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RESEARCH REPORT

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Cognitive brain activity before and after surgery in meningioma patients

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Abstract

Neuropsychological studies have demonstrated that meningioma patients frequently exhibit cognitive deficits before surgery and show only limited improvement after surgery. Combining neuropsychological with functional imaging measurements can shed more light on the impact of surgery on cognitive brain function. We aimed to evaluate whether surgery affects cognitive brain activity in such a manner that it may mask possible changes in cognitive functioning measured by neuropsychological tests. Twenty-three meningioma patients participated in a fMRI measurement using a verbal working memory task as well as three neuropsychological tests focused on working memory, just before and 3 months after surgery. A region of interest based fMRI analysis was used to examine cognitive brain activity at these timepoints within the central executive network and default mode network. Neuropsychological assessment showed impaired cognitive functioning before as well as 3 months after surgery. Neuropsychological test scores, in-scanner task performance as well as brain activity within the central executive and default mode network were not significantly different between both timepoints. Our results indicate that surgery does not significantly affect cognitive brain activity in meningioma patients the first few months after surgery. Therefore, the lack of cognitive improvement after surgery is not likely the result of compensatory processes in the brain. Cognitive deficits that are already present before surgery appear to be persistent after surgery and a considerable recovery period.

Abbreviations: 0B, 0-back task; 2B, 2-back task; CEN, central executive network; CNS VS, central nervous system vital signs; DMN, default mode network; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; FOV, field of view; GLM, generalized linear model; LACC, left anterior cingulate cortex; LAG, left angular gyrus; LDLPFC, left dorso-lateral prefrontal cortex; LIPSla, left intraparietal sulcus lateral anterior part; LIPSmp, left intraparietal sulcus medial posterior part; LMPFC, LEFT medial prefrontal cortex; LMTC, left medial temporal cortex; LPCC, left posterior cingulate cortex; LPCUN, left precuneus; LPMC, left premotor cortex; LVLPFC, left ventro-lateral prefrontal cortex; MNI, Montreal Neurological Institute Coordinates; POST, postoperative; PRE, preoperative; RACC, right anterior cingulate cortex; RAG, right angular gyrus; RDLPFC, right dorso-lateral prefrontal cortex; RIPSla, right intraparietal sulcus lateral anterior part; RIPSmp, right intraparietal sulcus medial posterior part; RMPFC, right medial prefrontal cortex; RMTC, right medial temporal cortex; ROI, region of interest; RPCC, Right medial temporal cortex; RPCUN, right precuneus; RPMC, right premotor cortex; RVLPFC, right ventro-lateral prefrontal cortex; SAT, shifting attention task; TE, echo time; TR, repetition time; SDC, symbol digit coding; WHO, World Health Organization; WM, working memory.

Our study shows potential leads that comprehensive cognitive evaluation can be of added value so that cognitive functioning may become a more prominent factor in clinical decision making.

KEYWORDS
cognition, functional MRI, meningioma, tumour resection, working memory

1 | INTRODUCTION

The majority of intracranial meningiomas are slowly growing, benign tumours that do not infiltrate the surrounding brain tissue (Whittle et al., 2004). Due to the low growth velocity of the tumour and the ability of the brain to slowly adapt to such physical disturbances (Duffau, 2008), meningiomas may remain undetected for a long period. Eventually, the mass effect of the tumour and/or perilesional oedema cause dysfunction of brain tissue or cranial nerves, which may lead to seizures or neurological deficits (Whittle et al., 2004). Additionally, the clinical presentation of meningioma patients may involve cognitive or behavioural dysfunction (Whittle et al., 2004). Recent neuropsychological studies have demonstrated that meningioma patients frequently exhibit cognitive deficits prior to treatment (Meskal et al., 2016; Pranckeviciene et al., 2019; Rijnen et al., 2019).

Surgical resection has been and still is the preferred treatment for meningioma patients when the tumour is considered symptomatic (Goldbrunner et al., 2016; Whittle et al., 2004). Main consideration for surgical resection is reduction of the mass effect, which may lead to improvement of neurological deficits and seizures (Englot et al., 2016; Schneider et al., 2019). Clinical decision making is still predominantly based on classic neurological concepts, and focusses on assessment of sensorimotor, language and visual functions. Although neurologists or neurosurgeons will judge cognition and behaviour in a subjective manner in their preoperative consultations, most clinicians do not routinely refer their meningioma patients to a neuropsychologist for formal and objective neuropsychological evaluation. Hence, the number of patients with cognitive impairments is underestimated (Meskal et al., 2015; Rijnen et al., 2019), indicating the relevance of formal cognitive evaluation prior to surgery. It is still an unresolved, but clinically very relevant question to what extent, and at what moment in time, resection of a meningioma is able to alleviate existing preoperative cognitive impairments.

Longitudinal studies indicate that cognitive deficits remain largely present in the first few months postoperatively (Dijkstra et al., 2009; Meskal et al., 2015; Rijnen et al., 2019; van der Vossen et al., 2014), with some improvement in cognitive functioning after one year (Rijnen et al., 2019). Cognitive deficits that are present before and after surgery (Rijnen et al., 2019) may be due to a combination of different causes. The mass effect of the tumour and/or perilesional oedema likely play an important role here, implying that preoperative cognitive deficits may be alleviated by resection. However, the surgery itself, even when it is uneventful from a clinical point of view, may cause damage to adjacent cortex and white matter during tumour removal, potentially leading to new cognitive deficits postoperatively. Additionally, it is also possible that the brain uses compensatory processes before, but also after surgery. These compensatory processes may counteract possible negative effects of surgery, masking possible differences in cognitive performance measured by neuropsychological tests at both timepoints. When the brain uses compensatory processes, the brain has to spend more energy to achieve the same level of cognitive performance (Callicott et al., 2000). Therefore, compensatory processes would lead to differences in brain activity levels before and after surgery. We think that brain activity maps are potentially of added value to current neuropsychological assessment when evaluating cognitive functioning of patients. Such a more comprehensive evaluation of the effects of surgery on cognitive functioning is desirable so that cognitive functioning can become a more prominent component in clinical decision making.

Functional imaging studies are especially well-suited to shed more light on the impact of surgery on cognitive functioning, as they are able to evaluate the spatiotemporal features of underlying cognitive brain activity (D'esposito et al., 1995; Raichle et al., 2001; Shulman et al., 1997; Smith et al., 1998; Tomasi et al., 2006). To date, unfortunately, imaging studies that investigated and compared preoperative and postoperative cognitive brain activity levels in meningioma patients are scarce.

Functional MRI studies have previously implicated two main networks in cognitive performance: the central executive network (CEN) (D'Esposito et al., 1995; Smith et al., 1998) and the default mode network (DMN) (Raichle et al., 2001; Shulman et al., 1997; Tomasi et al., 2006). Whereas CEN activity increases during

cognitive performance (Braver et al., 1997; Callicott et al., 1999; Jansma et al., 2000, 2007), DMN activity decreases (Jansma et al., 2007; McKiernan et al., 2003). Furthermore, the change in activity in these networks scales with task difficulty (Braver et al., 1997; Callicott et al., 1999; Jansma et al., 2000, 2007; McKiernan et al., 2003; Singh & Fawcett, 2008). CEN activity is typically associated with processes that are necessary to perform a task, such as perception, short-term storage and manipulation of stimuli (D'Esposito et al., 1995; Smith et al., 1998). DMN activity is often interpreted as interfering with cognitive task execution and thus needs to be inhibited (Raichle, 2015). Considering the important role of both networks in cognition, we investigated if surgery leads to a change in CEN or DMN activity evoked by a verbal working memory (WM) task in meningioma patients.

In order to achieve a more comprehensive evaluation of cognitive functioning of patients before as well as 3 months after surgery, we combined functional MRI (fMRI) and neuropsychological measurements with a focus on working memory in this study. Main goal of this study was to infer from these two measures the effects of tumour resection on cognitive brain function in meningioma patients. We specifically aimed to evaluate whether surgery affects cognitive brain activity in such a manner that it may mask possible underlying changes in cognitive functioning that were otherwise overlooked by traditional neuropsychological tests.

2 | MATERIALS AND METHODS

2.1 | Study population

All newly diagnosed meningioma patients undergoing tumour resection at the Elisabeth-TweeSteden Hospital in Tilburg (the Netherlands) between July 2016 and June 2018 were invited to participate in this 3T fMRI study. Exclusion criteria included: (1) age below 18 years and above 75 years, (2) infratentorial tumour, (3) history of intracranial surgery, (4) history of cranial radiotherapy, (5) history of neurological or psychiatric disorders, (6) lack of basic proficiency in Dutch, (7) inability to undergo the functional MRI scan session due to severe visual, motor or cognitive problems or a poor health condition, and (8) contraindications for the MRI-scan (such as magnetic elements in the body or claustrophobia).

Patients were scanned one to 5 days before (PRE) and 3 months after surgery (POST).

This study was approved by the Independent Ethical Committee (protocol number: NL51147.028.14). All participants gave written informed consent prior to the scan session and procedures were performed in accordance with the principles of the Declaration of Helsinki (2013).

2.2 | Neuropsychological assessment

As part of clinical care, patients were neuropsychologically assessed 1 to 5 days before and 3 months after surgery, on the same days the fMRI scanning sessions were conducted. Cognitive performance was examined using the formal Dutch translation of the computerized neuropsychological battery Central Nervous System Vital Signs (CNS VS LCC, Morrisville, USA) (Gualtieri & Johnson, 2006). In order to evaluate cognitive functioning of the meningioma patients, test results of three neuropsychological tests that involve WM were used, being: symbol digit coding (SDC), stroop III and a shifting attention task (SAT) (Rijnen et al., 2020).

2.3 | In-scanner task design

In order to examine preoperative and postoperative brain activity differences during cognitive performance, meningioma patients performed a 2-back verbal WM task (2B) inside the scanner at both timepoints. This task was previously used and described in our study in glioma patients (Schouwenaars et al., 2021). A 0-back task (0B) was used as a baseline to exclude activation associated with motor and visual processes. In both conditions, stimuli were presented as a sequence of white consonants in the centre of a black screen. However, task difficulty differed between 0B and 2B due to different instructions. For 0B, patients 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 two trials before. To respond to a target, patients had to push a button on a button box that was placed in their right hand (Schouwenaars et al., 2021).

The experiment also comprised conditions which were unrelated to this article. The sequence of conditions was counterbalanced to reduce possible effects of fatigue during the experiment. Each condition consisted of two task blocks of 30 s, and two to three consecutive task blocks of different conditions were interleaved with rest blocks of 15 s. The number of targets was identical for 0B and 2B, as each task block comprised 12 targets. The presentation time of each stimulus was 400 ms with an inter stimulus interval of 1 s. Prior to each task block, instructions were presented for 4 s (Schouwenaars et al., 2021).

In order to make the patients familiar with the task and to reduce possible practice effects during the fMRI scanning sessions, the N-back WM task was practiced on a laptop just before both fMRI scanning sessions.

2.4 | Image acquisition

Image acquisition was equal to the image acquisition described in our previous study (Schouwenaars et al., 2021). A 3T Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil was used for scan acquisition. For anatomical registration purposes, a 3D T1-weighted structural image was acquired (scan parameters: TR/TE: 8.4/3.8 ms, FOV: 254x254x158 mm^3, flip angle: 8°, voxel size 1 mm isotropic, 158 slices [sagittal orientation]). Functional MRI images were obtained using an Echo Planar Imaging (EPI) pulse sequence (scan parameters: TR/TE: 2000/28 ms, FOV: 240 × 240 × 111 mm, voxel size: 3 × 3 × 3 mm, 219 volumes). Each run also included other conditions and tasks that are not described in this study. Total scan time for the anatomical as well as functional images was 10 min and 8 s.

2.5 | fMRI analysis

Preprocessing steps for the functional images included registration, slice timing correction, normalization and smoothing for the PRE and POST scans. To correct for subject movement during the experiment, all functional scans were registered to the first scan. Subsequently, functional images were co-registered to the anatomical image. In order 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. The effect of functional anatomical differences between patients was minimized by using a 3D Gaussian filter (full-width at half-maximum: 12 mm) to spatially smooth the individual scans.

A blocked generalized linear model (GLM) regression analysis with separate regressors for the 0B and 2B condition was performed in order to evaluate the fMRI data. The GLM was designed such that the beta value represented a percentage signal change. Signal changes were calculated compared with rest for 0B and 2B separately. Functional MRI data were preprocessed and analysed using SPM12.

2.6 | Regions of interest

Signal changes were evaluated using a region of interest (ROI) analysis. Considering the important role of CEN as well as DMN in cognition (D'Esposito et al., 1995; Raichle et al., 2001; Smith et al., 1998; Tomasi et al., 2006), fMRI analysis was focused on the brain activity levels within these two networks. Selected ROIs for CEN and DMN were equal to the ROIs used in our previously published study in which we reported that brain activity within the DMN, but not the CEN, differed between glioma patients and healthy controls performing the same verbal WM task as conducted in the current study (Schouwenaars et al., 2021). Selected ROIs were based on a systematic system of cube shaped ROIs (15 × 15 × 15 mm) (Jansma & Rutten, 2017; Schouwenaars et al., 2021), allowing for comparison of signal changes between networks and regions, as well as quantitative replication of the findings of this study (Poldrack, 2007; Zandbelt et al., 2008). By using the same ROIs as used in our previously published study (Schouwenaars et al., 2021), we are able to compare results and we avoid circular analysis (Kriegeskorte et al., 2009).

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 (Schouwenaars et al., 2021). The DMN consisted of brain regions within the medial prefrontal cortex, posterior cingulate, angular gyrus, precuneus and medial temporal cortex (Schouwenaars et al., 2021). The location and other characteristics of the selected ROIs are presented in Table 1 and Figure 1.

The anatomical differences between the PRE and POST scans make the comparison of cognitive brain activity between both timepoints challenging. The tumour, which is obviously only present in the PRE scans, does not contain functional brain tissue due to the non-infiltrative character of a meningioma. When selected ROIs show overlap with the tumour, PRE brain activity levels in that particular ROI may be lower than POST brain activity levels due to the lack of activity within the tumour tissue. In order to make the comparison between both timepoints as fair as possible, ROIs that showed any overlap with the tumour were excluded from analysis for each individual patient, in PRE as well as POST scans. Brain activity levels were subsequently determined by averaging the remaining ROIs within the CEN and DMN respectively for further analyses.

TABLE 1 Description of selected regions of interest.

ROI	ROI full name	Abbreviation	BA	MNI_x	MNI_y	MNI_z
	Central executive network					
1	Left ventro-lateral prefrontal cortex	LVLPFC	47	−39	30	0
2	Right ventro-lateral prefrontal cortex	RVLPFC	47	39	30	0
3	Left dorso-lateral prefrontal cortex	LDLPFC	48	−39	30	30
4	Right dorso-lateral prefrontal cortex	RDLPFC	48	39	30	30
5	Left premotor cortex	LPMC	44	−39	15	30
6	Right premotor cortex	RPMC	44	39	15	30
7	Left anterior cingulate cortex	LACC	32	−9	15	45
8	Right anterior cingulate cortex	RACC	32	9	15	45
9	Left intraparietal sulcus lateral anterior part	LIPSla	40	−39	−45	45
10	Right intraparietal sulcus lateral anterior part	RIPSla	40	39	−45	45
11	Left intraparietal sulcus medial posterior part	LIPSmp	7	−24	−60	45
12	Right intraparietal sulcus medial posterior part	RIPSmp	7	24	−60	45
	Default mode network					
13	Left medial prefrontal cortex	LMPFC	10	−9	60	15
14	Right medial prefrontal cortex	RMPFC	10	9	60	15
15	Left medial temporal cortex	LMTC	48	−54	−15	15
16	Right medial temporal cortex	RMTC	48	54	−15	15
17	Left angular gyrus	LAG	39	−54	−60	30
18	Right angular gyrus	RAG	39	54	−60	30
19	Left posterior cingulate cortex	LPCC	23	−9	−45	30
20	Right posterior cingulate cortex	RPCC	23	9	−45	30
21	Left precuneus	LPCUN	0	−9	−60	30
22	Right precuneus	RPCUN	0	9	−60	30

Note: The numbers of the individual ROIs correspond to the ROIs presented in Figure 1. Indicated MNI coordinates represent the centre point of the 15 × 15 × 15 mm cube shaped ROIs.

Abbreviations: BA, Brodmann area; MNIxyz, Montreal Neurological Institute coordinates; ROIs, regions of interest.

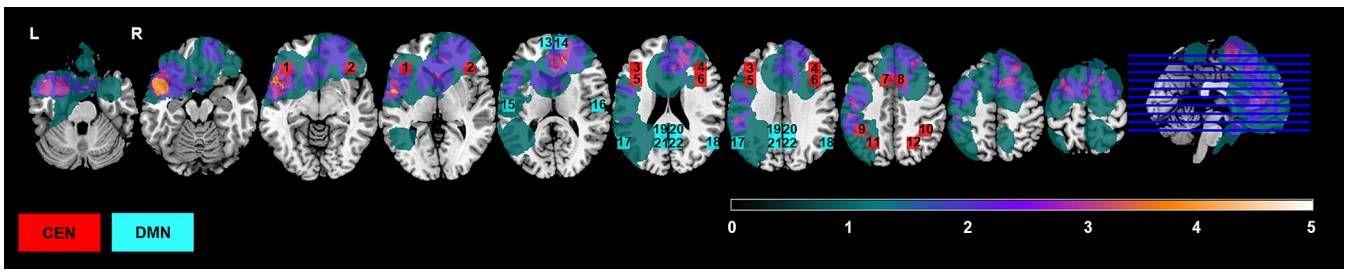

FIGURE 1 The distribution of tumour localization is presented here for meningioma patients ($n = 23$). The colour scale shows overlap between tumours (minimal: dark green, maximal: white). Additionally, selected regions of interest (ROIs) are indicated. ROIs belonging to the central executive network (CEN, red) and the default mode network (DMN, cyan) are superimposed on the tumour distribution. The numbers correspond to the numbers indicated in Table 1, where further characteristics of the individual ROIs can be found.

2.7 | Statistical analyses

In order to evaluate cognitive performance of meningioma patients outside the scanner, PRE and POST raw neuropsychological test scores were converted to socio-demographically adjusted *z*-scores based on a Dutch normative sample (Rijnen et al., 2020). The POST test scores were additionally corrected for practice effects

based on the same normative sample (Rijnen et al., 2020). To examine whether cognitive functioning of patients deviated from normal, the mean adjusted *z*-scores for each neuropsychological test were compared with the normative values using a one-tailed one-sample *z*-test (mean = 0, SD = 1) for PRE and POST respectively. Subsequently, two-tailed paired-sample *t*-tests were conducted on these adjusted *z*-scores, to investigate differences in cognitive performance between PRE and POST for each neuropsychological test separately.

In order to evaluate the in-scanner task performance of meningioma patients, the accuracy was calculated as incorrect responses as percentage of all responses (combining missed targets and false alarms) for 0B and 2B separately. Analogous to the fMRI analysis, we calculated the increase in percent incorrect responses between 0B and 2B for PRE and POST separately. Subsequently, we tested for performance differences between PRE and POST by conducting a two-tailed paired sample *t*-test.

Brain activity levels during 0B are subtracted from brain activity levels during 2B in CEN as well as DMN, such that the analyses focus on brain activity specifically related to verbal WM. Subsequently, we conducted separate two-tailed paired-sample *t*-tests for CEN and DMN activity levels to investigate differences between PRE and POST. In order to investigate whether activity patterns within CEN and DMN differ between PRE and POST, post hoc analysis included paired sample *t*-tests for each individual ROI separately. Bonferroni correction was applied in order to correct for multiple comparisons. All statistical analyses were performed using SPSS 24.

3 | RESULTS

3.1 | Patient characteristics

In total, 32 meningioma patients were scanned preoperatively, of which 27 patients were also scanned 3 months after surgery. Reasons for dropout were death ($n = 1$), fMRI experienced as too tiring ($n = 2$), or unexpected claustrophobia during the postoperative scanning session ($n = 2$). Since this study focusses on the comparison between PRE and POST brain activity, these five patients were excluded from further analyses. Additionally, neuropsychological assessment was not available for two patients either before or after surgery, and these patients were therefore also excluded from further analyses. Furthermore, two patients were excluded due to technical issues during one of the fMRI scanning sessions.

Consequently, 23 meningioma patients were included in the final data analyses. Detailed socio-demographical characteristics and clinical characteristics of the meningioma patients can be found in Table 2 (see Table S1 for sociodemographic and clinical characteristics of the individual patients). The level of education was classified by the Dutch Verhage scale (Verhage, 1964). The seven categories were combined into three ordinal categories: low (Verhage 1–4), middle (Verhage 5), and high educational level (Verhage 6 and 7) (cf., Rijnen et al., 2020). The distribution of tumour localization for the meningioma patients can be found in Figure 1.

TABLE 2 Sociodemographic and clinical characteristics.

Variable	MG ($N = 23$)
Age, year, mean ± SD (range)	53.78 ± 11.1 (32–73)
Sex, male/female	6 (26)/17 (74)
Education	
Low (Verhage 1–4)	5 (22)
Medium (Verhage 5)	8 (35)
High (Verhage 6 and 7)	10 (43)
Handedness, left/right	1 (4)/22 (96)
Histopathological diagnosis	
WHO grade I	21 (91)
WHO grade II, atypical	2 (9)
Tumour hemisphere, left/right/both	12 (52)/9 (39)/2 (9)
Tumour location	
Frontal	13 (56)
Temporal	2 (9)
Parietal	2 (9)
Frontotemporal	3 (13)
Temporoparietal	1 (4)
Paracentral lobule	2 (9)
Tumour volume (cm^3), mean (range)	47.63 (3.45–102.06)
Oedema, yes/no	9 (39)/14 (61)
Midline shift, yes/no/n.a.	7 (30)/14 (61)/2 (9)
Clinical debut (N)[a]	
Epileptic seizure	7
Headache	5
Sensorimotor deficits	3
Cognitive deficits	5
Vision problems	4
Coincidental	3
Time between PRE and POST, months, mean ± SD (range)	2.9 ± 0.3 (2.5–3.7)

Note: Sociodemographic and clinical characteristics of the MG patients. Values are indicated as number of subjects (%) unless indicated otherwise.
[a]Total N exceeds total number of patients, because the clinical debut of some patients included multiple problems.
Abbreviations: MG, meningioma; n.a., not applicable; POST, postoperative timepoint; PRE, preoperative timepoint; WHO, World Health Organization.

3.2 | Neuropsychological assessment

The neuropsychological results for SDC, SAT and stroop III tests to evaluate the cognitive abilities of the meningioma patients outside the scanner are presented in Figure 2. Statistical analyses for the SAT were based on 22 out of 23 patients, as one patient had an invalid POST test score for this test. The neuropsychological assessor scored this test as invalid because the patient stopped to perform the task after a few errors. Neuropsychological performance of the meningioma patients was significantly lower compared with the normative sample for all three tests, PRE (SDC: $z = -4.08$, $p < 0.001$; SAT: $z = -2.73$, $p = 0.006$; Stroop III: $z = -5.71$, $p < 0.001$) as well as POST (SDC: $z = -3.60$, $p < 0.001$; SAT: $z = -3.33$, $p = 0.001$; Stroop III: $z = -5.04$, $p < 0.001$). A direct comparison showed that cognitive performance of meningioma patients outside the scanner did not significantly differ between PRE and POST for all three neuropsychological tests (SDC: $t(22) = 0.64$, $p = 0.53$; SAT: $t(21) = -0.65$, $p = 0.52$; STROOP III: $t(22) = 0.42$, $p = 0.68$) (Figure 2).

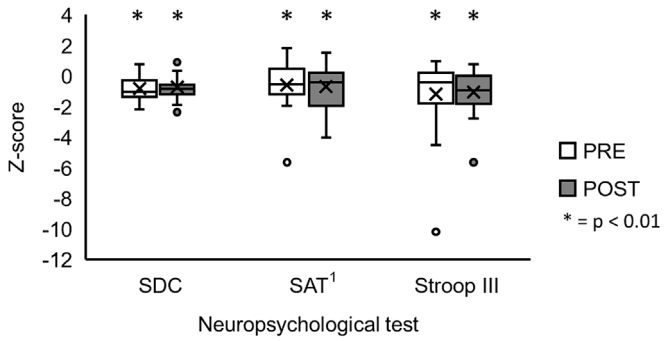

FIGURE 2 Boxplots of the z-scores for each of three neuropsychological tests are shown, preoperatively (PRE, white) as well as postoperatively (POST, grey). [1]$N = 22$, due to one invalid postoperative test score. The asterix (*) indicates that the neuropsychological performance of the meningioma patients was significantly lower compared with the normative sample.

3.3 | In-scanner task performance

In-scanner task performance results are presented in Figure 3a. The increase of incorrect responses between 0B and 2B was 14.4% ± 1.5 (mean ± SEM) for PRE, and 11.7% ± 1.8 for POST. Statistical analysis showed no differences in fMRI task performance between PRE and POST ($t(22) = -1.63$, $p = 0.12$).

3.4 | ROI analysis

WM brain activity patterns in CEN and DMN (difference between 2B and 0B) are presented in Figure 4 for PRE and POST separately. Combining all patients, 8.7% of all ROIs within the CEN and 3.9% of all ROIs within DMN showed some tumour overlap and were therefore excluded from further analyses. Detailed results of the ROI analyses are presented in Figures 3b, 5 and Table 3.

ROI analyses showed no significant PRE-POST differences in brain activity levels in CEN ($t(22) = 0.22$, $p = 0.83$), nor DMN ($t(22) = -1.30$, $p = 0.21$; Figure 3b). Post hoc analysis revealed that the brain activity levels of the individual ROIs within CEN and DMN also did not differ between PRE and POST (all p-values > 0.05, Table 3 and Figure 5).

4 | DISCUSSION

Main goal of this study was to measure effects of tumour resection on cognitive brain function in meningioma

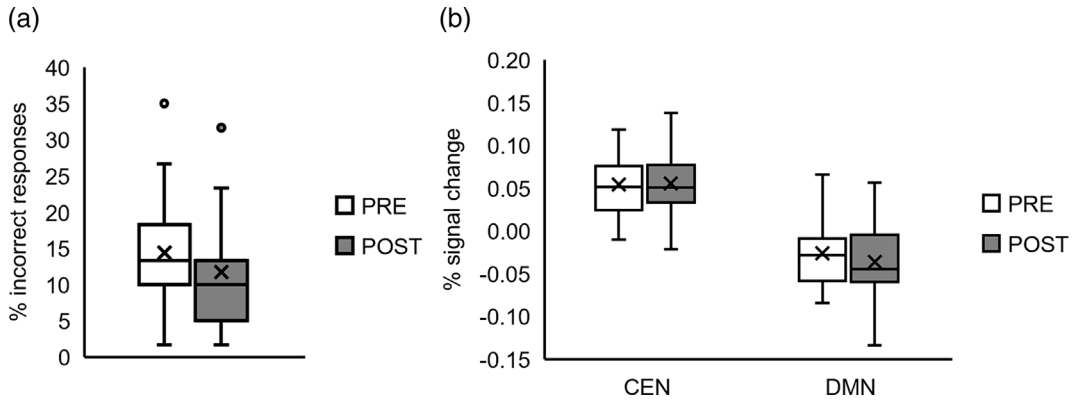

FIGURE 3 Functional MRI results of the meningioma (MG) patients before (PRE, white) and 3 months after surgery (POST, grey). The contrast between the 2-back and 0-back task condition is presented here. (a) In-scanner task performance, (b) signal change within the central executive network (CEN) and the default mode network (DMN).

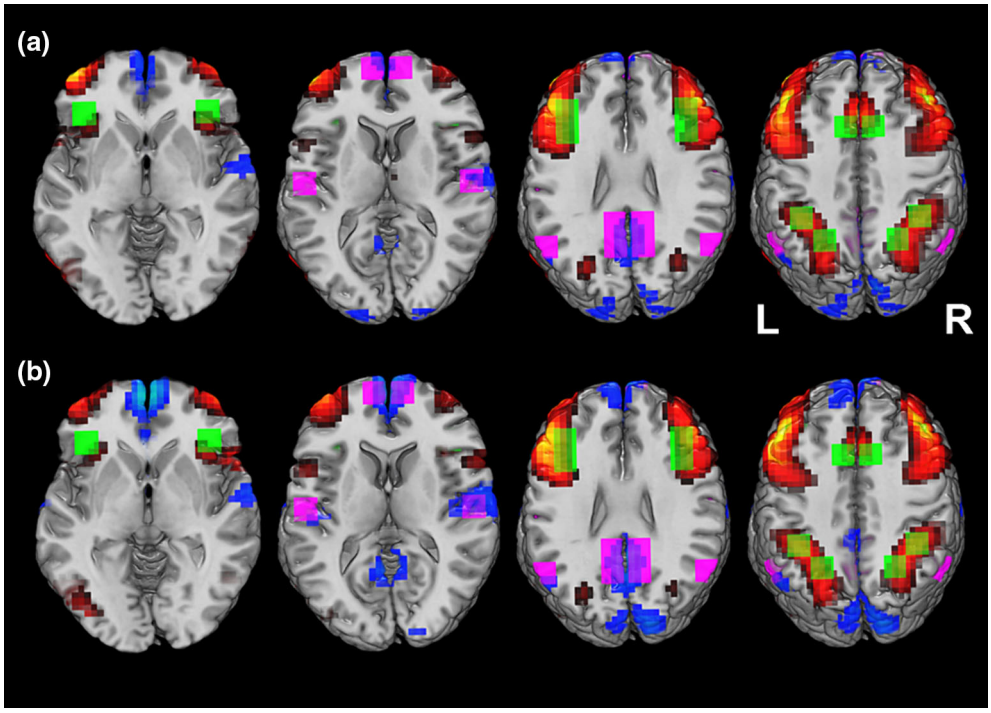

FIGURE 4 Illustration of preoperative and postoperative brain activity patterns induced by the N-back task for meningioma patients (PRE, upper panel; POST, lower panel). Contrast between the 2-back and 0-back task condition is presented here. Voxels in which brain activity showed a positive signal change of ≥0.04% are indicated in red, whereas voxels in which the brain activity showed a negative signal change of ≥0.04% are indicated in blue. Regions of interest (ROIs) are superimposed on the brain activity patterns (CEN, indicated in green; DMN, indicated in purple). The figure confirms that the ROIs are located in regions that respond to the task. Note that the brain activity patterns are quite similar between both timepoints within CEN as well as DMN.

patients. We specifically aimed to evaluate whether surgery affects cognitive brain activity in such a manner that it may mask possible underlying changes in cognitive functioning that were otherwise overlooked by traditional neuropsychological tests. For this purpose, we compared brain activity in CEN and DMN during a verbal WM task, just before and 3 months after surgery in combination with a set of neuropsychological tests.

The neuropsychological evaluation of the meningioma patients indicated that the patients suffered from cognitive deficits before surgery. There was no significant improvement 3 months after surgery. These findings are in line with several neuropsychological studies (Dijkstra et al., 2009; Meskal et al., 2015; Rijnen et al., 2019; van der Vossen et al., 2014). Rijnen et al. (2019) reported that although cognitive functioning did improve slightly over time, cognitive deficits were still present even at 12 months after surgery. FMRI task performance also did not change significantly over time.

The main finding of our study is that there seem no short-term (3 months) changes in CEN and DMN activity after surgery of a meningioma. Activity in each individual ROI also did not differ between both timepoints. We assume that possible compensatory processes in the brain would have been reflected in different brain activity levels before and after surgery. Our results therefore indicate that the lack of cognitive improvement after surgery, measured by neuropsychological tests, is not the result of compensatory processes in the brain that involve these networks. Also our fMRI results indicate that cognitive deficits that are already present before surgery appear to be persistent, even after resective surgery and a considerable recovery period.

Taken together, these results indicate that resective surgery has little impact, either positive or negative, on cognitive functioning in the first few months after surgery. Considering the slow growth of meningiomas it may have taken a considerable long period for the symptoms to develop and for the tumour to impact cognitive brain activity. Therefore, a longer period might also be needed for recovery processes in the brain. Possibly, alterations in brain activity levels still occur after longer periods, which may accompany cognitive improvements. In future research, fMRI studies with a longer follow-up time would be required to reveal any long term effects of surgery.

The results could reflect a combined cognitive relief from intracranial pressure reduction, and cognitive

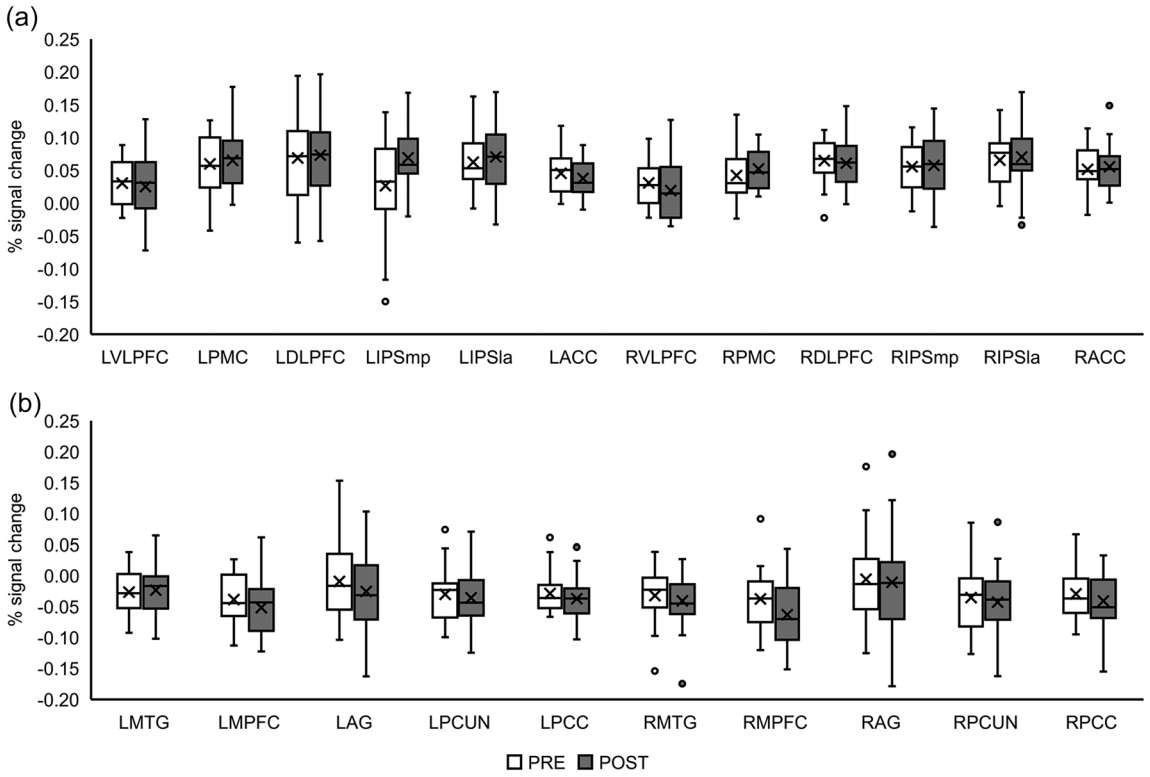

FIGURE 5 Boxplots of the brain activity levels for each individual region of interest (ROI) within the central executive network (CEN, a) and default mode network (DMN, b) are shown. The contrast between the 2-back and the 0-back condition is presented here. Post-hoc analyses showed no differences between preoperative and postoperative brain activity patterns (PRE, white and POST, grey) within CEN or DMN, as we found no significant differences between PRE and POST for any of the ROIs. Abbreviations of the ROIs are determined in Table 1.

decline due to surgical side effect, which cannot be disentangled in our study. Our findings do suggest that the possible surgical side effects did not pose a significant risk for (further) cognitive decline.

Investigating preoperative and postoperative differences in cognitive brain activity at a group level is an important and necessary first step towards a better understanding of the overall effects of surgery on cognitive functioning. However, ultimately one would also want to be able to evaluate the effect of surgery on cognitive brain activity for the individual patient. Possibly, our group-level results may mask individual improvement or decline. To be able to understand the effects of surgery for the individual patient, it is necessary to collect cognitive fMRI data on a large scale. In future research, individual analyses can then be performed in larger patient populations to better understand the influence of specific characteristics on cognitive brain activity (e.g., tumour location, tumour size, and presence of epilepsy).

Studies that have previously investigated the effect of surgery on cognitive brain activity in meningioma patients are unfortunately scarce. In one of the few available studies, van Nieuwenhuizen et al. (2018) reported reduced WM-capacity in meningioma patients after surgery compared with healthy controls, whereby lower WM performance was accompanied by lower DMN connectivity (van Nieuwenhuizen et al., 2018). A few presurgical fMRI studies have also associated reduced deactivation levels in the DMN with cognitive deficits and levels of fatigue in brain tumour patients (de Dreu et al., 2020; Schouwenaars et al., 2021). These results suggest that the DMN plays an important role in cognitive problems that meningioma patients encounter before as well as after surgery.

Clinical decision making is still predominantly based on classic neurological concepts, and focusses on assessment of sensorimotor, language and visual function. As formal neuropsychological tests are not part of routine clinical workup in most clinics, the number of patients with cognitive impairments is underestimated (Meskal et al., 2015; Rijnen et al., 2019). This is unfortunate, as cognitive functioning appears to require a long period to recover once cognitive deficits are already present preoperatively (Meskal et al., 2016; Rijnen et al., 2019). These long-term cognitive deficits can have a great impact on the socio-professional quality of life of patients (Benz et al., 2018; Mitchell et al., 2010; van Nieuwenhuizen et al., 2013; Waagemans et al., 2011; Zamanipoor

TABLE 3 Statistical results post hoc analyses individual regions of interest.

ROI	*df*	*t*	*p*
CEN			
LVLPFC	19	−0.61	0.55
RVLPFC	20	−1.07	0.30
LPMC	20	0.47	0.64
RPMC	21	1.04	0.31
LDLPFC	21	0.39	0.70
RDLPFC	19	−0.39	0.70
LIPSmp	21	0.69	0.50
RIPSmp	21	0.21	0.84
LIPSla	20	0.72	0.48
RIPSla	22	0.54	0.60
LACC	19	−1.37	0.19
RACC	17	0.57	0.59
DMN			
LMTG	21	0.30	0.77
RMTG	22	−0.86	0.40
LMPFC	20	−1.00	0.33
RMPFC	19	−1.65	0.12
LAG	21	−1.17	0.26
RAG	22	−0.51	0.61
LPCUN	21	−0.59	0.56
RPCUN	22	−0.65	0.52
LPCC	21	−1.27	0.22
RPCC	22	−1.26	0.22

Note: Post hoc analyses included paired sample *t*-test for all individual ROIs separately to investigate differences between preoperative and postoperative brain activity patterns within CEN and DMN. Abbreviations of the individual ROIs can be found in Table 1.

Abbreviations: CEN, central executive network; df, degrees of freedom; DMN, default mode network; ROI, region of interest.

Najafabadi et al., 2017). The persistent cognitive problems raise the question whether cognitive functioning should become a more prominent factor in clinical decision making. One may expect that as the tumour grows, the mass effect will be increased, leading to deterioration of cognitive function. A study by van Nieuwenhuizen et al. (2019) showed that larger preoperative mass effects caused by oedema and the tumour itself were associated with lower postoperative cognitive performance (van Nieuwenhuizen et al., 2019). Our study shows that surgery itself seems to have little impact on cognitive functioning as well as cognitive brain activity. One may speculate that surgery does at least successfully stop further cognitive decline, and that it should be considered in an earlier stage in order to reduce persistent cognitive deficits. The timing of surgery in relation to cognitive and functional outcome certainly needs attention in future studies.

Some limitations have to be taken into account when interpreting the results of this study. First, our inclusion criteria required 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 therefore excluded. Of note, our sample consisted of only five patients whereby the tumour clinically presented with cognitive impairments. Hence, our results are likely an underestimation of the problems that occur in the population of meningioma patients. Therefore, the effect of surgery on cognitive brain activity may be different in the more severely affected patients that are not included in our cohort. Second, although postoperative neuropsychological test scores were corrected for practice effects, we did not compare our meningioma patient group with a control group without surgery in our fMRI analyses. Therefore, we cannot clearly distinguish between effects of surgery and possible test–retest effects. However, to minimize practice effects, patients practiced the verbal WM task extensively on a laptop prior to each fMRI scan session. Therefore, the impact of test–retest effects on our main conclusions will be minimal. Third, two patients that were included in this study had an atypical meningioma and received additional radiotherapy. For these two patients, cognitive effects may not only be influenced by surgery, but also by the radiotherapy treatment. However, reanalysis of the data without these two patients did not affect our conclusions. Therefore, we are confident that the additional radiotherapy treatment of these two patients did not influence our main conclusions regarding cognitive effects of surgery. Fourth, in this study of the effect of surgery on cognitive functioning, we focused on changes in brain activity and neuropsychological test scores involving working memory. Possible effects of surgery on behavioural or personality changes and the impact on social reintegration were not considered in this study. Therefore, the role of tumour resection in the overall context of the disease may be underestimated and should be further elucidated in future research.

5 | CONCLUSION

Our study indicates that surgery does not significantly affect activity in cognitive brain networks in meningioma patients the first few months after surgery. Therefore, the lack of cognitive improvement after surgery is likely not the result of compensatory processes in the brain that involve these networks. Cognitive deficits that are already

present before surgery appear to be persistent after surgery and a considerable recovery period. Our study shows potential leads that comprehensive cognitive evaluation (i.e., functional imaging maps plus neuropsychological testing) can be of added value so that cognitive functioning may become a more prominent factor in clinical decision making.

AUTHOR CONTRIBUTIONS

Irena Schouwenaars: Conceptualization; formal analysis; investigation; methodology; project administration; software; visualization; writing - original draft. **Miek de Dreu:** Conceptualization; investigation; methodology; project administration; writing - review and editing. **Geert-Jan M Rutten:** Conceptualization; funding acquisition; supervision; writing - review and editing. **Nick F Ramsey:** Conceptualization; funding acquisition; methodology; supervision; writing - review and editing. **Johan Martijn Jansma:** Conceptualization; funding acquisition; methodology; software; supervision; writing - review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16378.

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