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Abstract

Background: Patients with a glioma in eloquent brain areas frequently suffer from language problems, before and after surgery. How these difficulties relate to their functional brain organisation can be studied with electroencephalography (EEG). Gliomas cause increased brain activity in lower frequency bands (0.5-8 Hz; slow-wave activity), which is correlated with cognitive dysfunction. However, relationship of this activity to language has not been investigated. We examined whether slow-wave activity is related to language functioning in glioma patients.

Method: Twenty-one presumed low-grade glioma patients, who underwent surgery, were retrospectively included. They had available language and EEG data, obtained within one year preoperatively or postoperatively. Mean composite language z-scores were calculated, consisting of object naming, verbal fluency, comprehension, repetition, reading and/or writing

scores. EEG recordings were analysed visually by categorising slow-wave activity, and quantitatively by calculating relative slow-wave power during wakeful, resting conditions.
Results: Visual EEG analysis showed that patients with moderate/severe slow-wave activity had lower language scores than patients with normal/mild slow-wave activity. Quantitative EEG analysis revealed a significant negative correlation between slow-wave power and language scores.
Conclusion: We demonstrate that slow-wave activity in resting-state EEG is related to language functioning in glioma patients. Limited slow-wave activity is associated with better language performance and increased slow-wave activity is associated with poorer language performance. These findings contribute to knowledge of the underlying neural mechanisms of language problems. The potential use of slow-wave activity for predicting language outcome after surgery remains to be investigated, as it may have clinical applications for the perisurgical procedure.

Keywords: brain tumour; glioma surgery; language; slow-wave activity; EEG

1. Introduction

Gliomas in eloquent brain areas can cause language deficits that impact everyday communication. This is evidenced by deficits in spontaneous speech and impaired performance in language production, comprehension, reading, and writing (Satoer, Visch-Brink, Dirven, & Vincent, 2016). Knowledge of the structural and functional organisation of the brain areas responsible for the different aspects of language, identified with non-invasive techniques, is of great importance when deciding to operate on a patient. The gold standard treatment for presumed low-grade gliomas in eloquent areas is an awake surgery procedure with direct electrical stimulation. Despite intensive language monitoring, about half of the patients suffer from language impairments after surgery (Santini et al., 2012). Several factors are associated with language functioning and the risk of postoperative language deficits, such as tumour location, language-positive sites within the tumour (Ilmberger et al., 2008), preoperative neural plasticity due to the nature of a slow growing tumour, and the peri and postoperative adaptation to surgery (Duffau, 2014).

Electroencephalography (EEG) is a non-invasive technique which can be used to study brain activity. This method is relative inexpensive and commonly used in clinical practice. It is yet unclear whether brain activity, specifically slow-wave activity, in the low-grade glioma patient population is associated with the perceived language deficits. Slow-wave activity refers to focal brain activity in the delta and theta range (0.5-8 Hz). Patients with a brain lesion frequently exhibit enhanced slow-wave activity during a wakeful resting state (Lüders & Noachtar, 2000). This is assumed to be a marker of brain dysfunction, generated by injured brain tissue around the lesion (Chu, Braun, & Meltzer, 2015; De Jongh et al., 2003; Oshino et al., 2007). Increased slow-wave activity is associated with poorer cognitive functions in low-grade glioma patients (working memory, information processing, and executive functioning; Bosma et al., 2008), and with the degree of language impairment in stroke patients (Chapman,

Pool, Finitzo, & Hong, 1989; Finitzo, Pool, & Chapman, 1991; Hensel, Rockstroh, Berg, Elbert, & Schönle, 2004).

For the current retrospective study, we combined this information to investigate whether slow-wave activity in resting-state EEG is related to language functioning in (presumed) low-grade glioma patients. We hypothesised that increased slow-wave activity is associated with poorer language performance, despite time point before or after surgery. Results can be important for prospective designs focusing on clinical (prognostic) applications of slow-wave EEG activity.

2. Method

2.1. Retrospective patient inclusion

Patient files (2004-2015) at the University Medical Centre Groningen (UMCG) and the Erasmus University Medical Centre Rotterdam (EMC) in the Netherlands were reviewed to search for patients who met the following inclusion criteria: (1) surgery for a glioma in or near eloquent brain areas; (2) radiologically 'presumed' low-grade glioma without contrast enhancement on MRI; (3) available language and EEG data: obtained within one year, either before or after surgery. Exclusion criteria were: (1) (history of) other neurological, medical or psychiatric conditions known to affect language or cognition; (2) severe visual disorder or deafness; (3) mental retardation; (4) (history of) substance abuse.

The study was approved by the institutional ethical review board of the EMC, which also applies to the UMCG. No informed consent of the patients was required due to the retrospective nature of the study and the possible burden for patients and/or (surviving) relatives by asking permission.

2.2. Patient characteristics

Twenty-one glioma patients were included (13 female; mean age = 39 years), of which 12 with preoperative language and EEG data (preoperative patients) and 9 with postoperative language and EEG data (postoperative patients). No patient data were available of both pre and postoperative EEG with language tests. Patient characteristics are shown in table 1.

Table 1

Demographic and clinical characteristics of the patient group (N = 21): number of patients (and percentage) or mean (and range)

Patients	
Female gender	13 (62%)
Mean age in years	39 (19-63)
Mean education [a]	5 (3-7)
Right-handed	19 (90%)
Preoperative patients	12 (57%)
Postoperative patients	9 (43%)
Mean time interval in months	
Language tests → surgery	1 (0-5)
EEG → surgery	5 (1-9)
Surgery → language tests	4 (0-12)
Surgery → EEG	1 (0-5)
Language tests ↔ EEG	5 (1-12)
Tumour location – left hemisphere	18 (86%)
Tumour location – lobe	
Frontal	6 (29%)
Fronto-temporal	3 (14%)
Temporal	5 (24%)
Temporo-insular	1 (5%)
Insular	2 (10%)
Temporo-parietal	1 (5%)
Parietal	2 (10%)
Temporo-occipital	1 (5%)
Tumour size	
≤ 5 cm	6 (29%)
> 5 cm	15 (71%)
Histology [b]	
Astrocytoma	7 (33%)
Anaplastic astrocytoma	1 (5%)
Oligodendroglioma	3 (14%)
Oligoastrocytoma	5 (24%)
Anaplastic oligodendroglioma	1 (5%)
Glioblastoma	4 (19%)
Grade	
Low-grade	15 (71%)
High-grade	6 (29%)

Diagnosis	
De novo	17 (81%)
Recurrent	4 (19%)
Use of anti-epileptic drugs	17 (81%)
Resection [c]	
≤ 90%	6 (67%)
> 90%	3 (33%)
Adjuvant therapy at the time of EEG [c]	5 (56%)
Radiotherapy	5 (56%)
Chemotherapy	3 (33%)

Note. Information on hemispheric language dominance (attested with fMRI) was not available in the majority of the patients.

[a] Education was classified according to seven categories (1= uncompleted primary school; 7= completed university; Verhage, 1964).

[b] Based on the former 2007 WHO classification (Louis et al., 2007).

[c] Only applicable to the postoperative patients.

2.3. Language assessment

Patients were assessed by an experienced clinical linguist with the following standardised tests: the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001), category fluency (producing words of a given category within 1 minute; Luteijn & Barelds, 2004), letter fluency (idem, but words starting with a given letter; Schmand, Groenink, & Van den Dungen, 2008), and subtests of the Aachen Aphasia Test (AAT; Dutch version; Graetz, De Bleser, & Willmes, 1992): the Token Test (executing tasks with geometric forms on verbal commands), repetition, reading aloud, and writing to dictation. Raw test scores were converted to z-scores, taking into account published normative data from a healthy control population. As not all patients completed all tests, a ‘mean composite language score’ was computed, consisting of the average z-score of the available language tests for each patient.

2.4. EEG

Clinical EEGs were recorded with 44-channel Schwarzer amplifiers (Natus Europe GmbH, Munich), placing 21 scalp electrodes according to the international 10-20 system. EEG

analysis of slow-wave activity was performed visually, the gold standard in clinical evaluation, and quantitatively.

Visual EEG analysis was performed in BrainRT software (v.2.0; Rumst, Belgium, 2013) by one of the authors (PJC), a board-certified Clinical Neurophysiologist, who was blinded to the patients' medical records. The presence and characteristics of activity in the delta (0.5-4 Hz), theta (4-8 Hz), and alpha (8-12 Hz) frequency bands were determined with EEG data reformatted to display standard antero-posterior bipolar montage and common average montages. Subsequently, slow-wave activity was classified according to the Mayo Classification System (Mayo Clinic and Mayo Foundation, 1998), complemented by guidelines of Lüders and Noachtar (2000). From this, four categories were created: normal, mild, moderate, and severe slow-wave activity. See table 2 for their definitions. For analysis purposes, ensuring enough data for group comparisons, the categories 'normal' and 'mild' were grouped together, as well as the categories 'moderate' and 'severe'.

Quantitative EEG analysis was performed in BrainVision Analyzer 2.0 (Brain Products GmbH, 2013) on eyes-closed, artefact-free EEG during wakeful resting conditions. Twenty 2-second epochs for each patient were selected by visual inspection (IB). Raw EEG data were resampled to 256 Hz and re-referenced to a new averaged reference consisting of 15 scalp electrodes: F3; F4; F7; F8; T3; T4; T5; T6; C3; C4; P3; P4; Pz; O1; and O2 (excluding: Fz and Cz, because they were used as reference electrodes; Fp1 and Fp2, because they generally contain eye-blink artefacts and muscle activity). Subsequently, the data were filtered (band-pass: 0.27-30 Hz, slope 24 dB/Oct; notch: 50 Hz, slope 24 dB/Oct). For every patient, spectral analysis was performed on the 20 epochs of 512 points by a Fast Fourier Transform (FFT) for all 15 electrodes. After averaging the 20 FFTs, relative slow-wave power was calculated by dividing the absolute power in the delta and theta range (0.5-8 Hz) by the

absolute power in the total spectrum (0.5-70 Hz). At last, relative slow-wave power was averaged over the 15 electrodes.

Table 2

Classification of slow-wave activity in EEG by visual analysis

Degrees of slow-wave activity	**Category from the Mayo Classification System**[a]	**Interpretation**[b]
Normal		No abnormal slow-wave activity
Mild	- Dysrhythmia grade I - Dysrhythmia grade II	Intermittent nonspecific theta or delta slowing < 50% of the recording: focal, bilateral, or diffuse with amplitudes < 60 μV
Moderate	- Dysrhythmia grade III	Intermittent nonspecific theta or delta slowing > 50% of the recording: focal, bilateral, or diffuse with amplitudes > 60μV [c]
	- Delta grade I	Persistent polymorphic (irregular) delta slowing: focal, bilateral or diffuse with amplitudes < 30 μV
Severe	- Delta grade II - Delta grade III	Persistent polymorphic (irregular) delta slowing: focal, bilateral or diffuse with amplitudes > 30 μV

Note. Persistent asymmetry in amplitude or frequency of >50% between the hemispheres was also scored, but not included in the analysis.
[a] Mayo Clinic and Mayo Foundation (1998).
[b] Complemented by guidelines of Lüders and Noachtar (2000).
[c] Dysrhythmia grade III can also refer to specific epileptiform activity (spikes, sharp waves and spike-waves as well as recorded ictal patterns). Even though this was scored during visual interpretation of EEG, it was not included for data analysis.

2.5. Statistical analysis

In IBM SPSS Statistics software (version 23, release 23.0.0.0), a one-sample *t* test was used to compare patients' mean composite language scores to normative data ($M = 0.00$). Possible effects of tumour and treatment-related factors on language performance, and later on slow-wave activity, were examined with independent-samples Mann-Whitney U tests. Language performance of the two groups from visual EEG analysis (normal/mild slow-wave activity and moderate/severe slow-wave activity) were compared to: (1) a control population with

one-sample Wilcoxon Signed-rank tests; (2) each other by means of an independent-samples Mann-Whitney U test. Slow-wave power from quantitative EEG analysis was correlated with language performance by a Spearman's rho correlation test.

3. Results

3.1. Language performance

The patient group had a mean composite language z-score of -0.61 (N = 21, SD = 0.70), which was significantly lower than that of a control population ($t(20) = -4.04$, $p < .001$, d = 0.71). An overview of z-scores on each separate language test can be found in the Appendix. No effect of tumour and treatment-related factors on language performance was found with regard to tumour size, extent of resection, tumour grade, diagnosis (de novo versus recurrent), use of anti-epileptic drugs, and postoperative radiotherapy or chemotherapy ($p > .05$).[1]

3.2. Slow-wave activity

In the visual EEG analysis, 13 patients were classified as having normal/mild slow-wave activity and 8 patients had moderate/severe slow-wave activity. For quantitative EEG analysis, three patients had to be excluded, due to the lack of sufficient artefact-free EEG segments. The remaining 18 patients had a mean (relative) slow-wave power of 0.61 (SD = 0.24). Patients with normal/mild slow-wave activity had a mean slow-wave power of 0.44 (N = 10, SD = 0.17) and patients with moderate/severe slow-wave activity had a mean slow-wave power of 0.83 (N = 8, SD = 0.08).

[1] Tumour location was not investigated; all tumours were located in or near eloquent brain areas, expected to be involved in language and/or sensorimotor functioning.

Abnormal slow-wave activity was most pronounced in the affected hemisphere in all patients. Furthermore, there was no effect of tumour and treatment-related factors on the level of slow-wave power: tumour size, extent of resection, tumour grade, diagnosis (de novo versus recurrent), use of anti-epileptic drugs, and postoperative radiotherapy or chemotherapy ($p > .05$).

3.3. Associations between language performance and slow-wave activity

3.3.1. *Visual EEG analysis*

Compared to a control population, both patients with normal/mild slow-wave activity ($N = 13$, $Mdn = -0.38$) and patients with moderate/severe slow-wave activity ($N = 8$, $Mdn = -1.12$) had significantly lower mean composite language scores ($Z = 11$, $p = .016$ and $Z = 3$, $p = .036$, respectively). Patients with moderate/severe slow-wave activity had lower mean composite language scores than patients with normal/mild slow-wave activity (marginally significant; $U = 25$, $p = .053$, $d = 0.82$; see figure 1).

3.3.2. *Quantitative EEG analysis*

Mean composite language scores showed a significant negative correlation with slow-wave power ($r_s(16) = -.53$, $p = .025$).

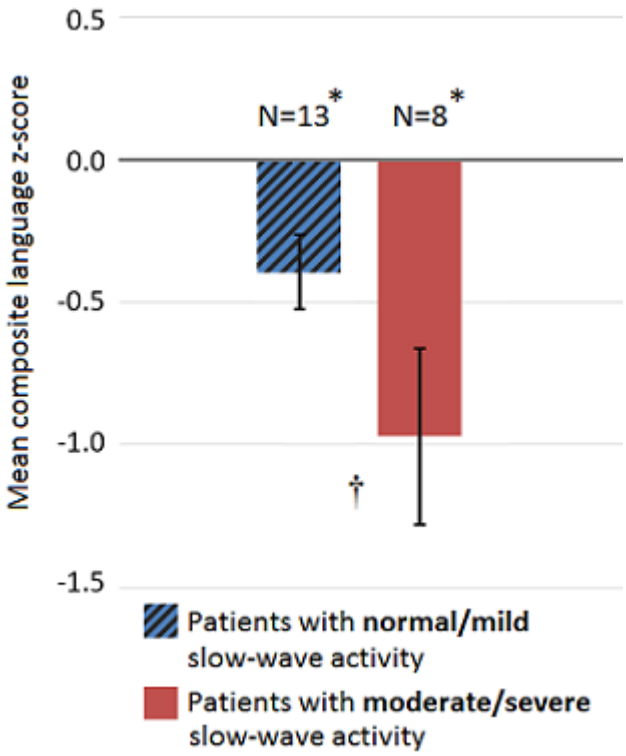

Figure 1. Overall language performance according to visual EEG analysis: patients with normal/mild slow-wave activity (striped blue) and patients with moderate severe slow-wave activity (red). Error bars represent standard errors.
* indicates a significantly lower score compared to a control population at the 0.05 level (2-tailed); † indicates a marginally significant difference between the groups.

3.4. Pre and postoperative patients

With regard to language performance, mean composite language scores of preoperative patients (N = 12) did not differ significantly from a control population ($t(11) = -2.02$, p = .068, d = 0.44), but postoperative patients (N = 9) had significantly lower scores ($t(8) = -4.20$, p = .003, d = 1.10). No significant relations between slow-wave activity and language performance were found in pre and postoperative patients as separate groups.

4. Discussion

We report for the first time on the relation between slow-wave brain activity and language functioning in glioma patients. Limited slow-wave activity in resting-state EEG is related to better language performance and more pronounced slow-wave activity is related to poorer language performance. This applies to the overall language performance in presumed low-grade glioma patients, irrespective of the timing of the assessments (language and EEG recording before or after surgery). When examining the group more closely by separating pre and postoperative patients, no relations between slow-wave activity and language performance are found, presumably due to small sample sizes.

These findings are in accordance with Bosma et al. (2008), who showed that increased slow-wave activity correlates with poorer working memory, information processing, and executive functioning in (pre and postoperative) low-grade glioma patients. With regard to language, a similar relation with slow-wave activity has previously been found in patients with traumatic brain injury (Thatcher, Biver, McAlaster, Camacho, & Salazar, 1998), Alzheimer's disease (Helkala et al., 1991; Van der Hiele et al., 2007), Parkinson's disease (non-demented stage; Olde Dubbelink et al., 2013), and post-stroke aphasia (Hensel et al., 2004). Hensel et al. (2004) demonstrated that a decrease of left-hemispheric slow-wave activity coincides with language recovery during the first year post-stroke.

4.1. Language performance

Presumed low-grade glioma patients have poorer language performance than a healthy control group, but this does not hold for preoperative patients only. Santini et al. (2012) and Papagno et al. (2011) confirm that language impairments in glioma patients are less prevalent preoperatively than postoperatively. The lower incidence and the relatively mild character of preoperative language impairments in low-grade glioma patients can (partly) be explained by

the slow tumour growth rate, which allows for the reorganisation of functions (Desmurget, Bonnetblanc, & Duffau, 2007).

However, the present findings on language performance must be interpreted cautiously, because the currently used tests do not provide a comprehensive language profile. Not all language levels were assessed (e.g., no test for sentence processing was included) and there was no measurement of language use in daily life (e.g. spontaneous speech). Furthermore, it is questionable whether the AAT subtests are sufficiently sensitive to detect the mild language deficits in this patient group (Satoer et al., 2014 and see Appendix).

Tumour and treatment-related factors did not influence language performance in our sample. Previous studies have reported that high-grade tumours, large tumour volume, and tumour location in frontotemporal areas and/or involving subcortical white matter tracts are associated with poor language functioning, whereas other studies report no effects of these factors (Satoer et al., 2016). Moreover, antiepileptic drugs and postoperative radio- and chemotherapy have been reported to negatively affect language and cognition (McAleer & Brown, 2015).

4.2. Slow-wave activity

Slow-wave activity was, as expected, maximally pronounced over the region corresponding to the tumour location. This has been demonstrated before (Baayen et al., 2003; De Jongh et al., 2003; Oshino et al., 2007) and can be explained by its origin in brain tissue adjacent to the tumour and surrounding oedematous areas (Fernández-Bouzas et al., 1999; Oshino et al., 2007). We did not find effects of other tumour or treatment-related factors on (the amount of) slow-wave activity, in contrast to De Jongh et al. (2003) who report that larger tumour volume and higher tumour grade are associated with higher slow-wave power. However, our patient

selection is slightly biased, because only presumed low-grade glioma patients who had an EEG recording on clinical indications were included.

For the analysis of slow-wave activity, we used relative instead of absolute slow-wave power, because the former is less sensitive to effects of different recording systems (as EEG was recorded at different centres). A disadvantage, however, is that relative slow-wave power can be influenced by deviations in other, higher frequency bands. Moreover, previous studies that investigated slow-wave activity in brain tumour patients used a different technique: magnetoencephalography (MEG). Apart from high temporal resolution as in EEG, MEG enables detailed examination of the spatial distribution of brain oscillations, without distortion by skull and scalp. Downsides of MEG are its susceptibility to metal artefacts (e.g. dental implants), high cost and limited availability. Therefore, MEG is better suited for scientific research, whereas EEG is more appropriate for application in clinical context.

4.3. Associations between language performance and slow-wave activity

The current findings indicate that increased slow-wave activity relates to poorer overall language performance in glioma patients. This link contributes to knowledge of the underlying mechanisms of language problems in this patient group. High levels of slow-wave activity are assumed to arise from cortical deafferentation due to subcortical injury (Gloor, Ball, & Schaul, 1977). It is known that intact subcortical structures are crucial for the preservation of language in awake glioma surgery (Trinh et al., 2013). Hence, when language deficits are present, slow-wave activity may be postulated to be seen as the intermediate between injured, subcortical brain tissue (by the tumour and its treatment) and apparent language problems, as suggested by Bosma et al. (2008) for cognitive dysfunction.

A closer examination of cognitive functioning in their study (Bosma et al., 2008) demonstrates that poor performance in working memory, information processing and

executive functioning is associated with increased slow-wave activity. However, it has been suggested that these cognitive domains make use of language skills (Baldo et al., 2005; Emerson & Miyake, 2003; Whiteside et al., 2016). As a glioma can affect cognitive functioning either directly, or indirectly via an underlying mechanism, we cannot exclude the possibility that the previously found relations between slow-wave activity and cognitive functions are caused by an underlying language deficit. In any case, it is essential to distinguish cause and effect in language and cognitive functioning, not only from a theoretical perspective, but also with regard to therapeutic intervention.

4.4. Clinical potential

Language outcome after glioma surgery varies between patients and its postoperative course is dynamic (Satoer et al., 2014). Therefore, the currently demonstrated relation between slow-wave activity and language functioning raises the question whether slow-wave EEG activity can predict language outcome after glioma surgery. Several studies in post-stroke aphasia have shown the prognostic value of slow-wave EEG activity (in the acute phase) for language recovery up to two years post-onset (Jabbari, Maulsby, Holtzapple, & Marshall, 1979; Szelies, Mielke, Kessler, & Heiss, 2002; Tikovsky, Kooi, & Thomas, 1960). Although acute brain injury after stroke differs from gradual neural changes due to a slow-growing glioma, these studies provide valuable information about the potential use of slow-wave EEG activity. Moreover, in epilepsy patients who undergo temporal lobe surgery, preoperative slow-wave activity predicts improvement or deterioration of memory functioning one year after surgery (Tuunainen et al., 1995). If slow-wave EEG activity can also be used as a prognostic tool for postoperative language functioning in glioma patients, this would aid patient counselling and can potentially be used for surgical planning.

5. Conclusion and future directions

We demonstrated that slow-wave activity in resting-state EEG is inversely related to language functioning in a group of glioma patients who were assessed before or after surgery. A larger prospective design with more sensitive language tests will give insight into separate time points (pre and postoperative) as to whether these effects are iatrogenic or tumour-related. More insight into language problems, underlying neural mechanisms (esp. plasticity) associated with slow-growing tumours, and glioma patients' vulnerability for postoperative language deficits is of utmost importance: it can lead to clinical implications regarding patient counselling and intraoperative language monitoring.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Informed consent: The institutional ethical review board of the EMC, also applying to the UMCG, decided that no informed consent of the patients is required due to the retrospective nature of the study. As the data were obtained a longer time ago, some patients have deceased and asking permission can be a burden for patients and/or (surviving) relatives.

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Appendix: Overview language scores

Mean z-scores (and standard deviations) for each separate language test and comparisons to a control population (M = 0.00)

	N	***M* (*SD*)**
Mean composite language z-score	21	-0.61 (0.70)***
Individual language tests		
Object naming	21	-1.36 (1.68)**
Category fluency	20	-0.93 (0.81)***
Letter fluency	20	-0.81 (1.17)**
Token Test (AAT)	15	-0.50 (1.82)
Repetition (AAT)	11	-0.18 (0.98)
Reading (AAT)	10	0.03 (1.01)
Writing (AAT)	10	0.22 (0.51)

* Significantly lower than a control population at the 0.05 level (2-tailed)
** Significantly lower than a control population at the 0.01 level (2-tailed)
*** Significantly lower than a control population at the 0.001 level (2-tailed)