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Working Memory Functioning and Intraoperative Testing in Glioma Patients Undergoing Awake Brain Surgery

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Abstract

Objectives: The current study was aimed at investigating working memory (WM) functioning in glioma patients undergoing awake brain surgery. Three main purposes were addressed: 1) to test the validity of the digit span as a WM test for intraoperative purposes, 2) to examine the relationship between WM and overall cognitive functioning, and 3) to evaluate the effect of intraoperative WM testing on postoperative WM functioning.

Methods: A validation study was carried out in 20 healthy participants to examine the validity of the digit span, which is a feasible WM task for awake brain surgery. Subsequently, a multiple regression analysis was performed to evaluate the relationship between WM and overall cognitive functioning in a clinical sample of 81 glioma patients undergoing awake brain surgery. In addition, differences in pre- and postoperative WM performance were examined. Patients who were intraoperatively tested for WM were compared to patients who were not.

Results: Validity of the digit span backward was supported. In the patient sample, no significant relationship between WM and overall cognitive functioning was demonstrated. No decline in WM performance was found following awake brain surgery, independent of intraoperative WM testing.

Conclusion: The current study suggests that WM performance is a not a reliable predictor of overall cognitive functioning in glioma patients. Furthermore, it suggests that WM functioning remains stable after intraoperative cognitive monitoring. However, it is not yet possible to provide solid conclusions on the protective value of intraoperative WM testing, since heterogeneity in the group of glioma patients may have masked differences between subgroups. The main implication of these results is that WM testing is not necessarily beneficial for all patients undergoing awake brain surgery, but when an individual patient is at risk for WM impairment, the digit span backward is a valid task for intraoperative purposes.

Keywords: awake brain surgery, glioma patients, electrocortical stimulation mapping, working memory, digit span

Working Memory Functioning and Intraoperative Testing in Glioma Patients Undergoing Awake Brain Surgery

Awake brain surgery is a method that allows a maximum degree of brain tumour resection or debulking while preserving cognitive functions, in order to maintain the patient's quality of life (Coello et al., 2013). During this procedure, electrocortical stimulation mapping and neuropsychological assessment are performed simultaneously in order to identify eloquent areas for cognitive functions. Although detailed knowledge on functional anatomy is available, interindividual variability in anatomy requires mapping of specific functional sites (Ojemann, 2003; Ribas, 2011). Presently, brain mapping has mainly been focused on language and motor functions (Duffau, 2011). A few studies have recently been published on intraoperative monitoring of non-linguistic cognitive functions (Duffau, 2010; Szelényi et al., 2010; Wager et al., 2013). However, as this body of research is limited, there is a lack of empirical research into tests for other cognitive domains during awake brain surgery.

One of the higher cognitive functions that could contribute to the prevention of postoperative impairments is working memory (WM; Coello et al., 2013; Kho et al., 2007). WM is responsible for maintaining and manipulating information that is consciously accessed (Baddeley, 2012; Conway et al., 2005). Moreover, WM is highly related to general fluid intelligence (*gf;* Colom et al., 2015; Conway, Kane, & Engle, 2003; Salthouse & Pink, 2008; Shipstead et al., 2014) and several cognitive functions, such as executive functioning (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010; Miyake et al., 2000), language comprehension (Daneman & Merikle, 1996), and problem solving (Kyllonen & Christal, 1990), and can be considered a prerequisite for effective functioning in daily life (Björkdahl, Åkerlund, Svensson, & Esbjörnsson, 2013). Hence, monitoring WM can be considered crucial for the preservation of cognitive functioning and quality of life.

In spite of the potential importance of WM for higher cognitive functioning, no studies on intraoperative assessment of WM in brain tumour patients have been conducted and only a few studies on pre- and postoperative WM functioning have been published. One case study reported on an epilepsy patient who suffered from WM impairments following resection of the dorsolateral prefrontal cortex (Kho et al., 2007). Another study demonstrated an improvement in verbal WM functioning three months after surgery in low grade glioma patients, but further studies on pre- and postoperative WM testing are scarce (Teixidor et al., 2007). Therefore, it is essential to examine WM functioning in glioma patients and to identify a neuropsychological test for WM that can be used before, during and after awake brain surgery.

Before proceeding to the discussion on WM testing, it is necessary to clearly define WM. The precise definition of WM is often problematic, as there is disagreement on how it should be

conceptualized (Miyake & Shah, 1999). Several approaches have been proposed, which can roughly be categorized as system models and state-based models (LaRocque, Lewis-Peacock, & Postle, 2014). Probably the most commonly used system model is Baddeley and Hitch's (1974) multi-component model of WM. According to this model, WM consists of four independent subsystems that operate independently: a storage system for verbal information, a storage system for visuospatial information, a central executive system that coordinates and manipulates information, and an episodic buffer that links WM to long term memory (Baddeley, 2012). On the other hand, state-based models posit that WM is a unitary system in which the focus of attention can activate information from several modalities in long-term memory (Cowan, 1999; Oberauer, 2002).

Although there is a lack of consensus on how WM can most accurately be conceptualized, some authors have attempted to adopt a neutral position by integrating both approaches. For example, Conway and colleagues (2005) view WM as a multicomponent system, in which a clear distinction exists between short-term memory components for storage of domain-specific – i.e. verbal and visuospatial - information and a WM capacity component for domain-general executive attention. Similarly, several authors have used latent variable analysis that resulted in an underlying mechanism that has been labelled 'executive attention', which accounts for the processing rather than the storage component of WM and is domain-general rather than domain-specific (Kane et al., 2004; Miyake et al., 2000). It is predominantly this domain-general executive component that is highly related to other cognitive functions (Kane et al., 2004). For this reason, mainly the executive component of WM is assumed to be essential in everyday functioning. Therefore, it is possibly the most useful component for intraoperative testing.

Considering the most important purpose of intraoperative WM testing - preservation of cognitive functioning in patients' daily life – the aim of this study is three-fold. The first aim is to identify the most valid and feasible measure of WM functioning in glioma patients. For this purpose, the feasibility of several measures of WM performance will be evaluated based on literature. Subsequently, the validity of the most feasible measure will be evaluated in a study with healthy participants.

The second aim is to examine the relationship between WM performance and overall cognitive functioning. Since strong relationships between WM and several abovementioned cognitive functions exist, WM measures can possibly be used as a measure of overall cognitive functioning. The expectation is that WM performance correlates with performance on other tasks. More specifically, a decrease in WM performance is expected to predict diminished performance in overall cognitive functioning.

The final aim is to evaluate the protective value of intraoperative WM testing. The expectation is that the level of WM performance will remain stable when WM is monitored intraoperatively, as intraoperative impairments as a consequence of electrocortical stimulation should lead to cessation of the resection and thereby to preservation of this cognitive function.

Part I: Validity of WM tests

The aim of the first part of the study is to determine the validity of a feasible WM test that can be used during awake brain surgery. Since WM is a complex system, involving both domain-specific storage and rehearsal processes as well as domain-general executive functioning, it is a challenge to identify a valid task that captures all components of WM. The most ecologically valid tasks for WM are complex span tasks, which can be described as dual tasks that assess both the storage and manipulation component (Conway et al., 2005). In a dual task, two different tasks are performed alternately. Thus, complex span tasks require storing and processing of information that is used for continuous mental activity, resembling WM function in everyday life. However, intraoperative testing requires cognitive testing methods that can be conducted in a very brief time interval of a few seconds (Duffau, 2011). This requirement puts a restraint on the selection of tests; regarding WM testing, it does not allow the application of the more valid complex WM span tests, as these are computerized tasks with a total duration of at least 20 minutes (Foster et al., 2014; Oswald, McAbee, Redick, & Hambrick, 2015). Alternatively, simple WM span tests can be used, because these tests are feasible within the time limits of electrocortical stimulation and can be performed per item. One of the most commonly used simple WM span tasks is the digit span (DS), a subtest of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Wechsler, 2008).

The DS requires a participant to memorize a series of digit numbers. The digits are presented in three conditions: forward, backward and sequencing. It is assumed that the forward condition mainly requires short-term retention of verbal information, assessing only verbal WM, whereas the backward condition also requires active manipulation of the information so that the central executive is involved as well. Since the sequencing condition was not included in earlier versions of the WAIS, research into this subtest is limited. It may be speculated that the sequencing condition taps into the central executive, but to a smaller extent than the backward condition, as sequencing numbers is a more structured and automatic process than reversing numbers. However, this assumption should be investigated further. Factor analyses and studies in clinical samples indicate that the forward and backward conditions measure different processes (Hale, Hoeppner, & Fiorello, 2002; Reynolds, 1997; Wilde, Strauss, & Tulsky, 2004). On the contrary, other studies fail to demonstrate differences between the forward and backward condition, suggesting that both conditions measure the same cognitive process (Bowden, Petrauskas, Bardenhagen, Meade, & Simpson, 2012; Hester, Kinsella, & Ong, 2004). Functional neuroimaging studies provide a more balanced view by suggesting that the forward and backward condition activate overlapping as well as unique portions of the prefrontal cortex (Duncan & Owen, 2000; Gerton et al., 2004; Owen, Lee, &

Williams, 2000). Hence, the DS backward can be considered a potentially useful measure for intraoperative assessment of the executive component of WM.

For the purpose of this validation study, the validity of the DS will be assessed by collecting evidence from several sources. First, convergent construct validity will be tested using a complex span task as a reference. Secondly, criterion-related validity will be tested using a measure of general fluid intelligence (*gf*), as the relationship between WM and *gf* is robust (Colom et al., 2015; Conway, Kane, & Engle, 2003; Salthouse & Pink, 2008; Shipstead et al., 2014). Lastly, since the conceptualisation of WM may have implications for the selection of intraoperative tests, the assumption that the complex span tasks are domain-general measures of WM will be tested. For this purpose, the relationship between the complex span task and both a verbal and non-verbal WM task will be investigated.

Method

Participants

A sample of 20 healthy participants was recruited by means of convenience sampling. The intention was to collect a sample with demographic characteristics comparable to the patient sample that was included for the analyses on WM in glioma patients. The sample of healthy participants consisted of 9 males and 11 females and the mean age was 46.3 years (*SD* = 17.6, range = 21-81). Participants were included if they had no history of cognitive impairment, (neurological) condition of influence on cognitive functioning or psychiatric disorder.

Materials and Procedure

Four tasks were administered: 1) the Digit Span of the fourth edition of the WAIS-IV, Dutch version, 2) the Operation Span, which is a complex WM test, which was used as a reference for convergent construct validity 3) the Corsi Block-Tapping Task, a visuospatial WM task that was used for convergent construct validity, and 4) the short version of the Raven Advanced Progressive Matrices as a reference to test criterion-related validity of all WM tests. The total duration of the tasks was approximately 30 minutes for each participant.

Digit Span (DS). The DS consists of three subtests: forward, backward and sequencing. In each condition, the subject is read a sequence of numbers. For the forward condition, the subject recalls the numbers in the same order. For the backward condition, the subject recalls the numbers in reverse order. For the sequencing condition, the subject recalls the numbers in ascending order. Each subtest contains eight trials. The number of digits increases in each trial, starting with two digits and ascending to a maximum of eight digits. One trial consists of two items of the same number of digits. Each item is given a score 0 (*incorrect*) or 1 (*correct*). Thus, the score for each trial can be 0, 1, or 2. If at least one of the items in a trial is performed correctly, the examiner precedes to the next trial. If both items in a trial are performed

incorrectly, the task is discontinued. The total score of de DS is the total number of items correct. The span score is the length of the last item performed correctly. Both the total score and the span score are obtained for the forward and backward condition separately (Wechsler, 2008).

In the current study, the scoring procedure was different from the official procedure. Instead of using the maximum span and the total correctly recalled items, a scoring procedure similar to the scoring of the OSpan was used, which is the sum of the length of all correctly recalled items. In this way, data were more comparable.

Operation Span (Ospan). The OSpan is a computerized task in which the subject is alternately shown a) to-be-remembered items and b) distractor items. The to-be-remembered items are letters and the distractor task consists of math problems (see Figure 1). First, a math problem is solved, then a letter is shown, another math problem is solved, and another letter is shown. This sequence is repeated three to seven times to increase the memory span. After each sequence, the subject is asked to recall the letters in the correct order by selecting them in a grid of letters. The partial score, which is the most sensitive method of scoring for complex tasks (Conway et al., 2005), is calculated by summing the length of all correctly recalled sequences of letters (Foster et al., 2014).

The shortened version of the OSpan has the most optimal psychometric qualities of the different types of complex span tasks. The internal consistency is high ($\alpha = 0.69$) and the test-retest reliability is high as well ($r = .83$). Furthermore, the correlation with measures of *gf* is comparable to the correlation of the original OSpan with *gf*, which respectively are 0.523 and 0.566 (Foster et al., 2014). Thus, reliability and construct validity can be considered good.

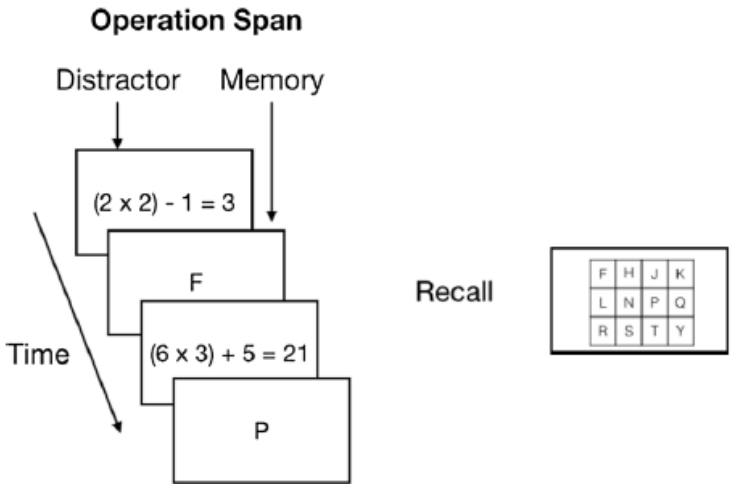

Figure 1. Example screens of the OSpan distractor items, to-be-remembered items and recall screen. From Foster et al. (2014).

Corsi Block-Tapping Task (Corsi task). The Corsi task is another simple span task, which is used to measure non-verbal WM. A board with nine blocks at fixed locations is shown to the subject. Similar to the DS, the Corsi task consists of a forward and backward condition. A pattern of an ascending number of locations is shown, which the subject is asked to memorize and repeat. In the forward condition, the subject is asked to tap the pattern in the same order. In the backward condition, the subject is asked to tap the pattern in reverse (Corsi, 1972).

In order to obtain comparable data, the scoring procedure was adapted to the procedure of the OSpan, which is the sum of the length of all correctly recalled items.

Raven's Advanced Progressive Matrices, short version (RAPM). The RAPM is a widely used measure of *gf*. The short version consists of 12 problems in which the subject is asked to complete a pattern by choosing one out of five options (Arthur & Day, 1994). The RAPM has been used to demonstrate the relationship between WM and *gf* (Redick et al., 2012). Therefore, this task was used as to examine criterion-related validity of the OSpan, DS and Corsi task.

Analyses

In order to examine convergent construct validity of the DS, the relationship between the several WM measures was examined. Therefore, as a first analysis, a correlation analysis was conducted for the maximum span on each subtest of the DS with the partial score of the OSpan. Pearson correlations were used if the data met the assumptions of parametric testing; otherwise, Spearman correlations were used. There is no specific minimum coefficient size that is acceptable for validity coefficients (Reynolds & Livingston, 2012). According to the Commissie Testaangelegenheden Nederland (COTAN), the official organization for psychometric test research in The Netherlands, construct validity is good when there is a significant correlation between tests that measure the same construct (Evers, Lucassen, Meijer, & Sijtsma, 2010). This criterion was used in the current study. In addition, effect sizes were calculated using Cohen's *d*, and interpreted according to Cohen (1988), who suggests that an effect size of .20 or lower can be considered small, .50 is medium, and .80 or higher is a large effect.

Secondly, in order to examine criterion-related validity of the OSpan, a correlation was calculated for the RAPM with the OSpan. This correlation is expected to be similar to the previous findings of Foster et al. (2014). In addition, the correlations between RAPM and the subtests of both the DS and Corsi task were computed. Significance of the correlation coefficients was used as a criterion to support criterion-related validity.

Lastly, in order to test the hypothesis that the OSpan is a domain-general measure of WM (Conway et al., 2005), a correlation analysis was conducted with the Corsi task and the OSpan. The correlation is expected to be comparable to the correlation between DS and OSpan.

Results

Three analyses were conducted in the current validation study. First, convergent construct validity of the DS was examined. For this purpose, the correlation between each subtest of the DS with the OSpan was calculated. The assumption of normality was met only for the forward span of the DS. Each of the other distributions was not normally distributed, as indicated by a significant Shapiro-Wilk test. Therefore, Spearman correlations instead of Pearson correlations were calculated.

The first correlation analysis demonstrated that the sum score of each of the subtests of the DS correlated significantly with the partial score of the OSpan. The highest correlation existed between the backward condition and the OSpan, $r = .77$, $p < .01$, with a medium effect size, $d = 0.59$. The second highest correlation existed between the forward condition and the OSpan, $r = .64$, $p < .01$, with a small effect size, $d = 0.41$. The smallest relationship existed between the sequencing condition and the OSpan, $r = .54$, $p < .05$, with a small effect size $d = 0.29$. These significant correlations suggest that the convergent construct validity of all subtests of the DS is satisfactory. Based on the effect sizes found in this first analysis, the backward condition can be considered the most valid measure of WM.

Secondly, in order to examine criterion-related validity, the relationship between *gf* and each WM measure was examined. The correlation between the OSpan and the RAPM was significant, $r = .54$, $p < .05$, $d = 0.29$. The value of the correlation found in the current study is comparable to previous findings discussed above, which ranged from 0.523 to 0.566 (Foster et al., 2014), supporting the criterion-related validity of the OSpan. In order to examine the criterion-related validity of the DS and Corsi, the relationship between those tests and the RAPM was calculated as well. A significant correlation between the backward condition of the DS and RAPM, $r = .46$, $p < .05$, $d = 0.21$. No other significant relationships were found in the current study, indicating that the criterion-related validity of the backward span is satisfactory, but other DS subtests and the Corsi task should be considered less valid measures of WM.

Lastly, the Spearman correlation between the Corsi and the OSpan was calculated. The correlation between the Corsi backward condition and the OSpan was significant, $r = .53$, $p < .05$, $d = 0.28$. No significant relationship was found between the Corsi forward condition and the OSpan, $r = .39$, $p = .08$. Thus, the Corsi backward condition can be considered a valid measure of WM, whereas the Corsi forward condition appears to be less valid.

Discussion and conclusion

The most important finding of the current validation study is that all subtests of the DS are significantly related to a complex WM test, indicating that all subtests have a good convergent construct validity according to COTAN criteria. Importantly, the highest correlation

exists between the backward condition of the DS and the OSpan, suggesting that the backward condition is the most valid of the three subtests. Moreover, when the correlation with a measure of *gf* is used as a criterion, only the backward condition of the DS has satisfactory criterion-related validity. These findings both indicate that from the three subtests of the DS, the backward condition is the most valid measure of WM. Based on these results, the backward span can be recommended as WM test that can be used during awake brain surgery.

Another finding is that the relationship between the Corsi task and the OSpan is somewhat less strong than the relationship between the DS and the OSpan. Assuming that the Corsi measures nonverbal WM, whereas the DS measures verbal WM, this finding casts doubt on the assumption that the OSpan is a domain-general measure of WM postulated by Conway et al. (2005). Conversely, this finding could imply that the Corsi task is a less valid measure of WM, which has been suggested previously (Kessels, Van den Berg, Ruis, & Brands, 2008). An extensive discussion on the conceptualisation of WM is beyond the scope of the current validation study. Nevertheless, it can be considered a finding that is rather in favour of the domain-specific perspective. Discrepancies between verbal and nonverbal WM have widely been studied (Baddeley, 2012; Cowan et al., 2008; D'Esposito & Engle, 2014) and the current study contributes to this body of literature. Although the conceptualisation of WM remains inconclusive, it is an important question in the context of intraoperative testing. The decision to use one conceptualisation or the other has relevant implications: if the domain-specific perspective is used, selective impairment of verbal and nonverbal WM can be expected, requiring domain-specific tests.

In conclusion, the findings of the current validation study are in support of both the convergent construct validity and criterion-related validity of the DS backward condition, as evidenced by the strong relationship with other measures of WM and *gf*. Hence, the backward span can be recommended as an intraoperative WM test. However, since convergent construct validity is satisfactory for the forward and sequencing condition as well, these might be considered useful when the backward span is not feasible for the patient.

Part II: Working memory functioning in glioma patients

Method

Participants

All high grade glioma (HGG) and low grade glioma (LGG) patients undergoing awake brain surgery at University Medical Centre Utrecht (UMCU) in the period from January 2010 to June 2015 were included in this study. Patients were included in the analyses if 1) pre- and postoperative assessment data were available, and 2) the DS and at least one test of each cognitive domain from the protocol described below was completed both pre- and postoperatively. A total of 81 patients was included. This sample consisted of 57 males and 24 females. The mean age was 52.0 years (*SD* = 16.0, range 19-82). Level of education was recorded using a coding system from *0* (less than primary school) to *7* (university), which was transformed in years of education. Glioma-related characteristics are specified in Table 1.

Procedure for awake brain surgery

Preoperative neuropsychological examination. An extensive neuropsychological examination was carried out for each patient within one week preceding the awake surgery. A standard testing protocol was used in which different cognitive functions are covered (Table 2). Because the study was conducted in clinical setting, testing possibilities were limited in some cases, either due to time restrictions or due to patient-related factors such as fatigue. As a consequence, it was not possible to complete the full protocol in all patients.

The DS forward and backward were included in the standard protocol as a WM test. Since the WAIS-IV version was introduced in 2014, patients who were tested before this period performed the WAIS-III version. DS forward and backward span scoring procedures are equivalent in both versions; thus, comparability of the data was not affected.

Performance during preoperative neuropsychological examination served as a baseline for intraoperative testing. In addition to neuropsychological assessment, the neuropsychologist offered a thorough explanation of the awake brain surgery procedure.

Operative protocol and intraoperative testing. Patients were continuously awake during the surgical procedure, unless the patient's condition required an asleep-awake-asleep procedure. Local anaesthesia was given for craniotomy; additional analgesics were only used if necessary, minimizing effects of medication on cognition. Patients were monitored by the neuropsychologist during the cognitive testing procedure. Neuropsychological tasks were selected based on tumour location, self-reported symptoms, and cognitive performance at preoperative assessment. Before the neurosurgeon started electrocortical stimulation, the neuropsychologist obtained a baseline performance on all selected intraoperative tasks. Subsequently, selected tasks were performed during the electrocortical stimulation. Resection

of tumour tissue was continued until the patient showed functional impairment, as indicated by a consistently diminished performance on the neuropsychological tasks.

Postoperative testing. An extensive postoperative neuropsychological examination was conducted 3 months after surgery for HGG patients and 6 months after surgery for LGG patients. This examination covered the same tasks as during the pre-operative examination. However, since many patients are limited due to illness and effects of chemo- and/or radiotherapy, the protocol was only performed completely when the patient's condition sufficiently allowed extensive testing.

Analyses

Two main analyses were conducted. First, a hierarchical multiple regression analysis was conducted in order to examine the relationship between WM performance and overall cognitive functioning. The analysis was performed separately for preoperative and postoperative data. As a measure of overall cognitive functioning, a mean score composed of the test scores from the standard testing protocol. To obtain this mean score, the test scores were transformed into *z*-scores based on mean and standard deviation of the current sample. Due to the clinical considerations mentioned above, not all patients completed the full testing protocol. Although patients were only included if they completed at least one test from each cognitive domain, variability in the tests completed by each individual patient was inevitable. Therefore, a weighted mean was calculated for each patient by dividing the sum of *z*-scores by the number of tasks completed. This mean *z*-score was used as outcome variable in the multiple regression analysis. Age and years of education were included in the first block of predictors, as these factors are expected to influence overall cognitive performance substantially. Forward span and backward span were used as predictor variables in the second block. In both blocks, the enter method was used. In order to control for differences between patients with normally functioning WM and WM impairment, a mixed design analysis of variance (ANOVA) was performed with pre- and postoperative overall cognitive functioning as within subjects factor and level of WM functioning (normal, mild impairment, or severe impairment) as between subjects factor. Effect sizes were calculated using η^2, and interpreted according to Cohen (1988), who suggests that a value of 0.01 or lower can be considered small, 0.059 is medium, and 0.138 or higher is a large effect.

Secondly, pre- and postoperative WM performance was compared using a dependent samples *t*-test. Since the population of glioma patients is a heterogeneous group, additional analyses were performed to detect any differences between groups based on tumour location and intraoperative WM testing. In order to compare patients with different tumour locations, a mixed design ANOVA was performed with pre- and postoperative assessment as within subjects factor and tumour location (frontal, temporal, parietal, and other) as between subjects factor.

An additional analysis was performed to detect any differences between patients who were explicitly tested for WM intraoperatively and patients who were not. For this purpose, an independent samples *t*-test was performed.

Table 1.

Glioma characteristics: hemisphere, location, and type of tumour.

Hemisphere	**Tumour location**	**Type of tumour**			Total
		HGG	LGG	Other	
Left	Frontal	17	7	0	24
	Temporal	8	7	0	15
	Parietal	5	2	5	12
	Occipital	0	0	0	0
	Insular	2	0	0	2
	Other	3	0	1	4
Right	Frontal	6	1	1	8
	Temporal	0	2	0	2
	Parietal	5	1	0	6
	Occipital	0	0	0	0
	Insular	0	1	0	1
	Other	1	5	1	7
Total		47	26	8	81

Table 2.

Neuropsychological examination protocol (for all tasks, the Dutch version was used).

Cognitive domain	**Neuropsychological task(s)**
General cognitive functioning	Cognitive Screening Test
Language	Boston Naming Task (short version)
	Token Test (short version)
	Verbal fluency (phonologic and semantic)
Working memory	Digit span – WAIS III or WAIS IV
Memory	15 Words Test (equivalent of Rey Auditory Verbal Learing Test)
	Rey-Osterrieth Complex Figure - Recall
Perception	Judgement of Line Orientation
Speed of processing	Trail Making Task A
Attention	Trail Making Task B
Executive functions	Stroop Colour Word Task (DKEFS)
	Frontal Assessment Battery
	Tower test (DKEFS)
Visuoconstruction	Rey-Osterrieth Complex Figure - Copy

Results

In the current study, two main analyses were performed. The first analysis was aimed at examining the relationship between WM and overall cognitive functioning. Prior to analysing the results of the multiple regression equation, assumptions were evaluated. Assumptions of normality of residuals, linearity and homoscedasticity were met. In addition, there was no evidence of multicollinearity or outliers.

The regression coefficients for both analyses are specified in Table 3. Preoperative cognitive functioning could significantly be predicted by age and years of education, which accounted for 20% of variance in the mean *z*-score, $R^2 = 0.20$, adjusted $R^2 = 0.18$, $F(2, 78) = 3.30$, $p < .01$. Forward and backward span performance did not significantly account for additional variance, $\Delta R^2 = 0.02$, $\Delta F(2, 76) = 0.94$, $p = 0.39$. Postoperative functioning could significantly be predicted by age and education as well, in which 17% of variance in the mean *z*-score was covered, $R^2 = 0.17$, adjusted $R^2 = 0.15$, $F(2, 78) = 7.84$, $p < .01$. Forward and backward span performance did not significantly contribute to the model, $\Delta R^2 = 0.03$, $\Delta F(2, 76) = 1.57$, $p = .22$.

In order to detect differences in overall cognitive functioning between patients with normally functioning WM and WM impairment, a mixed design ANOVA was performed. The assumption of heterogeneity of variances was met. However, Mauchly's test indicated that the assumption of sphericity was violated. Therefore, the Huynh-Feldt correction was applied. The ANOVA indicated that pre- and postoperative overall cognitive functioning were not significantly different, $F(1, 78) = 0.08$, $p = .77$. Groups based on level of WM functioning approached significant differences in overall cognitive functioning, $F(2, 78) = 3.06$, $p = .053$. Although not statistically significant, the effect size was medium to large, $\eta^2 = 0.07$. No interaction between pre- and postoperative functioning and level of WM functioning was found, $F(2,78) = 1.28$, $p = .28$.

The second analysis was aimed at evaluating the protective value of intraoperative WM testing. For this purpose, the difference between pre- and postoperative performance on the forward and backward condition of the DS was examined. The initial purpose was to include intraoperative functioning as well; however, based on clinical and ethical considerations, WM was monitored during awake craniotomy in less than half of the patients. Moreover, the intraoperative scoring procedure was different from pre- and postoperative testing. Consequently, intraoperative data were not comparable with pre- and postoperative data. Therefore, the analysis was only conducted for pre- and postoperative functioning.

A two-tailed, dependent samples *t*-test with an alpha level of .05 demonstrated that there was no significant difference between performance on the forward span pre- ($M = 5.43$, $SD = 1.05$) and postoperatively ($M = 5.44$, $SD = 1.13$), $t(80) = -0.11$, $p = .92$. In contrast, performance

on the backward span did show a significant change from pre- (M = 4.02, SD = 1.36) to postoperative examination (M = 4.31, SD = 1.05), $t(80) = -2.20$, $p < .05$. The effect size was small, d = 0.24. The mean difference between pre- and postoperative examination was 0.29, indicating a subtle improvement in performance. Table 4 shows details of pre- and postoperative WM performances, and the percentage of patients who were classified as having WM impairment based on DS performance. Based on this analysis, it can be concluded that there was a small improvement in WM functioning for the total group.

In order to compare pre- and postoperative WM functioning in patients with different tumour locations, a mixed design ANOVA was performed. The assumption of heterogeneity of variances was met. Mauchly's test indicated that the assumption of sphericity was violated. Consequently, the Huynh-Feldt correction was applied. The ANOVA demonstrated a significant difference between pre- and postoperative WM functioning, F (1, 77) = 4.97, $p < .05$. However, no differences between tumour location groups were found, F (3, 77) = 1.56, p = .21. Furthermore, no interaction effect was found, F (3, 77)= 0.36, p = .78.

An additional analysis was performed in order to compare patients who were explicitly monitored for WM functioning intraoperatively (n = 27) and patients who were not (n = 54). A two-tailed, independent samples t-test with an alpha level of .05 demonstrated that the difference in pre- and postoperative backward span performance was similar for both groups, $t(79) = 0.74$, p = .46.

Table 3.

Unstandardized (b), standard errors (SE b) and standardized (β) regression coefficients for each predictor in the multiple regression models for pre- and postoperative functioning.

	b	**SE b**	**β**
Preoperative			
Constant	-0.53	0.37	
Age	-0.01**	0.003	-0.34
Years of education	0.10*	0.04	0.29
Forward span	0.01	0.05	0.02
Backward span	0.06	0.05	0.14
Postoperative			
Constant	-0.27	0.37	
Age	-0.01**	0.003	-0.35
Years of education	0.07*	0.03	0,21
Forward span	0.07	0.04	0.18
Backward span	0.01	0.04	0.03

**p < .05, ** p < .01*

Table 4.

Pre- and postoperative WM functioning: mean and range of performance on the DS backward, and percentage of patients with WM impairment and normal WM function.

	Preoperative evaluation	**Postoperative evaluation**
Mean performance on DS backward	4.02 (*SD* = 1.05)	4.31 (*SD* = 1.36)
Range	2-7	2-8
Percentage severely impaired WM function (> 2 *SD* below mean)	11.9%	10.7%
Percentage mildly impaired WM function (1-2 *SD* below mean)	15.5%	19.1%
Percentage normal WM function (*SD* < 1 from mean)	72.6%	70.2%

Discussion

The current study focused on WM functioning in glioma patients undergoing awake brain surgery. The aim of the study was two-fold: firstly, to determine the relationship between WM and overall cognitive functioning, and secondly, to evaluate differences in pre- and postoperative WM testing.

The main finding was that WM performance could not significantly be predict overall cognitive performance. Based on previous studies, WM was expected to be a strong predictor of overall cognitive functioning, since it has consistently been demonstrated that WM is strongly related to *gf* and several complex cognitive functions such as executive functioning, language comprehension, and problem solving (Conway et al., 2003; Daneman & Merikle, 1996; Kyllonen & Christal, 1990; McCabe et al., 2010; Miyake et al., 2000; Shipstead et al., 2014). Contrary to this expectation, however, WM performance did not account for additional variance in overall cognitive functioning after controlling for age and education. Several possible explanations for this finding will be discussed here.

Firstly, an important difference between previous research and the current study is the population that was studied. Previous studies have been focused on healthy populations, whereas the current study was conducted in a population of glioma patients. The group of glioma patients is heterogeneous in specific levels of cognitive functioning. Each individual patient may suffer specific focal impairments, depending on the type of tumour and its location, severity, and treatment effects (Klein & De Witt Hamer, 2011). These focal impairments affect

the overall cognitive profile. At the level of the statistical analysis, variability due to focal impairments might not equivocally have affected the outcome variable and the predictor variables, attenuating the relationship. Moreover, the variability in the sample may have caused a decrease in statistical power (Field, 2009), which can partially explain the absence of a relationship. However, since variability is inevitable in the heterogeneous group of glioma patients, diminished power cannot be prevented. Since the patient sample of the current study can be considered a valid representation of the population, the current findings could indicate that WM is not a reliable reflection of the overall level of cognitive functioning in glioma patients.

A second possible explanation is the construct that was used as outcome measure. In previous research, measures of *gf* or isolated cognitive functions have been used as outcome measures. The current study was aimed at testing whether previous findings can be generalized to a relationship between WM and overall cognitive functioning. This hypothesis is not supported by the findings of the current study, which implies that the relationship may not be as strong for the overall level of cognitive functioning as suggested by research into the relationship between WM and *gf*. In other words, the level of *gf* cannot be equated with the overall level of cognitive functioning. Moreover, although WM is related to some complex cognitive functions as demonstrated in previous studies (Björkdahl et al., 2013; Daneman & Merikle, 1996; McAbe et al., 2010; Miyake et al., 2000), the current study suggests that it is not equally related to all cognitive functions.

When differences in overall cognitive functioning were compared in patients with a normal, mildly impaired, or severely impaired level of WM functioning, significant differences were closely approached. Although not statistically significant at the fixed alpha level, an alpha level that closely approaches it might be clinically relevant (Cicchetti, 2001; Dienes, 2011). Therefore, the effect size was calculated, which resulted in a medium effect. This finding suggests that WM impairment might be related to a decline in overall cognitive functioning. Thus, subtle differences in WM performance might not strongly influence overall cognitive functioning, but when it drops to the impairment level, it might indicate a reduction in the overall level as well. However, the direction of this relationship remains unclear. Furthermore, taking the findings of the multiple regression analysis into account, it can be concluded that there is no linear relationship between WM and overall cognitive functioning.

The implication for clinical practice in the population of glioma patients is that WM is probably not a reliable predictor of the overall level of cognitive functioning. Consequently, it is not advisable to use WM span as an indicator of cognitive functioning in general. Since several factors, such as fatigue or distraction, may affect cognitive functioning independent of electrocortical stimulation, it is desirable to identify a measure that can be used to assess the

overall level of cognitive functioning during awake brain surgery. Discriminating effects of electrocortical stimulation from effects of other factors is necessary to optimize the results of awake brain surgery. Therefore, future research aimed at identifying alternative measures for this purpose is warranted.

The evaluation of differences in pre- and postoperative functioning demonstrated a subtle improvement in WM functioning at postoperative follow-up, as evidenced by a slightly better performance on the DS backward condition. In contrast, no difference in performance of the DS forward condition was found. These findings are in line with the expectation that cognitive monitoring during awake brain surgery has a protective effect on cognitive functioning (Coello, et al, 2013; De Witt Hamer, Robles, Zwinderman, Duffau, & Berger, 2012; Duffau, 2011). Contrary to the expectation, however, no difference was found between patients who performed the DS backward as a WM test during awake brain surgery and patients who did not. Furthermore, no differences based on tumour location occurred.

A few factors in the current study limit the possibility to draw solid conclusions on the protective value of intraoperative WM testing. A first important limitation is the lack of a control group. Based on ethical considerations, patients cannot be denied best clinical care, and accordingly, all patients are monitored intraoperatively for WM if the tumour is located in an area associated with WM functioning. Patients in the comparison group of the current study, who did not perform WM tests during awake brain surgery, were for the most part not at risk for WM impairment. Thus, the lack of difference between the groups cannot be attributed to an isolated effect of intraoperative WM testing. Future studies might attempt to include alternative control groups, such as patients who are at risk of WM impairment but not capable of performing a WM test during the cognitive monitoring procedure, or patients who are operated under general anaesthesia instead of awake conditions. These options have other limitations, but might provide additional insight into the protective value of intraoperative WM testing.

Another limitation is related to postoperative dropout rates. Patients were included in the study if both pre- and postoperative assessment was completed. As a consequence, patients who were not capable of completing postoperative assessment are not represented. One possible reason for not completing the neuropsychological assessment is an insufficient level of cognitive functioning. Exclusion of these patients might have caused some bias in the results. To overcome this limitation, it may be useful to register reasons for dropout at postoperative follow-up assessment.

A final limitation is that the subgroups based on tumour location might have been insufficiently specific. WM functioning is associated with highly specific brain areas, such as the dorsolateral prefrontal cortex and striatal circuits (D'Esposito & Postle, 2014). In the current study, a global division into frontal, temporal, parietal, occipital, and insular lobes was used.

Thus, consequences of specific tumour locations may not have been detected. A suggestion for future research is to further specify tumour location and select patients in whom WM impairment can be expected.

Despite the limitations of the current study, the findings may imply that intraoperative WM testing is not crucial for the preservation of WM functioning. Although intraoperative testing is predominantly beneficial, as evidenced by a higher rate of preserved cognitive functioning, it also may have some drawbacks. For example, fatigue can play an important role in glioma patients, limiting the testing possibilities and the validity of cognitive performance. Therefore, the costs and benefits of extensive intraoperative testing should be considered, and careful selection of tests and testing intensity for each individual patient is recommended (Klein & De Witt Hamer, 2011). Before drawing conclusions on the costs and benefits of intraoperative WM testing, however, future research should focus on improving control group sampling, registering reasons for postoperative dropout, and comparing more specific subgroups in the population of glioma patients.

In conclusion, the current study suggests that WM performance is not a reliable predictor of overall cognitive functioning in glioma patients. Furthermore, it demonstrates that there is no decline in WM functioning after awake brain surgery. However, due to a few limitations of the current study, it is not yet possible to provide solid conclusions regarding the protective value of intraoperative WM testing. Most importantly, heterogeneity in the group of glioma patients may have masked differences between subgroups. Future research examining specific subgroups, e.g. based on tumour type and location, could improve insight into the costs and benefits of intraoperative WM testing and provide a more differentiated understanding of WM functioning and its relationship with other cognitive functions in glioma patients. The main implication of the current findings is that WM testing is not necessarily beneficial for all patients undergoing awake brain surgery, but when an individual patient is at risk for WM impairment, the digit span backward is a valid task for intraoperative purposes.

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