEM) increased during the most difficult condition in HCs (0B: 0.04 ± 0.32; 2B: 11.04 ± 1.49) as well as glioma patients (0B: 0.74 ± 0.23; 2B: 16.41 ± 1.05) (Figure 3A).

Taking age into account, performance differences were found between HCs and glioma patients, as glioma patients had an increased number of incorrect responses compared to HCs ($F = 6.04$, $P = .02$). The presented task performance results are corrected for age by showing results for the mean age of all participants (mean age = 45.6 years) (Figure 3A). Post hoc analyses showed no task performance differences between LGG and HGG patients ($F = 1.63$, $P = .21$).

Region of Interest Analysis

Task-induced brain activity patterns in CEN and DMN (difference between 2B and 0B) are presented in Figure 4 for HCs and glioma patients, respectively. The brain activity patterns presented in Figure 4 are not corrected for age

Figure 2. Schematic outline of the N-back task. The task consisted of 2 conditions with increasing task difficulty, due to different instructions (presented for 4 seconds prior to the relevant task block). Stimuli were identical for both conditions and consisted of a fast sequence of consonants. For 0-back (0B), participants needed to respond to the target consonant "X." For 2-back (2B), participants needed to respond if a stimulus was equal to a stimulus that was presented 2 trials before.

because we prefer to show the actual measured signal changes (which is in line with most fMRI studies). We included age as a covariate in our statistical design to evaluate whether differences in measured brain activity levels between HCs and glioma patients are statistically significant. Detailed results of these ROI analyses are presented in Figure 3B and 3C. The results presented in Figure 3 are corrected for age by showing results for the mean age of all participants (mean age = 45.6 years). Taking age into account, ROI analyses revealed no abnormal brain activity levels within the CEN in glioma patients compared to HCs ($F = 0.01$, $P = .91$). Furthermore, brain activity levels within the CEN did not differ between both patient groups ($F = 0.79$, $P = .38$). However, glioma patients did show reduced deactivation of the DMN compared to HCs ($F = 5.56$, $P = .02$), indicating reduced responsiveness of the DMN during cognitive performance. The level of deactivation did not differ between both patient groups ($F = 0.26$, $P = .61$).

Discussion

The main goal of this fMRI study was to examine whether cognitive deficits in glioma patients prior to surgical or other treatment can be associated with abnormal brain activity in either CEN or DMN during cognitive performance.

Cognitive evaluation of the glioma patient group using a battery of neuropsychological tests outside the scanner indicated impaired cognitive functioning in glioma patients (LGG and HGG), as well as a more severely affected cognitive functioning in HGG compared to LGG patients, matching observations in the literature of these patients.[4,16] CEN activity did not show a difference between any of the groups. In contrast, glioma patients did show significantly reduced deactivation in DMN compared to HCs. This effect

did not differ significantly between the 2 patient groups. Therefore, our study suggests that preoperative cognitive impairments in glioma patients are associated with reduced responsiveness of the DMN, whereas we did not find evidence for involvement of the CEN.

As expected, our fMRI results showed increased activity in the CEN as well as reduced activation in the DMN compared to rest. Increased brain activity in CEN is typically understood to represent the execution of a cognitive task.[10–12] Similar to the etiology of sensorimotor or language (ie, classical neurological) deficits, cognitive deficits may occur when these eloquent areas or pathways for executive processes are damaged during surgery.[30] Some brain-mapping studies have therefore imported preoperatively acquired WM-related brain activity into cranial neuronavigation to evaluate and preserve WM function[31].

Although this is important, it may only be part of the story. Deactivation of the DMN is well described in healthy individuals[13,14] and occurs in a variety of cognitive tasks. Deactivation of the DMN is therefore generally understood to be a necessary prerequisite for goal-oriented behavior, such as for a cognitive task.[13,15] The DMN has previously been associated with processes that are performed during rest, but interfere with goal-oriented behavior, such as "mind wandering."[32] DMN brain activity should therefore be suppressed during goal-oriented cognitive tasks. Other studies have suggested an association of DMN with mental effort[33] or regulation of bodily homeostasis.[34]

We found significantly reduced deactivation of the DMN during task performance in glioma patients. These results suggest that the various cognitive deficits in glioma patients that are already present prior to surgery may be associated with a reduced capacity to inhibit this DMN. Since deactivation of the DMN is generally understood to be a prerequisite for goal-oriented behavior, one may speculate that it could potentially indicate cognitive impairment
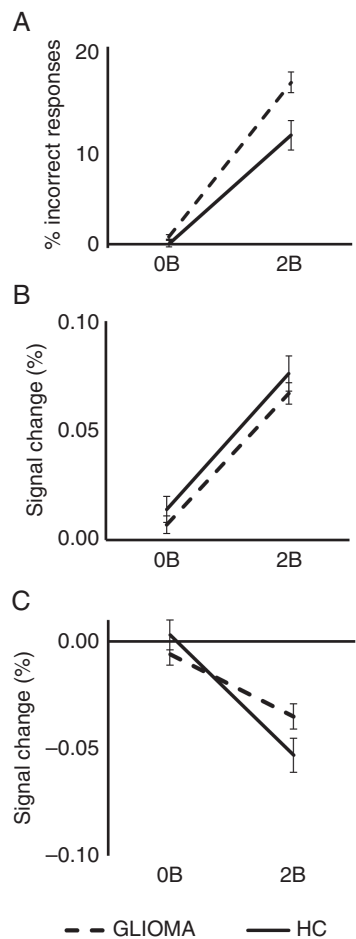
Figure 3. Task performance and brain activity measures of healthy controls (HC, solid line) and glioma patients (GLIOMA, dashed line) are presented here for the 0-back (0B) and the 2-back (2B) condition. Age-corrected results are presented by showing results for the mean age of all participants (mean age = 45.6 years). A, The percentage of incorrect responses (false alarms and missed targets combined) are shown (± SEM) for each group. Taking age into account, glioma patients showed reduced task performance compared to HCs. C and D, Signal change within the central executive network (CEN, C), and the default mode network (DMN, D) are shown (± SEM). Note the similar increase in activity within the CEN for HCs and glioma patients with increasing task difficulty. For the DMN, patients show reduced deactivation during 2B.

Figure 4. Illustration of the brain activity patterns induced by the N-back task for A, healthy control group (HC), and B, glioma patients (GLIOMA). The contrast between the 2-back and 0-back task condition is presented here. Voxels in which the brain activity exceeded the threshold value of b = 0.05 are indicated in red, whereas voxels in which the brain activity was below the threshold value of b = –0.05 are indicated in blue. Regions of interest (ROIs) are superimposed on the brain activity patterns (CEN, in green; DMN, in purple). Note that the positive brain activity patterns are quite similar between groups within CEN, whereas glioma patients show less negative brain activity compared to the HC group within the DMN.

and therefore serve as a cognitive biomarker in glioma patients. For example, it could be used to monitor effects of neurofeedback training.[35] From a surgical perspective, sparing this network could be important in preventing further loss of cognitive functions. At least, our findings imply that solely examining increases in brain activity in fMRI is likely insufficient to characterize the neuroanatomy of cognitive functions in glioma patients.

In summary, cognitive deficits that are found in glioma patients prior to surgery appear not to be related to deficits in brain regions associated with task execution, but rather to a r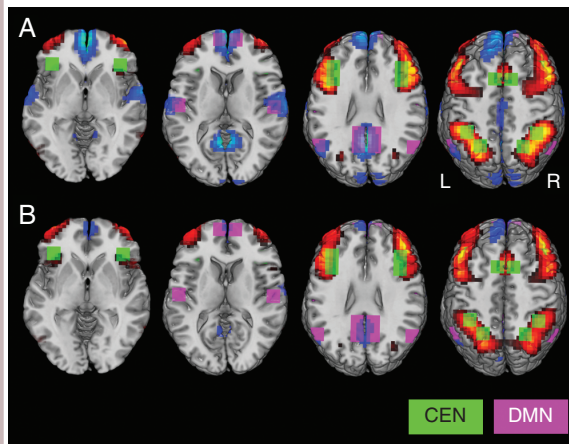educed capacity to achieve a brain state that is optimal for general cognitive functioning. Our results thus support our assumption that various cognitive deficits in glioma patients may be associated with abnormal functioning of one overarching brain function, rather than dysfunction of several task-specific brain regions or networks.

Task-based fMRI studies that examined cognitive functions in glioma patients prior to surgery are unfortunately rather scarce and often do not include healthy individuals as a reference.[31] Therefore, it is difficult to evaluate our results in regard to similar studies in glioma patients. Comparable studies in patients with other neurological or psychiatric disorders have shown altered cognitive brain activity patterns compared to HCs.[36–46] In regard to CEN activity, previous results are rather inconsistent, as both increased[36–39] as well as decreased[40,41] executive activity compared to HCs have often been reported. For instance, in a study of aneurysmal subarachnoid hemorrhage patients, cognitive impairment was associated with increased activity in executive brain regions.[36] This suggests a lack of efficiency in CEN, which could result in reduced performance, especially during difficult tasks. In contrast, studies of patients with schizophrenia[43] and mild traumatic brain injury[44] have suggested that cognitive impairments in these patient groups are associated with a reduced capacity to modulate brain activity in the CEN when tasks vary in difficulty. Whereas increased executive activity may be explained by a lack of efficiency, a decrease in executive activity can be caused by poorer performance.[41] This seemed not to be the case in our study because CEN activity was normal for glioma patients. This is a strong

argument that the patients kept performing the task despite a somewhat poorer performance, since brain activity within the CEN is a marker for task execution.[10–12]

In line with our findings in glioma patients, several previous task-based fMRI studies in patients with neurological or psychiatric disorders have also reported reduced DMN deactivation during cognitive performance.[38–42] The combination of normal CEN activity and diminished DMN deactivation was previously also reported in studies of chronic pain patients[45] and patients with remitted major depression.[46] Because patient in-scanner task performance was normal in these studies, Čeko et al[45] suggested that a responsive executive network may be sufficient for successful cognitive performance, regardless of DMN deactivation. In our study, reduced deactivation in the DMN was accompanied by decreased task performance in glioma patients, despite a responsive CEN. This suggests that in contrast to the study by Čeko and colleagues,[45] a normally responsive executive network alone may not be sufficient for normal cognitive task performance. Cognitive impairments have previously also been reported in chronic pain patients.[47] An alternative interpretation of the results presented by Čeko et al[45] may be that despite normal performance on the relatively short fMRI task, subtle cognitive impairments did exist in their patient group, explaining the reduced DMN deactivation that they found.

Some limitations have to be taken into account when interpreting the results of this study. Because of our selection criteria that patients should be able to undergo and complete the fMRI scan session, patients with severe visual, motor, or cognitive problems or a poor health condition were excluded from this study. Therefore, the cognitive abilities of the participating glioma patients may be an overestimation of the actual cognitive abilities in this population. Hence, our results may be an underestimation of the problems that occur in glioma patients. Furthermore, age may be a factor that influences task performance as well as the level of brain activity. Therefore, we have minimized the effect of age by matching HCs on a group level with the glioma group so that the mean age and range in age did not significantly differ between the glioma patient group and the HC group. Additionally, age was included as a covariate in all statistical analyses to further control for the possible effect of age in each group. Therefore, the influence of a possible age effect on our results regarding the comparison between patients and HC was minimal. For our post hoc analyses, the average age of HGG patients was considerably older than the average age of the LGG patient group. Whereas LGG occurs most commonly in the second through fourth decades of life, the average age of HGG patients is considerably higher at diagnosis, as the incidence of HGG increases with age.[48,49] Therefore, the relatively large age difference between LGG and HGG patients is inherent to glioma subtype. By including age as a covariate in our post hoc analyses, the effect of age was minimized in our comparison between LGG and HGG patients. Finally, the infiltrative character of glioma tumors can induce tissue distortion, which complicates the comparison of brain activity levels between glioma patients and HCs. To minimize the effect of deformation, images were spatially normalized into standard MNI space during preprocessing using deformation fields that quantify the amount of displacement for each location in 3D space. Combining all patients, 11.6% of all ROIs within the CEN showed some tumor overlap, whereas in the DMN this was 7.6%. Considering the relatively low tumor overlap, and the fact that we did not find differences in brain activity levels within the CEN between glioma patients and HCs, while tumor overlap was larger in CEN than in DMN, we believe the influence of deformation and tumor overlap on our results regarding reduced DMN deactivation was minimal.

In conclusion, our study suggests that cognitive deficits in glioma patients prior to treatment are associated with reduced capacity to deactivate the DMN, whereas we found no evidence of abnormal CEN function. Thus, it appears that cognitive deficits in glioma patients do not reflect abnormal functioning of executive brain regions, but rather a reduced capacity to achieve a brain state necessary for normal cognitive task performance. Solely focusing on increases in brain activity may be insufficient to study and understand cognitive impairment in patients, as our results indicate the importance of assessing deactivation. Our results constitute an important step toward a better understanding of the underlying mechanism of cognitive decline in glioma patients and provide a lead to development of a biomarker to guide the effects of new surgical treatment or rehabilitation methods.

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