Pre- to Postoperative Longitudinal Follow-up of Phoneme Perception in Glioma Patients: Evidence from the Mismatch Negativity and P300

Yana Criel[1], Edward Baert[2], Jean-Pierre Kalala Okito[2], Giorgio Hallaert[2], Dirk Van Roost[2], Luc De Baerdemaeker[3], Wouter Degrève[3], Marijke Miatton[4], Patrick Santens[4], Pieter van Mierlo[5], Miet De Letter[1]

[1] Research Group BrainComm, Department of Rehabilitation Sciences, Ghent University, Ghent, Belgium

[2] Department of Neurosurgery, Ghent University Hospital, Ghent, Belgium

[3] Department of Anesthesiology, Ghent University Hospital, Ghent, Belgium

[4] Department of Neurology, Ghent University Hospital, Ghent, Belgium

[5] Medical Imaging and Signal Processing Group, Department of Electronics and Information Systems, Ghent University, Ghent, Belgium

Corresponding Author

Yana Criel - Yana.Criel@UGent.be – ORCID: 0000-0001-6455-1803

Word count: 8262 words

Abstract

Background and Aims: Glioma growth in eloquent language areas induces adaptive activation changes in the language network. The present study aimed to (1) investigate the pre- to postoperative evolution of neural phoneme perception processes in glioma patients and (2) assess if event-related potentials (ERPs) reflecting phoneme perception can provide added value to the diagnostic approach in individuals undergoing awake surgery.

Methods and Procedures: In five persons undergoing an awake craniotomy for the resection of a glioma, pre- and postoperative behavioural language assessment (Aachen Aphasia Test, Comprehensive Aphasia Test and Boston Naming Test) and electrophysiological investigation of phoneme perception was performed. For the latter, ERPs were obtained through the administration of an inattentive (Mismatch Negativity; MMN) and attentive (P300) oddball paradigm containing a phonemic articulation place contrast during EEG recording.

Outcomes and Results: Aberrant phoneme categorization processing was evidenced in all five participants preoperatively based on the MMN and P300 amplitude and latency. Moreover, mild behavioural impairments were found in four participants at this time. Postoperatively, three out of five participants reached behavioural ceiling effects, while four individuals displayed normalization of electrophysiological measures.

Conclusions: While neural processing of phoneme contrasts was preoperatively affected by glioma-induced disturbances, a high potential for postsurgical plasticity was shown. As four participants presented with a high grade glioma, tumour grade might partially account for this pattern. Addition of electrophysiological tests to the language assessment could provide benefits in both the pre- and postoperative clinical diagnostic approach in glioma patients. These preliminary results need validation in a larger sample.

Keywords: glioma, ERP, Mismatch Negativity (MMN), P300

1. Introduction

Gliomas rarely induce pronounced aphasia symptoms, even when invading brain areas that are strongly engaged in language processing (for a review see Desmurget et al., 2007; Plaza et al., 2009). The slow-growing nature of these brain tumours is thought to underly this resilience, as it allows the dynamic brain to fully engage its capacitance for neuroplasticity (Desmurget et al., 2007). Cirillo et al. (2019) defined neuroplasticity in the context of gliomas as 'the biological dynamic ability of the central nervous system to reorganize itself in response to injuries'. It consists of structural and functional neural changes that occur in order to retain or restore networks that facilitate a certain function. The neurosurgical approach towards the resection of a glioma in an eloquent area aims at resecting the maximum volume of tumour tissue while maintaining favorable language outcome postoperatively by considering preoperative cerebral plasticity and preserving neural structures essential to language processing. This is accomplished through tumour resection during an awake craniotomy in order to perform intraoperative language mapping using cortical and subcortical direct electrical stimulation (DES) (Rahimpour et al., 2019; Surbeck et al., 2015). Compared to glioma resection under general anesthesia, this approach has proven to provide better outcome in terms of both the extent of the resection and the persistence of postoperative severe neurological deficits (De Witt Hamer et al., 2012).

Adaptive tumour-induced changes in the language network have their onset preoperatively and progresses in the postoperative phase (Cargnelutti et al., 2020). Evidence on the nature of these neural activation changes in the pre- and postoperative stadium mainly originates from functional magnetic resonance imaging (fMRI), intraoperative language monitoring (IOM), positron emission tomography (PET) and transcranial magnetic stimulation (TMS). Although plasticity patterns exhibit substantial interindividual variability (Deverdun et al., 2020), a review by Cargnelutti et al. (2020) identified some general trends. Apart from residual

functional activity that may be present in the tumour itself, compensatory recruitment of intrahemispheric perilesional areas is the primary mechanism in preoperative stages (Thiel et al., 2001; Cirillo et al., 2019). In addition, activation of contralateral homologous areas has been reported (Holodny et al., 2002). However, the gain of this latter cortical reorganization pattern in terms of language outcome remains a matter of debate (Saur et al., 2006). Postoperatively, cortical reorganization was found to continue as either an activation shift to the non-dominant hemisphere or the restoration of original activation patterns in the compromised hemisphere (Cargnelutti et al., 2020). While slow-evolving gliomas are generally associated with superior language outcome as compared to acute lesions (Desmurget et al., 2007), a differentiation should be made between low (LGG) and high (HGG) grade gliomas. HGGs more frequently give rise to severe preoperative language impairments compared to LGGs (Deng et al., 2015; Zhang et al., 2018). That is, as a result of HGG's more rapidly growing character and more invasive nature, the opportunity for preoperative compensatory recruitment of the non-dominant hemisphere is limited as compared to LGGs (Deng et al., 2015; Kawashima et al., 2013). Postsurgical plasticity is therefore of particular importance in high grade tumours, as it may yet contribute to functional improvement.

The aforementioned observations stem from an extensive amount of research investigating the impact of glioma growth on language, as well as the associated structural and functional neural changes (Cargnelutti et al., 2020; for a review see Cirillo et al., 2019). Tasks used to map the neural activation underlying language processing include picture naming, story listening, reading, verbal fluency and sentence generation (Benzagmout et al., 2007; Cho et al., 2018; Deng et al., 2015; Deverdun et al., 2020; Krieg et al., 2013). These tasks capture changes that occur in the generic language network as they combine several linguistic sublevels (phonological, lexical, semantic and/or syntactic processing). However, at present, our understanding as to how these specific sublevels, which engage different neural subnetworks,

are each impacted by glioma growth is limited. Similarly, the characteristics of glioma-induced plasticity in these networks remain a matter of debate.

In parallel, it can be argued that the clinical approach to the pre- and postoperative language assessment in this population lacks an in-depth assessment of linguistic sublevels, as well as changes that occur in the neural processing at these sublevels. A wide variety of tasks has been reported with regard to the behavioural language assessment prior to and following awake surgery (Martin-Monzon et al., 2020). Typically, standardized batteries assessing general language function, such as the Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1972) and Aachen Aphasia Test (AAT; Graetz et al., 1992), are administered for this purpose (De Witte & Mariën, 2013). Specifically object naming and verbal fluency tasks were shown to be part of the perioperative language assessment in most centers performing awake craniotomies (Rofes et al., 2017). However, standardized batteries often prove insufficiently sensitive to identify the mild language disturbances induced by glioma growth. The Dutch Diagnostic Instrument for Mild Aphasia (DIMA) was developed to address this challenge, including tasks to explore individual linguistic sublevels in depth (Satoer et al., 2022). Although this test may be valuable in identifying subtle language impairments in individuals with a brain tumour, the assessment is restricted to the behavioural level, hence not allowing any interferences on alterations in the spatiotemporal aspects of specific neurolinguistic processes. In addition to behavioural batteries, functional Magnetic Resonance Imaging (fMRI) is reported to be part of the standard clinical approach to the preoperative mapping for glioma resection in 49,8% of European centers performing surgery in patients with a glioma (Thust et al., 2018). Preoperative fMRI primarily aims at mapping functional language organization and assessing language lateralization. Nevertheless, varying results in terms of sensitivity and specificity of this technique for language mapping as compared to intraoperative DES have been reported, ranging from 59-100 % and 0-97 %, respectively (Guissani et al., 2009). Moreover, a wide

variety of tasks has also been used in preoperative fMRI, including verbal fluency, repetition, object naming, verb generation and story-listening (De Witte & Mariën, 2013). Only a limited amount of time is available during awake surgery, highlighting the need for a comprehensive preoperative language assessment that constitutes the optimal starting point for intraoperative language mapping by (1) providing detailed measures at the level of linguistic subprocesses and (2) providing insight into tumour-induced changes in their neural processing. Postoperatively, De Witte and Mariën (2013) reported a general lack of in-depth and long-term linguistic follow-up, as it was proven to be mainly restricted to the administration of standardized language batteries. A recent survey confirmed that postoperative speech/language assessment following brain surgery is limited to bedside evaluation (< 10 days post-surgery) or early postoperative follow-up (< 5 months post-surgery) in most centers (Sierpowska et al., 2022). This highlights the need for a more extensive postoperative follow-up which determines postoperative function levels and enables the mapping of neurolinguistic processing changes.

Considering the relevance of investigating pre- and postoperative alterations that occur in the neural processing of specific linguistic levels from both a fundamental scientific and clinical point of view, language-related potentials (ERPs) could potentially prove valuable. ERPs are obtained by electro-encephalographic (EEG) recording during the administration of linguistic paradigms. They enable the mapping of neurolinguistic processes with a high temporal resolution (Luck, 2014). Application of these ERPs could determine the extent to which linguistic (sub)networks are disrupted by glioma growth. As such, in the preoperative phase ERPs could provide insight into the integrity of functional language networks. In addition, both pre- and postoperatively, they may highlight mechanisms of recovery and rehabilitation processes. Furthermore, ERPs were demonstrated to be more sensitive than behavioural language assessment in people with aphasia (Cocquyt et al., 2020a). Thus, in patients with gliomas, who generally exhibit minimal behavioural language impairment as a result of

plasticity-driven cerebral reorganization of language functions (Ilvonen et al., 2003), electrophysiological assessment could be beneficial. The present study focuses specifically on the perceptual processes of phoneme discrimination and categorization, which can be studied through the Mismatch Negativity (MMN) and P300 ERP components, respectively (Bledowski et al., 2004; Luck & Kappenman, 2012; Näätänen et al., 1997). Phoneme perception, as a part of the auditory-phonological processing stage, constitutes one of the initial steps for achieving auditory language comprehension. In this respect, it will also be a determinant for subsequent processing at the lexico-semantic and syntactic level. As auditory language comprehension deficits can find their origin in various stages, including the initial stage of phoneme-level processing, the current study set out to specifically investigate alterations in the neurolinguistic processes underlying phoneme perception in glioma patients. Nevertheless, the investigation of phoneme perception merely serves as a first step in mapping different linguistic subprocesses, including lexico-semantics and syntax.

The MMN and P300 are ERP components that are elicited by an inattentive and attentive oddball paradigm, respectively. Whereas these components are mostly evoked using tonal auditory contrasts, they have also been studied in tasks adopting linguistic stimuli, such as phonemic contrasts (Aerts et al., 2013). The MMN (Näätänen et al., 1978) is a negative peak that arises between 160 and 220 ms after stimulus onset and has a fronto-central midline distribution (Luck, 2014). According to the predictive coding hypothesis (Garrido et al., 2009), the MMN is said to reflect the comparison of a newly presented (speech) sound against the prediction that was made based on the previously presented (speech) sounds, and is therefore associated with passive, preconscious phoneme discrimination (Ilvonen et al., 2004). The P300 (Sutton et al., 1965) is a positive component initiating around 300 ms after stimulus onset with an increasing amplitude from frontal to parietal sites over the midline electrodes (Luck, 2014). This component is thought to reflect attention processes that are associated with updating

working memory stimulus representations and active categorization of (speech) stimuli (Luck, 2014; Polich, 2007). In the study of phoneme perception, these components provide complementary information in various respects. First, discrimination (MMN) and categorization (P300) of phonemes are considered to be two distinct substages in the auditory-phonological processing of a speech signal (Becker & Reinvang, 2007), thus requiring separate assessment. Moreover, both components call on domain-general cognitive operations to a different degree (Garrido et al., 2009; Polich et al., 2007) Lastly, evidence suggest that these components are differentially affected in relation to aphasia. Aerts et al. (2015) demonstrated significantly reduced P300, but not MMN, amplitudes for the perception of articulation place contrasts in people with stroke-induced aphasia in the acute phase of recovery compared to healthy controls. In three out of four examined individuals with aphasia in the subacute stage, Cocquyt et al. (2020b) observed normal MMN amplitude and latency values but aberrant P300 amplitude or latency values. Moreover, the authors provided evidence that these components allow for the evaluation of neural processing changes during aphasia recovery.

In summary, on the one hand there is a lack of longitudinal evidence on the changes that occur both pre- and postoperatively in the neural processing of specific linguistic sublevels in people with a glioma undergoing an awake craniotomy. On the other hand, the current approach to the clinical pre- and postoperative language assessment in this population might benefit from the assessment of these linguistic sublevels in function of neuroplasticity. From this context, the current study set out to explore the neural processes underlying phoneme perception in people with a glioma, prior to and following awake tumour resection. This was achieved by studying the MMN and P300 ERPs. In this respect, we aimed to address the following objectives: (1) To assess changes that occur in the neural processing of phoneme perception in the preoperative and postoperative stage in glioma patients undergoing awake surgery, in comparison with neurotypical adults. (2) To determine the added value of phonemic ERPs, in addition to

behavioural language batteries, in the pre- and postoperative diagnostic approach in individuals with a brain tumour undergoing an awake craniotomy. To this end, five persons with a glioma in an eloquent language area were subjected to pre- and postoperative language investigation using behavioural tasks and EEG recording during the administration of an inattentive and attentive auditory oddball paradigm containing a phonemic articulation place contrast.

2. Materials and Methods

2.1.Participants

Five participants diagnosed with a glioma in an eloquent language area were recruited from the department of Neurosurgery at Ghent University Hospital, Belgium. Diagnosis and establishment of tumour location were performed by an experienced neurosurgeon and neuroradiologist based on magnetic resonance imaging (MRI), complemented with Diffusion Tension Imaging (DTI) to assess subcortical glioma infiltration. Based on this, all participants were selected as candidates for an awake craniotomy with intraoperative language mapping. All included participants were Dutch native speakers, aged between 27 and 72 years at the time of surgery and mean age being 46.6 years (*SD* = 19.14). This study was approved by the Ghent University Hospital Ethical Committee (ONZ-2022-0127) and all participants provided informed consent. Participant characteristics including sex, age, handedness, language dominance as determined by fMRI and tumour characteristics (localization, type, grade and extent of resection) are displayed in table 1.

2.2.Intraoperative Procedure

All five participants underwent awake craniotomies with intraoperative language mapping. Surgical resection was performed by a senior neurosurgeon of the Ghent University Hospital Neurosurgery staff and intraoperative language monitoring was performed by an experienced

speech-language pathologist. An asleep-awake-asleep procedure was followed in all surgeries. The awake stage of the intraoperative procedure included cortico-subcortical mapping of eloquent language areas using direct electrical stimulation (DES) and language monitoring during tumour resection. For this purpose, the administration of tasks from the Dutch Linguistic Intraoperative Protocol (DuLIP; De Witte et al., 2015) and spontaneous speech monitoring were continuously alternated. Patient-specific DuLIP tasks were selected based on individual tumour localization and preoperative language assessment.

2.3.Pre- and Postoperative Experimental Procedure

The participants underwent pre- and postoperative language assessment including a behavioural evaluation and electrophysiological language assessment through the recording of ERPs (MMN and P300) in response to auditory phonemic contrasts. Linguistic assessment was performed at 1 week preoperatively and 3 months postoperatively in P1, P2, P3 and P5. Participant 3 underwent an additional assessment at 6 months post-surgery. P4 underwent assessment at 1 week preoperatively and 5 months postoperatively. None of the participants received postoperative language rehabilitation. Both the behavioural and ERP data were processed on a single-subject level. No group level statistics were performed.

2.3.1. Behavioural Language Assessment

Behavioural language assessment included the administration of the Dutch version of the Aachen Aphasie Test (AAT; Graetz et al., 1992) in all participants, with the exception of participant 2, who was assessed using the Dutch translation of the Comprehensive Aphasia Test (CAT-NL; Swinburn et al., 2005). The AAT is an assessment battery comprising the following six subtests: spontaneous language production, a version of token test, repetition, writing, naming and comprehension. Based on these tasks, the test differentiates between people with aphasia and people without aphasia, and is able to diagnose both standard and non-standard

aphasia syndromes. The CAT-NL is a diagnostic instrument developed to evaluate language skills and associated cognitive disabilities in people with aphasia. Language assessment includes five subtests evaluating both spoken and written language comprehension and 16 subtests evaluating verbal and written language production. The cognitive screening is made up of six subtests. In addition to the administration of the AAT or CAT-NL, the Boston Naming Test (BNT; Kaplan et al., 1983) was administered in all cases except for participant 3. In the BNT, the participant is asked to name 60 black line drawings depicting objects of increasing naming difficulty. As such, the test aims to assess word finding abilities, vocabulary skill and cognitive functions associated with this task.

2.3.2. Electrophysiological Assessment

EEG recording - The EEG was recorded using Neuron-Spectrum-5 (4EPM) recording software (Neurosoft, Moscow, Russia). Electrodes were placed at 20 electrode sites (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and Oz) according to the international 10-20 system by means of a universal electrode cap (Haube-S2). A ground electrode was applied to the forehead and an online linked ears reference was used. In order to optimize signal impedance, an impedance reducing gel (Elektro-Gel TM, Elektro-Cap International, Inc.) was applied and impedance in all channels was kept below 5kΩ. A 32 channel SynAmp (Neuroscan) amplifier was used to collect EEG data and the sampling frequency was set at 500 Hz. A 0.5-75 Hz band-pass filter was applied during recording. No online notch filter was set.

ERP paradigms - Electrophysiological assessment consisted of the measurement of ERPs through EEG recording during the administration of the two auditory oddball paradigms containing a phonemic contrast: (1) an inattentive auditory oddball paradigm, eliciting a mismatch negativity (MMN) and (2) an attentive auditory oddball paradigm, eliciting a P300 waveform. Auditory stimuli and paradigms developed by Aerts et al. (2013) were used for this purpose. In both oddball paradigms, stimuli with phonemic contrast in articulation place, more

specifically the standard stimulus /be/ and deviant stimulus /ge/, were used to elicit the ERPs. The standard and deviant stimulus were auditorily presented with a probability of 80% and 20%, respectively, in both paradigms. In the inattentive condition (MMN), on average 606 (*SD* = 19.20) standard and 142 (*SD* = 11.05) deviant trials were presented. Standard and deviant stimuli were presented ad random with an inter-stimulus interval of 500 ms. As a distraction, participants were asked to watch a silent movie during auditory presentation of the stimuli. The average number of standard and deviant trials in the attentive condition (P300) equalled 125 (*SD* = 10.15) and 30 (*SD* = 5.52), respectively. Stimuli were presented ad random with an inter-stimulus interval of 2000 ms. In order to focus attention on the stimuli, participants were asked to press a button when hearing a deviant stimulus. Total duration of the electrophysiological assessment, including head preparation (20 min.) and administration of the inattentive (7 min.) and attentive (8 min.) oddball paradigm, was approximately 40 minutes.

ERP data analysis - The obtained EEG data were analyzed using Brain Vision Analyzer 2.2 (Brain Products, Munich, Germany). ERP analysis was performed for each participant separately. Data of the individual participants were not averaged on a group level. Firstly, a high-pass filter of 0.5 Hz (slope 12dB/oct), a low-pass filter of 30 Hz (slope 48dB/oct) and notch filter of 50 Hz were applied to the data. Subsequently, artefacts caused by eye blinking and eye movements were removed using independent component analysis (ICA). Standard and deviant trials were segmented separately. For the MMN paradigm, the EEG was segmented in 500 ms epochs, ranging from 100 ms pre-stimulus to 400 ms post-stimulus. As for the P300 paradigm, the EEG was segmented in 1100 ms epochs, ranging from 100 ms pre-stimulus to 1000 ms post-stimulus. Following segmentation, baseline correction was applied to each epoch, using a pre-stimulus window of 100 ms, and trials containing data exceeding ± 100 µV were rejected. For the P300 paradigm, trials containing an incorrect button press response of the participant, both in terms of a button press in response to the standard stimulus and the absence

of a button press in response to the deviant stimulus, were not rejected. Finally, an average waveform was computed for the standard and deviant trials separately. A difference wave was computed by subtracting the average standard from the average deviant waveform.

Single-subject level interpretation of ERPs is most reliable when multiple analysis techniques are combined (Kallionpää et al., 2019). The current study combined visual inspection of the ERP waveforms and comparison of peak amplitude and latency measures to normative data (Aerts et al., 2013). First, the morphology of the obtained average waveforms and the associated topographical distribution were visually inspected by two researchers. The presence of the MMN and P300 component was assessed by both researchers independently in the predetermined time windows of 100-300 ms and 300-750 ms, respectively. This was done based on the exact figures that are presented in this paper (Figures 1 – 10). A component was labeled as present only when both researchers classified it as such. The visual inspection constitutes an essential step in avoiding type II statistical errors. That is, the classification of a waveform as being typical based on comparison of amplitude and latency values of an automatically identified peak with a control group, when no component can in fact be perceived. Following the visual assessment, in case of a present component, the peak was identified based on visual inspection in the predefined time window. To allow comparison with age-specific normative data (Aerts et al., 2013), peak amplitude (μV) and latency (ms) were extracted. For the MMN, peak amplitude and latency of the average difference wave were determined at Fz and Cz electrodes, as the MMN is associated with a fronto-central midline distribution (Luck, 2014). Subsequently, in accordance with the normative data collected by Aerts et al. (2013), mean peak amplitude and latency of the two electrodes were calculated using the following formula: (Fz + Cz)/2. With regard to the P300 waveform, peak amplitude and latency of the average deviant waveform were determined at the Pz electrode, as P300 amplitude has been reported to be maximal at midline parietal sites (Luck, 2014).

To compare individual participant MMN and P300 peak amplitude and latency values with normative data composed by age decade (Aerts et al., 2013), the modified t-test for case-control comparison by Crawford et al. (2010) was adopted. A significance level of $p < 0.05$ was adopted. Two-tailed p-values were interpreted for both amplitude and latency. In terms of amplitude, we identified significantly increased and decreased amplitude values, whereas in terms of latency only increased values were considered to be of interest.

3. Results

As participant data were processed and statistically analyzed on a single-subject level, the results are reported for each case separately. In the first part of the following result section, behavioural and electrophysiological results of each participant are discussed in comparison to age-specific normative values. Subsequently, postoperative language outcome of the participants is described in relation to the preoperative results. Finally, electrophysiological outcome is reported in relation to behavioural language results.

3.1.Cases

Individual results of behavioural language assessment using the AAT and the BNT are listed in table 2. Raw MMN peak amplitude (µV) and latency (ms) values at each assessment, as well as comparison of these measures to age-specific normative values (Aerts et al., 2013), are reported in table 3. For the P300 paradigm, this information, complemented with the percentage of correct button presses in response to a deviant stimulus, is displayed in table 4. The number of participants obtaining behavioural and ERP measures that are comparable to age-specific controls at pre- and postoperative assessment is summarized in table 5.

Participant 1 (P1)

P1, a 56 year old righthanded male, was first diagnosed with an oligodendroglioma grade II in the frontal lobe at the age of 43. Over the course of 13 years, resective surgery was performed twice. Linguistic assessment following the second surgery revealed normal functional communication. However, both semantic and phonological paraphasias were observed on the BNT. Follow-up neuroimaging by means of MRI and DTI revealed recurrence of the lesion in the left frontal operculum with subcortical disruption of the arcuate fasciculus (AF), whereupon a third resection during an awake craniotomy with an asleep-awake-asleep protocol was performed.

- Preoperatively

Behavioural results – Preoperative assessment using the AAT indicated mildly impaired language comprehension (84^{th} percentile). Qualitative error analysis revealed this score originated from the identification of several semantically related test items in relation to both auditory and written word and sentence comprehension. Moreover, mildly impaired naming, characterized by semantic descriptions, neologisms and semantic paraphasias, was evidenced by the BNT (48/60). The latter symptoms were also present in the spontaneous language. Additionally, the participant reported mild concentration and memory deficits.

ERP results – Based on visual inspection of Figure 1, the MMN was found to be present preoperatively. Comparison to the age-specific normative control group revealed amplitude values that did not differ significantly from neurotypical adults (-3.40 µV; $p = 0.705$). Marginally significant results were found in relation to MMN latency values (266 ms; $p = 0.028$). The P300 was found to be absent by two independent assessors (Figure 2).

- 3 Months postoperatively

Behavioural results – Performance on the AAT and BNT was within the normal range.

ERP results – Based on visual inspection of the ERP waveforms, both the MMN (Figure 1) and P300 (Figure 2) were found to be present. Furthermore, peak amplitude (-2.27 µV; p = 0.272) and latency (225 ms; p = 0.317) of the MMN were in accordance with age-related normative values. The P300, as well, exhibited amplitude (11.46 µV; p = 0.884) and latency (392 ms; p = 0.620) characteristics that did not differ significant from the control group.

Participant 2 (P2)

P2 is a 72 year old, right handed male who initially reported worsening complaints of dizziness and vertigo. A grade III anaplastic astrocytoma in the left frontal lobe with mass effect on the anterior horn of the lateral ventricle was identified using MRI. DTI showed normal white matter tract diffusion properties in the area of the infiltrative tumour.

- Preoperatively

Behavioural results – Preoperative language assessment using the CAT-NL, as well as assessment of spontaneous speech, revealed no overt symptoms indicating language impairment. In contrast, an aberrant performance was achieved on the BNT (48/60), primarily driven by semantic descriptions, semantic paraphasias and neologisms. The participant himself did not report any communicative disturbances.

ERP results – Based on visual inspection of Figure 3, the MMN proved to be present. Comparison to healthy controls indicated both peak amplitude (-3.37 µV; p = 0.845) and latency (183 ms; p = 0.776) to be within the normative range. The P300 was absent preoperatively upon visual inspection of Figure 4.

- 3 Months postoperatively

Behavioural results – Postoperative language assessment by means of the CAT-NL indicated normal language function. Impaired word retrieval, however, was evidenced by a score of 46/60

on the BNT, with errors of mainly semantic nature (semantic descriptions, paraphasias and neologisms).

ERP results – Based on visual inspection (Figure 3), the MMN was found to be present and showed amplitude (-2.53 µV; p = 0.420) and latency (184 ms; p = 0.758) values in accordance with age-specific normative data. In contrast to preoperative assessment, the P300 was judged to be present (Figure 4) and exhibited peak amplitude (7.36 µV; p = 0.276) and latency (404 ms; p = 0.412) values that were not significantly different from controls.

Participant 3 (P3)

P3, a 27 year old, left handed male with left lateralized language dominance based on fMRI results, was diagnosed with a grade II oligodendroglioma following an epileptic seizure. MRI confirmed a glioma in the anterior part of the left medial temporal gyrus, with cortical and subcortical mass effect. A second lesion was identified in the anterior part of the inferior temporal gyrus. DTI revealed medially displaced white matter tracts in the left temporal lobe.

- Preoperatively

Behavioural results – Preoperative assessment by means of the AAT showed moderately impaired comprehension (79th percentile). Qualitative error analysis disclosed that errors mainly occurred at the level of auditory word comprehension, where a semantically related image was identified at multiple occasions. Spontaneous speech, however, revealed no pronounced impairments, nor did the participant report any functionally limiting communication impairments.

ERP results – Visual inspection of Figure 5, as well as comparison to normative amplitude and latency values, revealed the presence of an MMN with a peak amplitude (-1.84 µV; p = 0.271) and latency (207 ms; p = 0.206) within the age-specific control range. The P300, although

present (3.62 µV; $p = 0.152$), showed a severely delayed latency (750 ms; $p < 0.001$) compared to healthy controls (Figure 6).

- 3 Months postoperatively

Behavioural results – At 3 months post-surgery, the AAT revealed mild comprehension impairment (pc 89), mainly originating at the level of auditory word comprehension.

ERP results – Visual inspection of Figure 5 showed a present MMN with amplitude (-2.13 µV; $p = 0.324$) and latency (169 µV; $p = 0.948$) values not significantly differing from the normative group. As for the P300, the component was present (4.46 µV; $p = 0.188$; Figure 6) but peak latency remained severely delayed (632 ms; $p < 0.001$).

- 6 Months postoperatively

Behavioural results – The established comprehension impairment at 3 months post-surgery did not persist at 6 months post-surgery, where normal AAT and BNT outcome were obtained.

ERP results – At 6 months post-surgery, impairments in ERP results resolved as both the MMN (Figure 5) and the P300 (Figure 6) were shown to be present upon visual inspection. At this time, MMN amplitude (-3.80 µV; $p = 0.768$) and latency (152 ms; $p = 0.540$) values, nor peak amplitude (6.53 µV; $p = 0.307$) and latency (364 ms; $p = 0.290$) of the P300, were significantly different from neurotypical controls.

Participant 4 (P4)

P4 is a 52 year old righthanded male with a recurrent glioblastoma multiforme (GBM) (WHO grade IV) in the temporal lobe. Prior to the awake surgery, P4 had already undergone two partial resections in the course of two years. Following the second surgery, behavioural linguistic assessment indicated severe memory impairment and mildly impaired semantic and grammatical processing. MRI prior to the third resection surgery revealed a recurrent lesion at

the level of the left anterior superior temporal gyrus and medial temporal gyrus with latero-basal deviation and disruption of the AF.

- Preoperatively

Behavioural results – Preoperative behavioural assessment indicated performance on the AAT to be within the normal range, but mildly impaired BNT outcome (44/60). Qualitative error analysis revealed impaired word retrieval was characterized by semantic descriptions, semantic paraphasias and neologism. Semantic self-cueing was adopted as a strategy to overcome the word finding deficits and the participant proved sensitive for phonological cueing. Also, the participant reported mildly impaired concentration and working memory and impaired retrieval of proper names.

ERP results – Visual inspection of Figure 7 revealed the presence of an MMN component which exhibited amplitude values comparable to the normative group (-2.92 µV; $p = 0.491$) and occurred within the expected time frame (158 ms; $p = 0.522$). Based on visual inspection of Figure 8, it was concluded that the P300 was present (4.26 µV; $p = 0.126$). Comparison to healthy controls, however, identified an increase in latency (616 ms; $p = 0.001$).

- 5 Months postoperatively

Behavioural results – Behavioural assessment at 5 months post-surgery revealed mildly impaired outcome on the AAT subtests 'repetition' (89th percentile) and 'naming' (83th percentile). Impaired repetition was specified to the sentence level, showing an increased number of errors with increasing phrase length. Based on the BNT (45/60), impaired naming, characterized by semantic descriptions, semantic neologisms and phonological paraphasias, was established.

ERP results – Visual inspection of Figure 7 revealed the presence of an MMN with amplitude (-3.86 µV; p = 0.937) and latency (220 ms; p = 0.378) in accordance with age-specific normative values. The P300 was found to be absent (Figure 8).

Participant 5 (P5)

P5 is a 28 year old, right handed male, who was first diagnosed with an oligo-astrocytoma grade III located in the anterior left frontal gyrus, reaching to the supplementary motor area/precentral motor cortex, at the age of 25. At this time, DTI showed no involvement of white matter tracts. Although resective surgery was performed twice, MRI confirmed the high-grade recurrent growth of an anaplastic oligodendroglioma (grade III) on the posterior side of the previously resected area. No communication deficits were reported following the first two resections.

- Preoperatively

Behavioural results – Preoperative language assessment by means of the AAT and BNT revealed no aphasia symptoms. Similarly, spontaneous language did not reveal any impairment and the participant himself did not report any preoperative changes in language.

ERP results – Visual inspection of Figure 9 confirmed the presence of the MMN (-5.32 µV; p = 0.717) with a latency that was marginally significantly increased (231 ms; p = 0.078) compared to healthy controls. The P300 component was judged to be absent upon visual inspection of Figure 10.

- 3 months postoperatively

Behavioural results – At 3 months post-surgery, no language deficits were observed based on the administration of the AAT and BNT.

ERP results – Based on visual inspection of Figure 9 and 10, the presence of the MMN and P300, respectively, was confirmed at postoperative assessment. MMN amplitude (-4.07 µV; p

= 0.589) and latency (202 ms; p = 0.327) did not differ significantly from the age-matched control group. Similarly, the P300 showed amplitude (12.93 µV; p = 0.987) and latency (368 ms; p = 0.332) values comparable to the controls.

3.2.Pre- to Postoperative Evolution of Phoneme Perception Processes and Language Outcome

Three out of the five included participants (P1, P3 and P5) exhibited complete postoperative normalization of behavioural and/or electrophysiological linguistic outcome, compared to preoperative assessment. Behaviourally, P1 and P3 showed mildly aberrant preoperative results on the AAT and BNT. Postoperatively, however, all three participants reached behavioural ceiling effects. For P1 and P5, this was the case at three months postoperative, whereas P3 only reached an outcome comparable with age-matched controls six months after tumour resection. An MMN with marginally significantly latency values in terms of increased latency was identified in P1 and P5 preoperatively. MMN normalized at postoperative assessment resulting in amplitude and latency values in accordance with age-specific normative values in all participants. All five participants displayed either increased P300 latency or an absent P300 component preoperatively. At three (P1, P2, P5) to six (P3) months postoperatively, a P300 component was present in these four participants and amplitude and latency values were within the age-specific normative range. In contrast, aggravated postoperative language outcome was obtained in P4, compared to preoperative assessment. Behavioural postsurgical assessment demonstrated mildly aberrant outcome on the BNT, as well as on the subtests ‘naming’ and ‘repetition’ of the AAT, in this participant. Although an MMN was present and not significantly different from controls both pre- and postoperatively, no P300 component could be identified following tumour resection. Preoperatively, this component was merely delayed. Figure 11 visualizes the evolution of MMN and P300 peak amplitude and latency values between pre- and postoperative assessment for each participant using a line plot.

3.3.Behavioural versus Electrophysiological Language Outcome

Behavioural ceiling effects on the AAT/CAT-NL were assessed in relation to ERP measures (MMN and P300 peak amplitude and latency) to establish the added diagnostic value of linguistic ERPs in glioma patients. Although no preoperative linguistic impairments were established in P2 aside from a mildly reduced score on the BNT, the P300 component was missing. Similarly, despite preoperative behavioural assessment using the AAT indicating normal language function in P4, a delayed P300 component was observed. P5 exhibited normal preoperative language outcome on the AAT, while electrophysiological assessment revealed a MMN that was marginally significantly delayed and absent P300 component. In both P1 and P3, no discrepancy was observed between preoperative behavioural and electrophysiological outcome, as both were found to be impaired. Nevertheless, whereas behavioural assessment indicated only mild impairment on the AAT 'comprehension' subtest, electrophysiological assessment revealed a marginally significantly delayed MMN component and absent P300 component in P1, as well as a P300 with a severe delay in P3.

4. Discussion

This study aimed to assess the neural processes underlying phoneme perception both pre- and postoperatively in patients with a glioma undergoing an awake craniotomy. To this end, five individuals with a glioma in an eloquent language area were subjected to pre- and postsurgical linguistic follow-up. The assessment included the administration of an inattentive (MMN) and attentive (P300) oddball paradigm containing a phonemic articulation place contrast, as well as the administration of the AAT/CAT-NL and BNT. Secondly, it was set out to determine the added value of ERPs reflecting phoneme perception, in addition to the behavioural language

batteries, in the pre- and postoperative clinical approach to the language assessment in these patients.

4.1.Pre- to Postoperative Evolution of Phoneme Perception Processes

Gliomas infiltrating eloquent cortical areas and white matter tracts can cause disruptions of functional linguistic (sub)networks, thus interfering with network connectivity (Herbet and Duffau, 2020). In turn, altered network connectivity may affect the neurolinguistic processes (e.g., acoustic-phonological processing, lexico-semantic processing, syntactic processing) supported by these connections and result in functional language deficits. Due to their high temporal resolution, ERPs provide insight in neurolinguistic processes (Luck, 2014). An aberrant or absent ERP component could therefore be interpreted to reflect suboptimal functioning of the involved linguistic (sub)networks as a result of glioma infiltration. Moreover, it can be argued that an absent or aberrant ERP component in terms of amplitude or latency might indicate rearrangement of compromised functional linguistic (sub)networks. That is, due to the slow-growing character of gliomas, they induce various patterns of dynamic reorganization in the affected functional networks (Desmurget et al., 2007), in an attempt to maintain optimal neurolinguistic processing and to preserve language function.

Suboptimal unfolding of the neural processes underpinning phoneme perception was evidenced preoperatively in all participants by an aberrant or absent MMN and/or P300. Tumour-induced changes in the cortical activation patterns underlying these processes might account for these alterations. In particular the P300, more so than the MMN, was found to be highly subject to preoperative changes. That is, while a MMN latency delay was only found in two participants, the P300 was aberrant (either absent or delayed) in all participants. As both components reflect different substages of phoneme perception, the differential impact of tumour growth on the MMN and P300 is little surprising. While the MMN reflects inattentive phoneme discrimination, active attention to speech stimuli and the involvement of domain-general

attentional and working memory related processes is required to elicit a P300. The recruitment of additional domain-general networks might explain why the P300 would appear to be more sensitive to tumour-induced changes. Additionally, the dissociation between these two components highlights the importance of assessing both passive and active perceptual processes in function of identifying the specific stage in which deficits find their origin.

In addition to the atypical neural activity related to phoneme perception, four out of five participants (P1, P2, P3 and P4) exhibited preoperative functional language impairments. An absolute comparison of behavioural and electrophysiological measures would be incorrect, since behavioural measures in the current study were generic, rather than directed at the assessment of phoneme discrimination and categorization, specifically. Nevertheless, anomalous behavioural outcome could be interpreted as the inadequacy of preoperative recruitment to compensate for functional loss in these individuals. As four out of five participants (P1, P2, P4 and P5) presented with a HGG (grade III or IV), tumour grade might partially explain the preoperative findings. That is, the limited potential for preoperative reorganization that has been associated with the rather fast growing character of HGGs compared to LGGs (Deng et al., 2015; Kawashima et al., 2013) could account for the aberrant neural processing governing phoneme perception in these four participants. The increased severity of preoperative functional impairment that was evidenced in these types of tumours by Zhang et al. (2018) is also supported by part the current sample (P1, P2 and P4). Finally, it should be noticed that partial tumour resections had been performed prior to the current surgery in P1, P4 and P5. Since no electrophysiological data were collected prior to or following these previous surgeries, it remains inconclusive whether the preoperatively measured neurophysiological abnormalities stem solely from the current glioma growth or originated earlier.

Postoperatively, three participants (P1, P3 and P5), exhibited complete normalization of preoperatively impaired behavioural and/or electrophysiological linguistic results. Generally, an immediate postoperative language decline is described, followed by a return to the preoperative language level within 3 to 6 months post-surgery (Bonifazi et al., 2020; Norrelgen et al., 2020; Santini et al., 2012). The three participants described above, however, all exceeded their preoperative behavioural and/or electrophysiological language level within 3 (P1 and P5) to 6 months (P3) postoperatively. P2 as well showed postoperative normalization of ERP results, while mild preoperative behavioural impairments did remain present. These findings could be interpreted as reflecting effective tumour resection following the accurate identification and preservation of essential cortico-subcortical structures underlying language processing, in particular phoneme perception, during intraoperative language mapping. Cargnelutti et al. (2020) argued that postoperative conservation or improvement of language function is not solely the result of preservation of fundamental brain areas. Preserving connectivity within the entire linguistic network is crucial for cerebral plasticity. In particular, white matter integrity proves to be a major determinant for the brain's adaptation capacity. A low potential for neuroplasticity is generally attributed to white matter tracts (Herbet et al., 2016; Ius et al., 2011). For instance, glioma infiltration at the level of the inferior fronto-occipital fasciculus (IFOF) and AF, two pathways described to be part of the language network (Friederici, 2011; Friederici, 2015), was found to induce severe language disorders (Almairac et al., 2015; Fang et al., 2021). In light of this, the current results suggest that adequate preservation of fundamental brain areas and white matter connectivity in these four participants allowed for the linguistic (sub)network governing phoneme perception to recover postoperatively (Cargnelutti, et al., 2020; Duffau, 2014). In relation to HGG's specifically, Kawashima et al. (2013) established that the limited preoperative plasticity potential can nevertheless be accommodated postoperatively. Despite preoperative impairment, two out of

the four participants with a HGG (P1 and P5) in the present study showed postoperative recovery of behavioural measures and neurolinguistic activation patterns during phoneme perception. The present results therefore add to the assumption of a high postoperative neural adaptation potential in HGG patients.

In contrast to the four participants discussed above, postoperative language assessment in P4 revealed a decline in language function compared to presurgical results. The established linguistic deterioration suggests an inadequate intraoperative identification of fundamental language areas, resulting in the impossibility to maintain functional connectivity of the involved linguistic networks. However, a number of factors should be taken into account when interpreting these findings: (1) P4 was diagnosed with a type IV glioblastoma multiforme, reported to be aggressive, highly invasive tumours that tend to infiltrate white matter (Esmaeili et al., 2018). Neuroimaging did, indeed, reveal invasion of the AF. White matter tracts, and specifically the AF, have been extensively described to exhibit limited neuroplastic potential (Cargnelutti et al., 2020; Ius et al., 2011; Herbet et al., 2016; Kong et al., 2016). (2) Despite the proven worsening of ERP measures, the participant reported only mild impairments in functional communication. Moreover, adequate performance on the subtest 'comprehension' of the AAT indicated the absence of any auditory comprehension deficits, suggesting that abnormalities in the neural processing of phoneme characteristics do not necessarily translate to severe functional language impairment. Alternatively, qualitative error analysis of the mildly impaired BNT outcome did reveal production errors of a phonological nature (phonological paraphasias) and the P300 task was associated with poor button press accuracy (31.58%), indicating functional difficulties with the categorization of phonemes based on articulation place. (3) Preoperative neuroplasticity in patients with a glioma primarily manifest in perilesional tissue (Cargnelutti et al., 2020; Desmurget et al., 2007). As P4 previously

underwent two resective surgeries, one can argue that the possibility of perilesional reorganization was limited.

4.2. Clinical Application of Linguistic ERPs: added Value to Pre- and Postoperative Diagnostics

The present study investigated whether complementing the generally administrated generic aphasia batteries (Martin-Monzon et al., 2020) with the mapping of neurolinguistic subprocesses can provide added value in the clinical approach to the language assessment in glioma patients. Due to the slow growth of gliomas and the associated adaptive plasticity, language in patients with brain tumours is generally characterized by minimal or absent functional communication impairments, often resulting in ceiling effects on behavioural assessment (Deverdun et al., 2020; van Dokkum et al., 2019). We can presume that the interference of tumour growth with the neural processing underlying a particular language aspect will induce changes in the ERP component reflecting this process. These changes can either be accompanied by functional preservation or loss, indicating satisfactory or inadequate compensatory reorganization, respectively (Laganaro et al., 2008). All participants included in the present study exhibited preoperative abnormalities in neural phoneme discrimination and/or categorization processes, as evidenced by aberrant MMN and P300 measures. Four out of these five individuals presented with accompanying behavioural communication deficits on the AAT, CAT-NL or BNT, as well as inadequate identification of the deviant phonemes on the button press response associated with the attentive oddball task. As the glioma-induced neural processing changes were accompanied by optimal function on phoneme categorization and general language domains in only one participant, these results may imply inadequate preoperative compensatory activation changes in the other participants. As discussed before, the type III or IV tumour grade observed in four out of five participants and the reduced potential for preoperative neural adaptation associated therewith, could contribute to this.

Based on these results, we argue that the combination of behavioural and electrophysiological language assessment might provide added value in the preoperative diagnostic protocol in the context of glioma resection. An understanding of the effect of tumour growth on the neural processing underlying specific linguistic sublevels supplemented by information on the corresponding behavioural level, could influence the degree to which this is addressed during the intraoperative language mapping. Nevertheless, it must be emphasized that the behavioural tests administrated in the present study oblige us to interpret these results with caution. The AAT and CAT-NL identify general language deficits but are unable to detect the specific linguistic processes assessed by the ERPs. Future research should address the complementarity of MMN and P300 measures on the one hand and behavioural tests investigating phoneme perception in specific, such as the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay et al., 1996) or DIMA (Satoer et al., 2022), on the other.

Postoperatively, a lack of linguistic follow-up has been reported in patients with a glioma (De Witte & Mariën, 2013; Martin-Monzon et al., 2020). Whereas behavioural ceiling effects might be rapidly achieved postoperatively, ERPs enable the mapping of minimal longitudinal plasticity induced changes in neurolinguistic processing. Thus, ERPs could postoperatively facilitate the identification of minimally impaired neurolinguistic processing and contribute to the subsequent identification of therapeutic goals. Although participant 4 exhibited postoperative clinically meaningful impairments, the patient did not wish to receive rehabilitation, as the impairments were not of a functionally limiting nature. Additionally, as gliomas are often resected only partially or subtotally in order to optimize the onco-functional balance (Ferracci & Duffau, 2018), they exhibit a high recurrence rate. ERPs might provide added value in the follow-up of resected gliomas where they could potentially serve as a first indicator of recurrence in combination with other neuroimaging methods (MRI, PET).

4.3.Limitations and Directions for Future Research

When interpreting the presented results, some limitations of this study should be taken into account. Firstly, the administered ERP paradigms are limited to the assessment of phoneme perception. While this provides considerable information, future research should include paradigms assessing semantic and syntactic processing (Cocquyt et al., 2021; Dorme et al., 2023). Secondly, two limitations relating to the ERP recording and analysis parameters, that were adopted from Aerts et al. (2013) in function of comparison with the normative control data, should be discussed. While a high-pass filter of 0.5 Hz was applied, Duncan et al. (2009) stated that a 0.1 Hz filter is preferred in relation to MMN and P300 ERP analysis. That is, high-pass filters set above 0.3 Hz may generate artefacts, potentially resulting in false conclusions (Tanner et al., 2015). Moreover, the use of an online linked ears reference is not recommended as this induces distortion of the topographic voltage distribution (Yao et al., 2019). In contrast, the adoption of an online nose reference with subsequent offline re-referencing to the mastoid electrodes is advised (Duncan et al., 2009). Thirdly, due to the low number of participants included, the reported results are preliminary and require statistical validation in a larger sample. Fourthly, a heterogeneous population was included in terms of tumour grade, type, location, the number of previous surgeries… While this reflects the heterogeneity of the clinical population of patients with a brain tumour undergoing awake surgery, it limits the possibility to draw conclusions that relate to a specific subgroup. Lastly, postoperative follow-up is limited to one assessment in our sample. Future research should consider long-term follow-up with multiple assessments to provide longitudinal insight in postoperative recovery mechanisms.

In addition, a number of limitations associated with the use of ERPs must be addressed. The reliability of ERPs at the single-case level has been widely debated and depends on a number of factors. Firstly, personal anatomical factors such as skull thickness and cortical folding patterns influence individual ERPs (Beres, 2017). In this respect, more specifically the issue of volume conduction arises (van den Broek et al., 1998). Both glioma growth and the surgical

resection thereof induce changes in the cerebral anatomy and histological properties of the brain (Latikka & Eskola, 2019). Event-related potentials of glioma patients were compared with those of neurotypical adults on one hand, and compared between the pre- and postsurgical stage on the other. Differences or changes in brain and tumour properties, affecting the signal conductivity may therefore partially underly the reported differences in ERP characteristics. Secondly, despite a high temporal resolution, the limited spatial resolution of ERPs is generally cited as a major shortcoming, as this impedes the identification of the ERP components' neural generators (Kaan, 2007; Luck, 2014). The reported topographical distribution can hardly provide information on neural generators of the ERP and should therefore not be interpreted as such. Increasingly improved techniques for ERP source localization and functional connectivity analysis (Gaudet et al., 2020; Hnazaee et al., 2018; Hnazaee et al., 2020), however, allow the mapping of neural generators and (sub)networks underlying linguistic processes using high-density EEG. Applying these techniques to pre- and postoperatively collected electrophysiological data could therefore provide a higher precision in the spatial domain in future research.

Acknowledgments

This work was supported by the Research Foundation Flanders (FWO) under Grant G000720N.

Declaration of interest statement

None

Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

References

Aerts, A., van Mierlo, P., Hartsuiker, R., Santens, P., & De Letter, M. (2015). Neurophysiological sensitivity for impaired phonological processing in the acute stage of aphasia. *Brain & Language, 149*, 84–96. doi:10.1016/j.bandl.2015.07.001.

Aerts, A., van Mierlo, P., Hartsuiker, R.J., Hallez, H., Santens, P., & De Letter, M. (2013). Neurophysiological investigation of phonological input: Ageing and development of normative data. *Brain & Language, 125*, 253-263. doi:10.1016/j.bandl.2013.02.010.

Almairac, F., Herbet, G., Moritz-Gasser, S., de Champfleur, N. M., & Duffau, H. (2014). The left inferior fronto-occipital fasciculus subserves language semantics: a multilevel lesion study. *Brain Structure and Function, 220*(4), 1983–1995. doi:10.1007/s00429-014-0773-1

Benzagmout, M., Gatignol, P., & Duffau, H. (2007). Resection of World Health Organization Grade II gliomas involving Broca's area. *Neurosurgery*, *61*(4), 741–753. doi:10.1227/01.neu.0000298902.69473.77

Beres, A. (2017). Time is of the essence: A review of Electroencephalography (EEG) and Event-Related Brain Potentials (ERPs) in language research. *Applied Psychophysiology and Biofeedback, 42*, 247-255. doi:10.1007/s10484-017-9371-3.

Becker, F., & Reinvang, I. (2007). Event-related potentials indicate bi-hemispherical changes in speech sound processing during aphasia rehabilitation. *Journal of Rehabilitation Medicine, 39,* 658-661. doi:10.2340/16501977-0112.

Bledowski, C., Prvulovic, D., Hoechstetter, K., Scherg, M., Wibral, M., Goebel, R., & Linden, D. (2004). Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. *The Journal of Neuroscience, 24*(42), 9353-9360. doi:10.1523/JNEUROSCI.1897-04.2004.

Bonifazi, S., Passamonti, C., Vecchioni, S., Trignani, R., Martorano, P. P., Durazzi, V., … Ricciuti, R. A. (2020). Cognitive and linguistic outcomes after awake craniotomy in patients with high-grade gliomas. *Clinical Neurology and Neurosurgery, 198*, 106089. doi:10.1016/j.clineuro.2020.106089.

Cargnelutti, E., Ius, T., Skrap, M., & Tomasino, B. (2020). What do we know about pre- and postoperative plasticity in patients with glioma? A review of neuroimaging and intraoperative mapping studies. *NeuroImage, Clinical, 28.* doi:10.1016/j.nicl.2020.102435.

Cho, N.S., Peck, K.K., Zhang, Z., & Holondy, A. (2018). Paradoxical activation in the cerebellum during language fMRI in patients with brain tumors: Possible explanations based on neurovascular uncoupling and functional reorganization. *Cerebellum, 17*(3), 286-293. doi:10.1007/s12311-017-0902-5.

Cirillo, S., Caulo, M., Pieri, V., Falini, A., & Castellano, A. (2019). Role of functional imaging techniques to assess motor and language cortical plasticity in glioma patients: A systematic review. *Neural Plasticity*, 2019, 1–16. doi:10.1155/2019/4056436

Cocquyt, E.M., Knockaert, N., van Mierlo, P., Szmalec, A., Duyck, W., Santens, P., & De Letter, M. (2020a). The phonological Mismatch Negativity and P300 as diagnostic tools in stroke-related aphasia recovery: A longitudinal multiple case study. *Aphasiology*, 1-18. doi:10.1080/02687038.2020.1787946.

Cocquyt, E.-M., Vandewiele, M., Bonnarens, C., Santens, P., & De Letter, M. (2020b). The sensitivity of event-related potentials/fields to logopedic interventions in patients with stroke-related aphasia. *Acta Neurologica Belgica.* doi:10.1007/s13760-020-01378-3.

Cocquyt, E. M., Santens, P., van Mierlo, P., Duyck, W., Szmalec, A., & De Letter, M. (2021). Age- and gender-related differences in verbal semantic processing: The development of

normative electrophysiological data in the Flemish population. *Language, Cognition and Neuroscience*, 1–27. doi:10.1080/23273798.2021.1957137

Crawford, J.R., Garthwaite, P.H., & Porter, S. (2010). Point and interval estimates of effect sizes for the case-controls design in neuropsychology: Rationale, methods, implementations, and proposed reporting standards. *Cognitive Neuropsychology, 27*, 245-260. doi:10.1080/02643294.2010.513967

Deng, X., Zhang, Y., Xu, L., Wang, B., Wang, S., Wu, J., … Zhao, J. (2015). Comparison of language cortex reorganization patterns between cerebral arteriovenous malformations and gliomas: A functional MRI study. *Journal of Neurosurgery, 122*(5), 996–1003. doi:10.3171/2014.12.jns14629

De Witt Hamer, P.C., Robles, S.G., Zwinderman, A.H., Duffau, H., & Berger, M.S. (2012). Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. *Journal of Clinical Oncology, 30,* 2559-2565. doi:10.1200/JCO.2011.38.4818.

De Witte, E., Mariën, P. (2013). The neurolinguistic approach to awake surgery reviewed. *Clinical Neurology and Neurosurgery, 115*, 127-145. doi:10.1016/j.clineuro.2012.09.015.

De Witte, E., Satoer, D., Robert, E., Colle, H., Verheyen, S., Visch-Brink, E., & Mariën, P. (2015). The Dutch Linguistic Intraoperative Protocol: A valid linguistic approach to awake brain surgery. *Brain & Language, 140,* 35-48. doi:10.1016/j.bandl.2014.10.011.

Desmurget, M., Bonnetblanc, F., & Duffau, H. (2007). Contrasting acute and slow-growing lesions: a new door to brain plasticity. *Brain, 130,* 898-914. doi:10.1093/brain/awl300.

Deverdun, J., van Dokkum, L.E.H., Le Bars, E., Herbet, G., Mura, T., D'agata, B., …, & Moritz-Gasser, S. (2020). Language reorganization after resection of low-grade gliomas: An fMRI task based connectivity study. *Brain Imaging and Behavior, 14*, 1779-1791. doi:10.1007/s11682-019-00114-7.

Dorme, A., Van Oudenhove, B., Criel, Y., Depuydt, E., De Groote, E., Huysman, E., … , & De Letter, M. (2023). Effect of healthy aging and gender on syntactic input processing: A P600 Event-Related Potential study. *Journal of Speech Language and Hearing Research.*

Duffau, H. (2014). The huge plastic potential of adult brain and the role of connectomics: New insights provided by serial mappings in glioma surgery. *Cortex, 58,* 325-337. doi:10.1016/j.cortex.2013.08.005.

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., … Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology, 120*(11), 1883–1908. doi:10.1016/j.clinph.2009.07.045

Esmaeili, M., Stensjoen, A.L., Berntsen, E.M., Solheim, O., & Reinertsen, I. (2018). The direction of tumor growth in glioblastoma patients. *Scientific Reports, 8,* 1199. doi:10.1038/s41598-018-19420-z

Fang., S., Liang, Y., Li, L., Wang, L., Fan, X., Wang, Y., & Jiang, T. (2021). Tumor location-based classification of surgery-related language impairments in patients with glioma. *Journal of Neuro-oncology, 155,* 1433-152. doi:10.1007/s11060-021-03858-9

Ferracci, F-X., & Duffau, H. (2018). Improving surgical outcome for gliomas with intraoperative mapping. *Expert Review of Neurotherapeutics, 18*(4), 333-341. doi:10.1080/14737175.2018.1451329.

Friederici, A.D. (2011). The brain basis of language processing: from structure to function. *Psychological Reviews, 91,* 1357-1392. doi:10.1152/physrev.00006.2011

Friederici, A. D. (2015). White-matter pathways for speech and language processing. *Handbook of Clinical Neurology*, 177–186. doi:10.1016/b978-0-444-62630-1.00010-x

Garrido, M. I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009). The mismatch negativity: a review of underlying mechanisms. *Clinical Neurophysiology, 120*(3), 453-463. doi:10.1016/j.clinph.2008.11.029

Gaudet, I., Hüsser, A., Vannasing, P., & Gallagher, A. (2020). Functional brain connectivity of language functions in children revealed by EEG and MEG: A systematic review. *Frontiers in Human Neuroscience, 14*. doi:10.3389/fnhum.2020.00062.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). Boston Naming Test (BNT). *Lea & Febiger.*

Goodglass, H. & Kaplan, E. (1972). The assessment of aphasia and related disorders. *Philadelphia, Boston: Lea & Febiger.*

Graetz, P., De Bleser, R., & Willmes, K. (1992). Akense afasietest (AAT). *Hogrefe.*

Guissani, C., Roux, F.E., Ojemann, J., Sganzerla, E.P., Pirillo, D., & Papagno, C. (2009). Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. *Neurosurgery, 66*(1), 113-120. doi:10.1227/01.NEU.0000360392.15450.C9.

Herbet, G., & Duffau, H. (2020). Revisiting the functional anatomy of the human brain: toward a meta-network theory of cerebral functions. *Physiological Revalidation, 100,* 1181-1228. doi:10.1152/physrev.00033.2019.

Herbet, G., Maheu, M., Costi, E., Lafargue, G., & Duffau, H. (2016). Mapping neuroplastic potential in brain-damaged patients. *Brain, 139,* 829-844. doi:10.1093/brain/awv394.

Hnazaee, M.F., Khachatryan, E., Chehrazad, S., Kotarcic, A., De Letter, M., & Van Hulle, M. (2020). Overlapping connectivity patterns during semantic processing of abstract and concrete words revealed with multivariate Granger Causality analysis. *Scientific Reports, 10(1),* 2803. doi:10.1038/s41598-020-59473-7.

Hnazaee, M.F., Khachatryan, E., & Van Hulle, M. (2018). Semantic features reveal different networks during word processing: An EEG source localization study. *Frontiers in Human Neuroscience, 12,* 503. doi:10.3389/fnhum.2018.00503.

Holodny, A. I., Schulder, M., Ybasco, A., & Liu, W.-C. (2002). translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. *Journal of Computer Assisted Tomography, 26*(6), 941–943. doi:10.1097/00004728-200211000-00014

Ilvonen T.M., Kujala, T., Kiesiläinen, A., Salonen, O., Kozou, H., Pekkonen, E.,…, & Näätänen, R. (2003). Auditory discrimination after left-hemisphere stroke: A mismatch negativity follow-up study. *Stroke, 34*(7), 1746-1751. doi:10.1161/01.STR.0000078836.26328.3B.

Ilvonen, T., Kujala, T., Kozou, H., Kiesilainen, A., Salonen, O., Alku, P. & Naatanen, R. (2004). The processing of speech and non-speech sounds in aphasic patients as reflected by the mismatch negativity (MMN). *Neuroscience Letters, 366,* 235-240. doi:10.1016/j.neulet.2004.05.024.

Ius, T., Angelini, E., de Schotten, M.T., Mandonnet, E., & Duffau, H. (2011). Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: Towards a "minimal common brain". *NeuroImage, 56,* 992-1000. doi:10.1016/j.neuroimage.2011.03.022.

Kaan, E. (2007). Event-related potentials and language processing: A brief overview. *Language and Linguistics Compass, 1*(6), 571-591. doi:10.1111/j.1749-818X.2007.00037.x.

Kallionpää, R. E., Pesonen, H., Scheinin, A., Sandman, N., Laitio, R., Scheinin, H., … Valli, K. (2019). Single-subject analysis of N400 event-related potential component with five different methods. *International Journal of Psychophysiology, 144,* 14-24 doi:10.1016/j.ijpsycho.2019.06.012.

Kawashima, A., Krieg, S. M., Faust, K., Schneider, H., Vajkoczy, P., & Picht, T. (2013). Plastic reshaping of cortical language areas evaluated by navigated transcranial magnetic stimulation in a surgical case of glioblastoma multiforme. *Clinical Neurology and Neurosurgery, 115*(10), 2226–2229. doi:10.1016/j.clineuro.2013.07.012

Kay, J., Lesser, R., & Coltheart, M. (1996). Psycholinguistic assessments of language processing in aphasia (PALPA): An introduction. *Aphasiology, 10*(2), 159–180. doi: 10.1080/02687039608248403

Kong, N.W., Gribb, W.R., & Tate, M.C. (2016). Neuroplasticity: Insights from patients harboring gliomas. *Neural plasticity, 2016*, 1-12. doi:10.1155/2016/2365063.

Laganaro, M., Morand, S., Schwitter, V., Zimmermann, C., & Schnider, A. (2008). Normalisation and increase of abnormal ERP patterns accompany recovery from aphasia in the post-acute stage. *Neuropsychologia, 46*(8), 2265–2273. doi:10.1016/j.neuropsychologia.2008.02.013

Latikka, J., & Eskola, H. (2019). The resistivity of human brain tumours in vivo. *Annals of Biomedical Engineering, 47*(3), 706–713. doi:10.1007/s10439-018-02189-7

Luck, S.J. (2014). An introduction to the event-related potential technique. *The MIT Press, Cambridge*.

Luck, S.J., & Kappenman, E.S. (2012). The Oxford handbook of event-related potential components. *Oxford University Press.* doi: 10.1093/oxfordhb/9780195374148.001.0001

Martin-Monzon, I., Rivero Ballagas, Y., & Arias-Sanchez, S. (2020). Language mapping: A systematic review of protocols that evaluate linguistic functions in awake surgery. *Applied Neuropsychology: Adult,* 1-10. doi:10.1080/23279095.2020.1776287.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta psychologica, 42*(4), 313-329. doi:10.1016/0001-6918(78)90006-9

Näätänen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., … & Luuk, A. (1997). Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature, 385*(6615), 432-434. doi:10.1038/385432a0

Norrelgen, F., Jensdottir, M., & Östberg, P. (2020). High-level language outcomes three and twelve months after awake surgery in low grade glioma and cavernoma patients. *Clinical Neurology and Neurosurgery, 195,* 105946. doi:10.1016/j.clineuro.2020.105946.

Plaza, M., Gatignol, P., Leroy, M., & Duffau, H. (2009). Speaking without Broca's area after tumor resection. *Neurocase, 15*(4), 294–310. doi:10.1080/13554790902729473

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*(10), 2128-2148. doi:10.1016/j.clinph.2007.04.019.

Rahimpour, S., Haglund, M.L., Friedman, A.H., & Duffau, H. (2019). History of awake mapping and speech and language localization: From modules to networks. *Neurosurgical focus, 47*(3). doi:10.3171/2019.7.FOCUS19347.

Rofes, A., Mandonnet, E., Godden, J., Baron, M. H., Colle, H., Darlix, A., … Wager, M. (2017). Survey on current cognitive practices within the European low-grade glioma network: Towards a European assessment protocol. *Acta Neurochirurgica, 159*(7), 1167–1178. doi:10.1007/s00701-017-3192-2

Santini, B., Talacchi, A., Squintani, G., Casagrande, F., Capasso, R., & Miceli, G. (2012). Cognitive outcome after awake surgery for tumors in language areas. *Journal of Neuro-Oncology, 108*(2), 319–326. doi:10.1007/s11060-012-0817-4.

Satoer, D., De Witte, E., Bulté, B., Bastiaanse, R., Smits, M., Vincent, A., … & Visch-Brink E. (2022). Dutch Diagnostic Instrument for Mild Aphasia (DIMA): Standardization and first clinical application in two brain tumour patients. *Clinical Linguistics & Phonetics, 36*(11), 929-953. doi:10.1080/02699206.2021.1992797

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain, 129,* 1371-1384. doi:10.1093/brain/awl090

Sierpowska, J., Rofes, A., Dahlslätt, K., Mandonnet, E., ter Laan, M., Polczynska, M., … & Piai, V. (2022). The aftercare survey: Assessment and intervention practices after brain tumor surgery in Europe. *Neuro-Oncology Practice, 9*(4), 328-337. doi:10.1093/nop/npac029

Stalpaert, J., Miatton, M., Sieben, A., Van Langenhove, T., van Mierlo, P., & De Letter, M. (2021). The electrophysiological correlates of phoneme perception in primary progressive aphasia: a preliminary case series. *Frontiers in Human Neuroscience, 15*. doi:10.3389/fnhum.2021.618549

Surbeck, W., Hildebrandt, G. & Duffau, H. (2015). The evolution of brain surgery on awake patients. *Acta Neurochirurgica, 157,* 77-84. doi:10.1007/s00701-014-2249-8.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150*(3700), 1187-1188. doi:10.1126/science.150.3700.1187

Swinburn, K., Porter, G., & Howard, D. (2014). Comprehensive aphasia test Nederlandstalige bewerking (CAT-NL) (E. Visch-Brink, D. Vandenborre, H. J. de Smet, & P. Mariën, Trans.). Pearson Assessment and Information B.V.

Tanner, D., Morgan-Short, K., & Luck, S. (2015). How inappropriate high-pass filters can produce artifactual effects and incorrect conclusions in ERP studies of language and cognition. *Psychophysiology*, 52(8), 997-1009. doi: 10.1111/psyp.12437

Thiel, A., Herholz, K., Koyuncu, A., Ghaemi, M., Kracht, L. W., Habedank, B., & Heiss, W.-D. (2001). Plasticity of language networks in patients with brain tumors: A positron emission tomography activation study. *Annals of Neurology, 50*(5), 620–629. doi:10.1002/ana.1253

Thust, S. C., Heiland, S., Falini, A., Jäger, H. R., Waldman, A. D., Sundgren, P. C., … Smits, M. (2018). Glioma imaging in Europe: A survey of 220 centres and recommendations for best clinical practice. *European Radiology, 28*(8), 3306–3317. doi:10.1007/s00330-018-5314-5

van den Broek, S. P., Reinders, F., Donderwinkel, M., & Peters, M. J. (1998). Volume conduction effects in EEG and MEG. *Electroencephalography and Clinical Neurophysiology, 106*(6), 522–534. doi:10.1016/s0013-4694(97)00147-8

Van Dokkum, L.E.H., Moritz-Gasser, S., Deverdun, J., Herbet, G., Mura, T., D'Agate, B., …, &, Le Bars, E. (2019). Resting state network plasticity related to picture naming in low-grade glioma patients before and after resection. *NeuroImage: Clinical,* 24, 102010. doi:10.1016/j.nicl.2019.102010.

Yao, D., Qin, Y., Hu, S., Dong, L., Bringas Vega, M. L., & Valdés Sosa, P. A. (2019). Which reference should we use for EEG and ERP practice? *Brain Topography.* doi:10.1007/s10548-019-00707-x

Zhang, N., Xia, M., Qiu, T., Wang, X., Lin, C., Guo, Q., … Zhou, L. (2018). Reorganization of cerebro-cerebellar circuit in patients with left hemispheric gliomas involving language network: A combined structural and resting-state functional MRI study. *Human Brain Mapping*. doi:10.1002/hbm.24324

Table 1. Demographic participant information.

ID	Sex	Age (years)	Handedness	Language dominance[a]	Tumour characteristics				Extent of resection	Number of previous resections
					Lobe	Localization	Type	WHO grade		
P1	Male	55	Right	Left	Frontal	Frontal operculum; arcuate fasciculus	oligodendroglioma	III	partial	2
P2	Male	72	Right	Left	Frontal	Frontal; mass effect on anterior horn of the lateral ventricle	anaplastic astrocytoma	III	partial	0
P3	Male	27	Left	Left	Temporal	aMTG; aITG	oligodendroglioma	II	partial	0
P4	Male	51	Right	Left	Temporal	aSTG; aMTG; sylvian fissure; arcuate fasciculus	glioblastoma multiforme	IV	partial	2
P5	Male	28	Right	Left	Frontal	SFG; anterior cingulate gyrus; reaching to the SMA	oligodendroglioma	III	partial	2

Note. aSTG = anterior superior temporal gyrus, aMTG = anterior medial temporal gyrus, aITG = anterior inferior temporal gyrus, SFG = superior frontal gyrus, SMA = supplementary motor area.

[a] Language dominance was established by means of preoperative fMRI.

Table 2. Participant's outcome obtained on the behavioural linguistic assessment using the Aachen Aphasia Test (AAT), reported in percentiles, the Comprehensive Aphasia Test (CAT-NL), reported in raw scores, and the Boston Naming Test (BNT), reported in raw scores, at pre- and postoperative assessments.

ID	Time of assessment	AAT											CAT-NL					BNT (/60)
		Spontaneous language production						TT	RE	WR	NA	CO	Language comprehension		Language production			
		CB	AP	AL	SE	PH	SY						VLC	WLC	RE	NA	REA	
P1	**preop**	5	5	5	4	5	5	91	98	100	99	84*	-	-	-	-	-	48*
	3 M postop	5	5	5	5	5	5	99	93	100	99	97	-	-	-	-	-	56
P2	**preop**	-	-	-	-	-	-	-	-	-	-	-	65	62	59	96	70	48*
	3 M postop	-	-	-	-	-	-	-	-	-	-	-	64	62	59	91	70	46*
P3	**preop**	5	5	5	5	5	5	100	100	99	99	79**	-	-	-	-	-	-
	3 M postop	5	5	5	5	5	5	100	100	100	100	86*	-	-	-	-	-	-
	6 M postop	5	5	5	5	5	5	100	100	100	100	96	-	-	-	-	-	54
P4	**preop**	5	5	5	5	5	5	98	97	100	96	94	-	-	-	-	-	44*
	5 M postop	5	5	5	5	5	5	97	89*	100	83*	95	-	-	-	-	-	45*
P5	**preop**	5	5	5	5	5	5	100	99	99	99	94	-	-	-	-	-	53
	3 M postop	5	5	5	5	5	5	98	100	100	100	99	-	-	-	-	-	54

Note. preop = preoperative assessment, postop = postoperative assessment, M = months; AAT = Aachen Aphasia Test, CB = communicative behaviour, AP = articulation and prosody, AL = automatic language, SE = semantics, PH = phonology, SY = syntax, TT = subtest 'Token Test', RE = subtest 'repetition', WR = subtest 'written language', NA = subtest 'naming', CO = subtest 'comprehension'; CAT-NL = Comprehensive Aphasia Test – Dutch version, VLC = verbal language comprehension; WLC = written language comprehension; RE = repetition; NA = naming; REA = reading; BNT = Boston Naming Test; *mildly impaired; **moderately impaired.

Table 3. MMN peak amplitude (µV) and peak latency (ms) values as the average of the difference wave at Fz and Cz electrodes ((Fz+Cz)/2) at pre- and postoperative assessments. Values are compared with normative data (Aerts et al., 2013) using Crawford's modified t-test for case-control comparison (Crawford et al., 2010).

ID	Time of assessment	MMN peak amplitude (µV)					MMN peak latency (ms)				
		control group[a]	raw value	p *two-tailed*	t	effect size	control group[a]	raw value	p *two-tailed*	t	effect size
P1	***preop***	-3.98 (1.46)	-3.40	0.705	0.386	0.397	184 (38.6)	266	0.056	2.066	2.126
	3 M postop	-3.98 (1.46)	-2.27	0.272	1.138	1.171	184 (38.6)	225	0.317	1.033	1.063
P2	***prepop***	-3.64 (1.17)	-3.38	0.845	0.206	0.222	172 (34.0)	183	0.776	0.300	0.324
	3 M postop	-3.64 (1.17)	-2.53	0.420	0.878	0.949	172 (34.0)	184	0.758	0.327	0.353
P3	***preop***	-4.48 (2.12)	-1.84	0.271	1.181	1.245	171 (28.2)	207	0.260	1.211	1.277
	3 M postop	-4.48 (2.12)	-2.13	0.324	1.052	1.108	171 (28.2)	169	0.948	-0.067	-0.071
	6 M postop	-4.48 (2.12)	-3.80	0.768	0.304	0.321	171 (28.2)	152	0.540	-0.639	-0.674
P4	***preop***	-3.98 (1.46)	-2.92	0.491	0.706	0.726	184 (38.6)	158	0.522	-0.655	-0.674
	5 M postop	-3.98 (1.46)	-3.86	0.937	0.080	0.082	184 (38.6)	220	0.378	0.907	0.933
P5	***preop***	-4.48 (2.12)	-5.32	0.717	-0.376	-0.396	171 (28.2)	231	0.078	2.018	2.128
	3 M postop	-4.48 (2.12)	-4.07	0.589	0.183	0.193	171 (28.2)	202	0.327	1.043	1.099

Note. preop = preoperatively; postop = postoperatively; M = months

[a] Reported values are mean (standard deviation).

* $p < 0.05$

** $p < 0.01$

Table 4. P300 peak amplitude (µV) and peak latency (ms) values at the Pz electrode at pre- and postoperative assessments. Values are compared with normative data (Aerts et al., 2013) using Crawford's modified t-test for case-control comparison (Crawford et al., 2010).

ID	Time of assessment	P300 peak amplitude (µV)					P300 peak latency (ms)					correct button presses (%)
		control group[a]	raw value	p *two-tailed*	t	effect size	control group[a]	raw value	p *two-tailed*	t	effect size	
P1	***preop***	12.19 (4.78)	AB	-	-	-	418 (50.1)	AB	-	-	-	55,56
	3 M postop	12.19 (4.78)	11.46	0.884	-0.148	-0.153	418 (50.1)	392	0.620	-0.504	-0.519	97,06
P2	***prepop***	11.45 (3.10)	AB	-	-	-	479 (77.5)	AB	-	-	-	100,00
	3 M postop	11.45 (3.10)	7.36	0.276	-1.221	-1.319	479 (77.5)	404	0.412	-0.896	-0.968	90,63
P3	***preop***	13.03 (5.65)	3.62	0.152	-1.580	-1.665	409 (37.7)	750	<0.001**	8.581	9.045	72,73
	3 M postop	13.03 (5.65)	4.46	0.188	-1.439	-1.517	409 (37.7)	632	<0.001**	5.612	5.915	100,00
	6 M postop	13.03 (5.65)	6.53	0.307	-1.091	-1.150	409 (37.7)	364	0.290	-1.132	-1.194	100,00
P4	***preop***	12.19 (4.78)	4.26	0.126	-1.612	-1.659	418 (50.1)	616	0.001*	3.841	3.952	10,00
	5 M postop	12.19 (4.78)	AB	-	-	-	418 (50.1)	AB	-	-	-	31,58
P5	***preop***	13.03 (5.65)	AB	-	-	-	409 (37.7)	AB	-	-	-	92,31
	3 M postop	13.03 (5.65)	12.93	0.987	-0.017	-0.018	409 (37.7)	368	0.332	-1.032	-1.088	85,00

Note. preop = preoperatively; postop = postoperatively; M = months; AB = absent component.

[a] Reported values are mean (standard deviation).

* $p < 0.05$

** $p < 0.01$

Table 5. Number of participants in which behavioural (AAT/CAT-NL and BNT) and ERP (MMN and P300 peak amplitude (µV) and latency (ms) measures are comparable with the age-specific control group (Aerts et al., 2013) at pre- and postoperative assessment.

Test parameter		Number of participants obtaining normal outcome at preoperative assessment	Number of participants obtaining normal outcome at postoperative assessment
Behavioural outcome (AAT/CAT-NL and BNT)		1	3
MMN	**peak amplitude**	5	5
	peak latency	3	5
P300	**peak amplitude**	2	4
	peak latency	0	4

Note. AAT = Aachen Aphasia Test; CAT-NL = Comprehensive Aphasia Test – Dutch version; BNT = Boston Naming Test

Figure 1. MMN results of participant 1. Difference waveform of the MMN at Fz and Cz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the MMN difference waveform at preoperative assessment (C) and postoperative assessment (D).

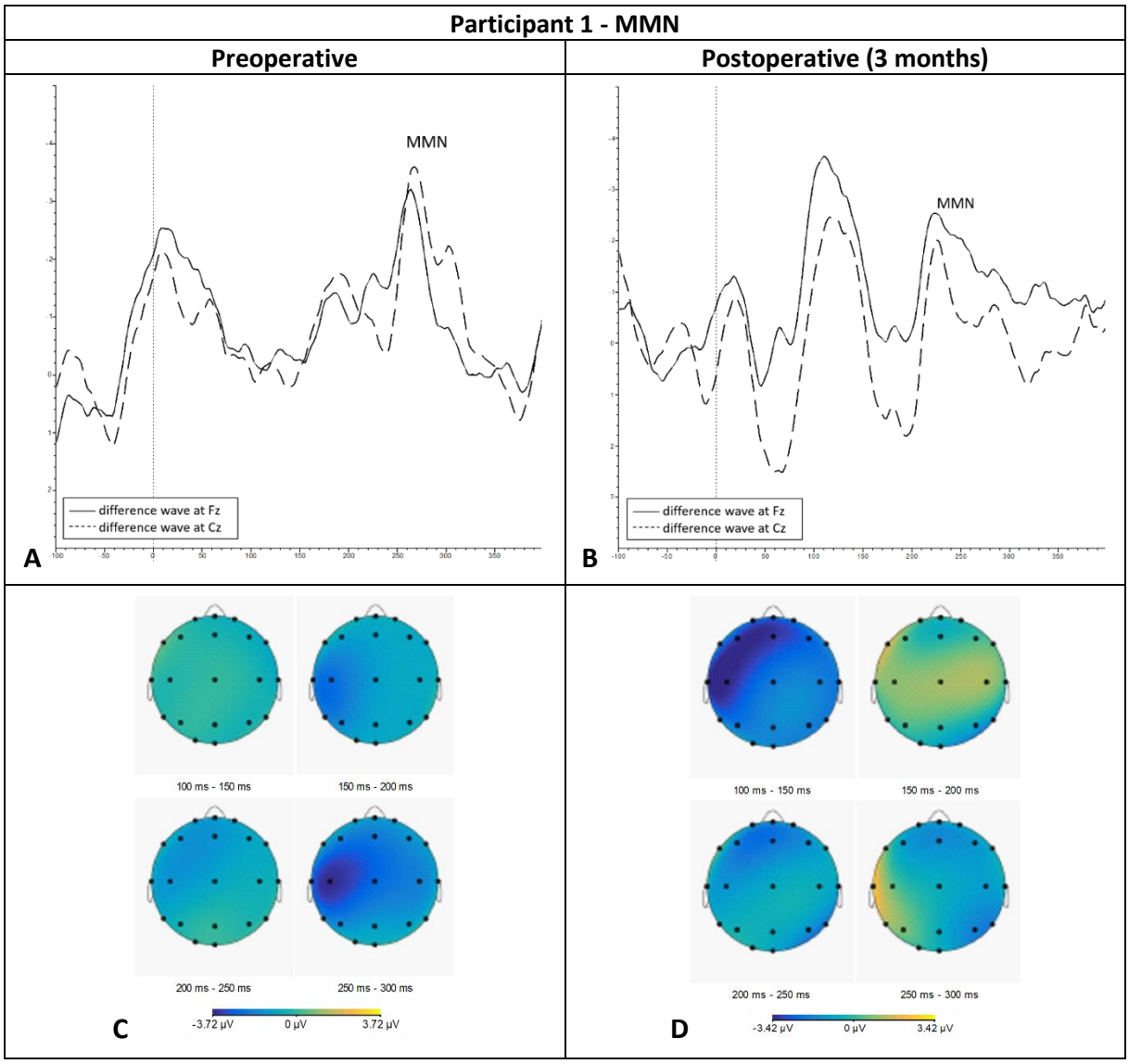


Figure 2. P300 results of participant 1. Standard and deviant waveform of the P300 at Pz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the P300 difference waveform at preoperative assessment (C) and postoperative assessment (D).

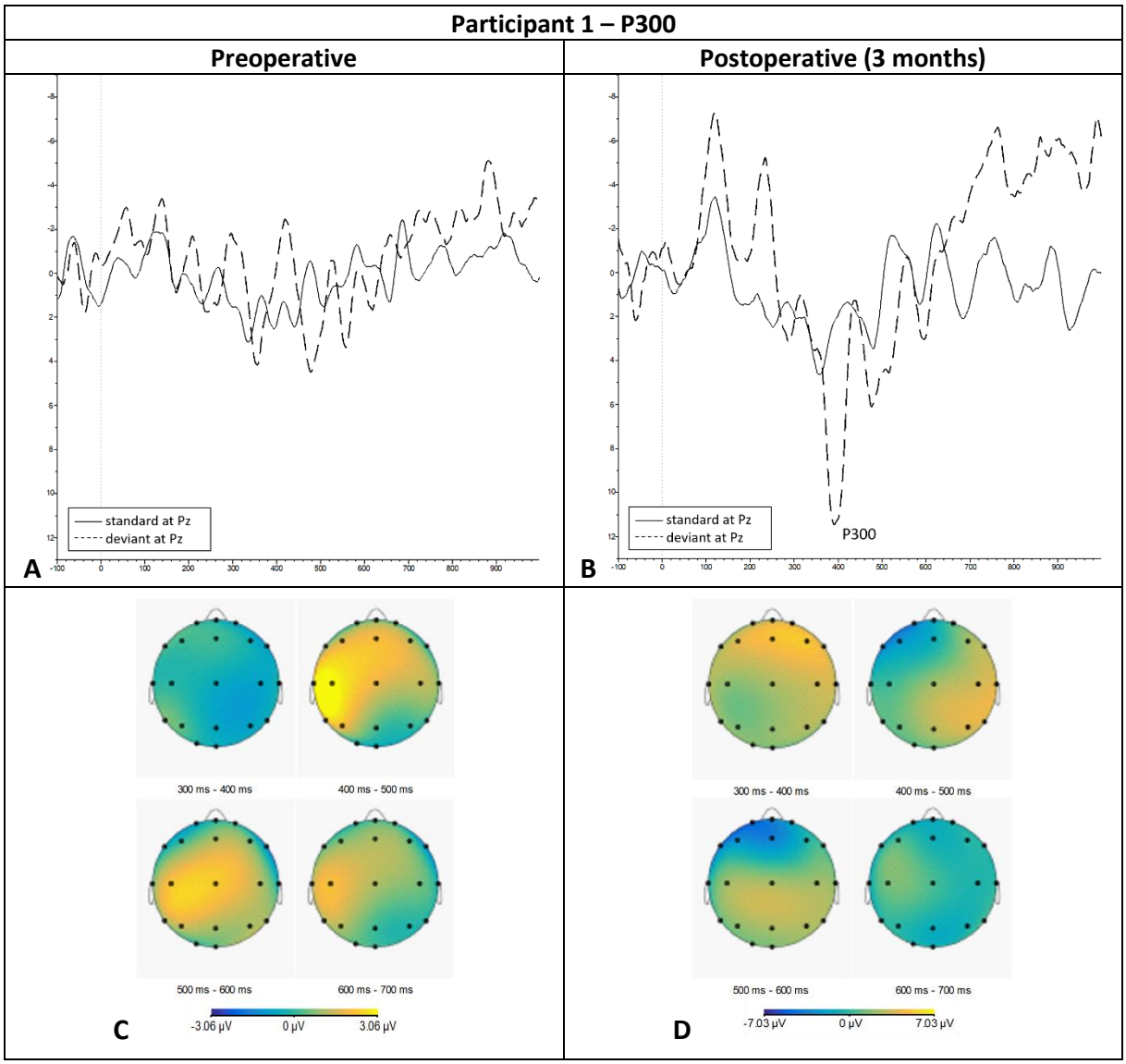


Figure 3. MMN results of participant 2. Difference waveform of the MMN at Fz and Cz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the MMN difference waveform at preoperative assessment (C) and postoperative assessment (D).

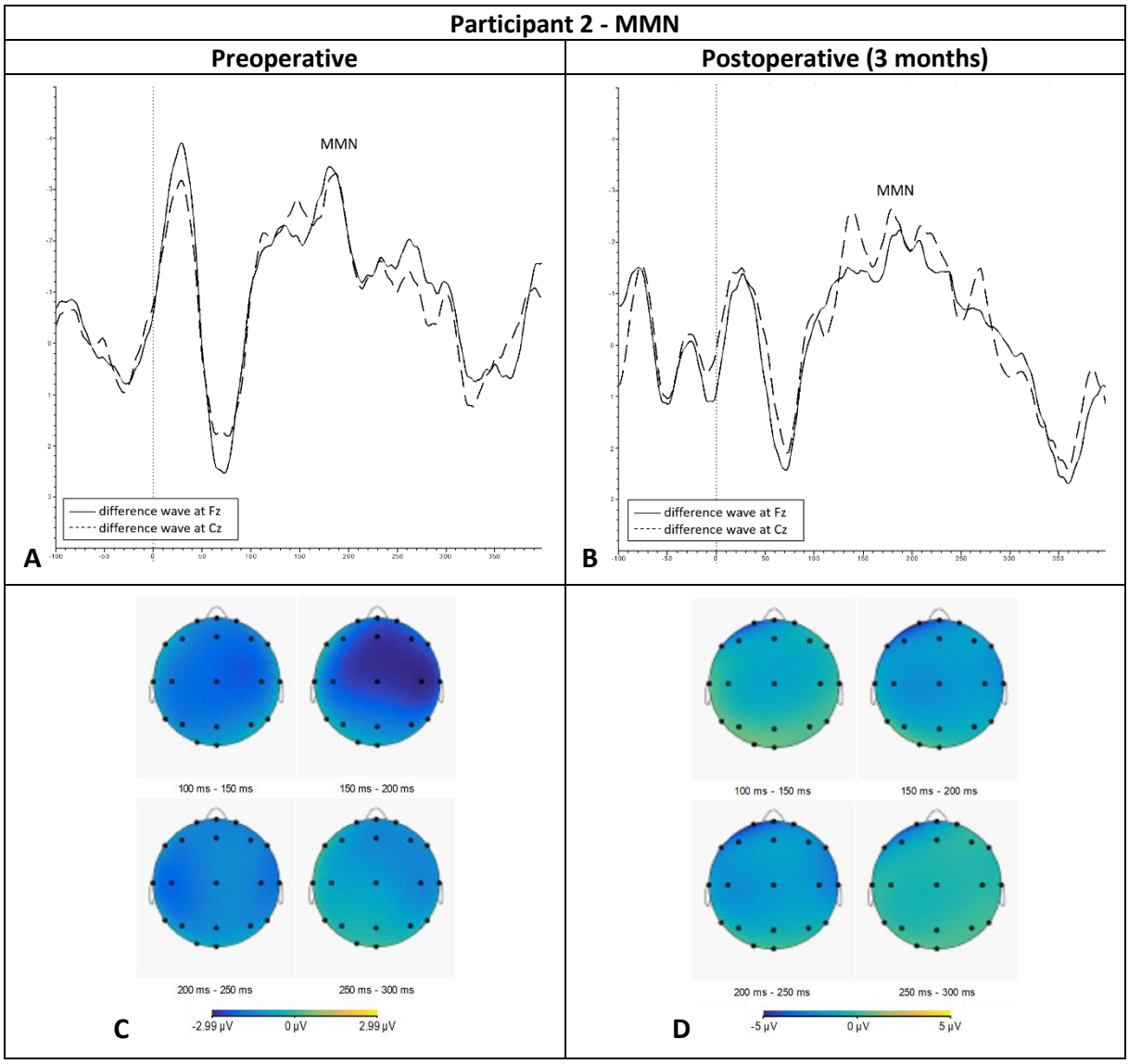


Figure 4. P300 results of participant 2. Standard and deviant waveform of the P300 at Pz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the P300 difference waveform at preoperative assessment (C) and postoperative assessment (D).

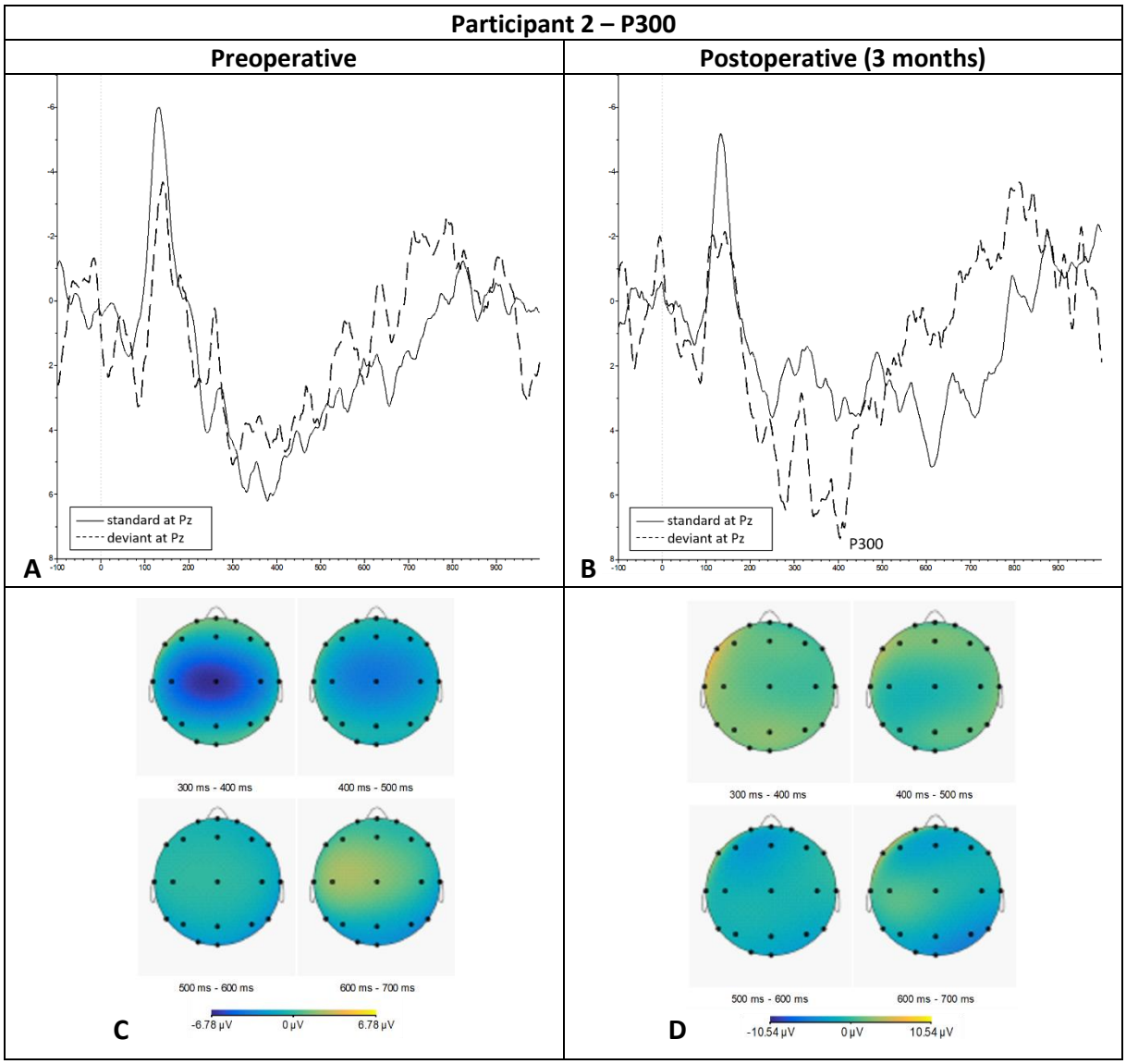
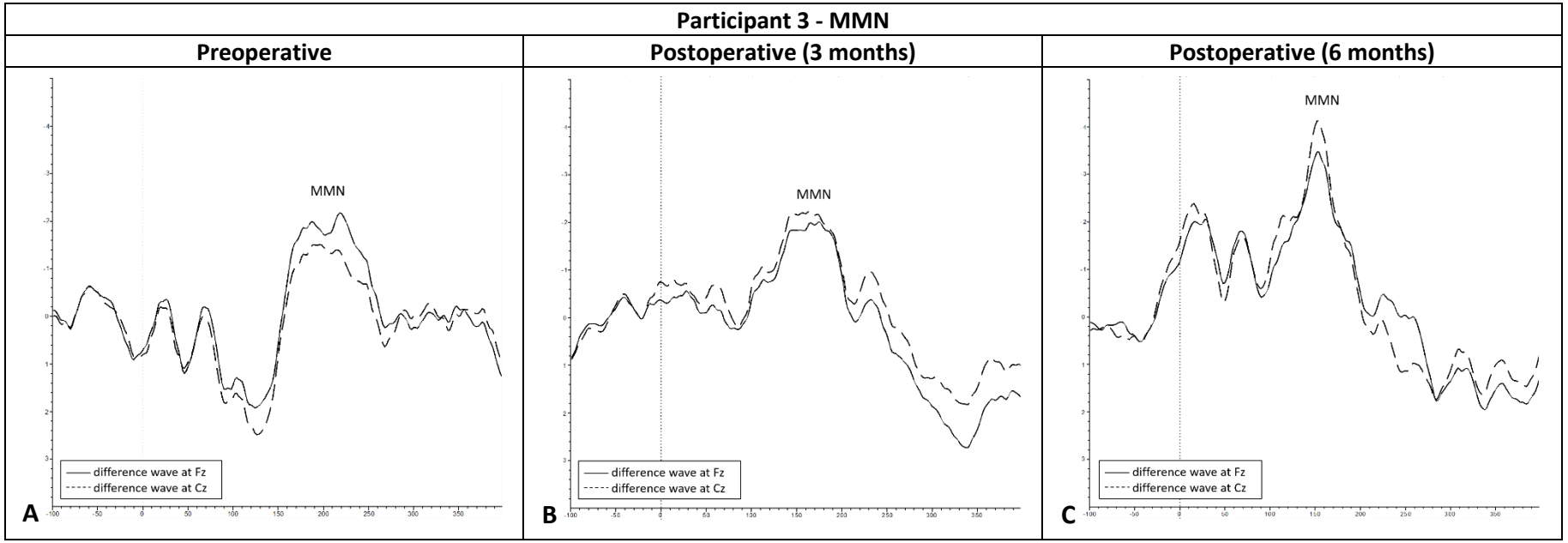


Figure 5. MMN results of participant 3. Difference waveform of the MMN at Fz and Cz at preoperative assessment (A), 3 months postoperative assessment (B) and 6 months postoperative assessment. Topographic distribution of the MMN difference waveform at preoperative assessment (D), 3 months postoperative assessment (E) and 6 months postoperative assessment.



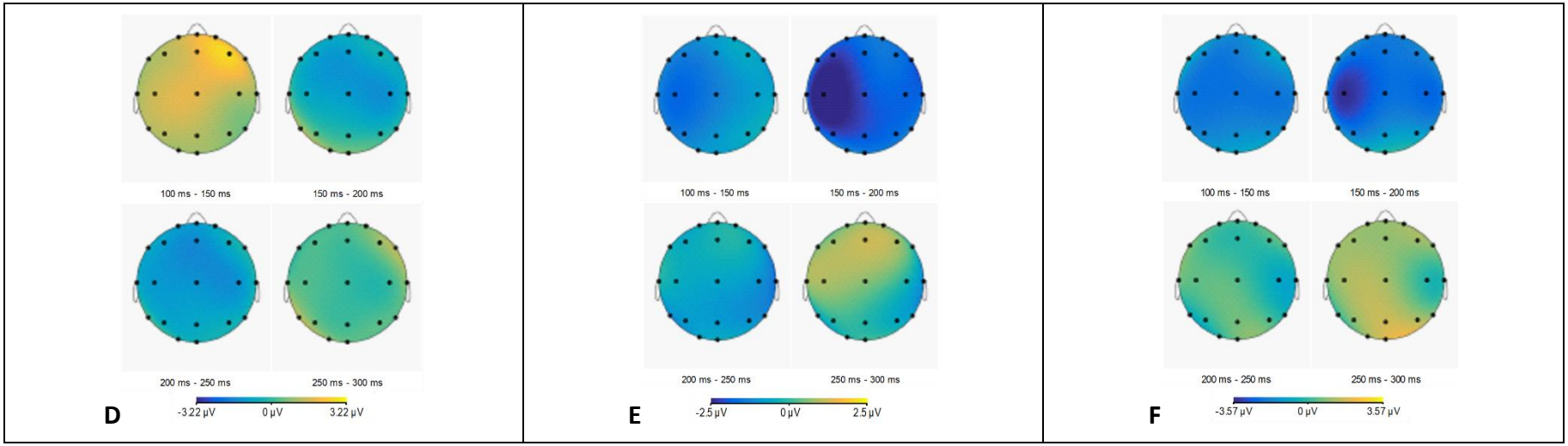
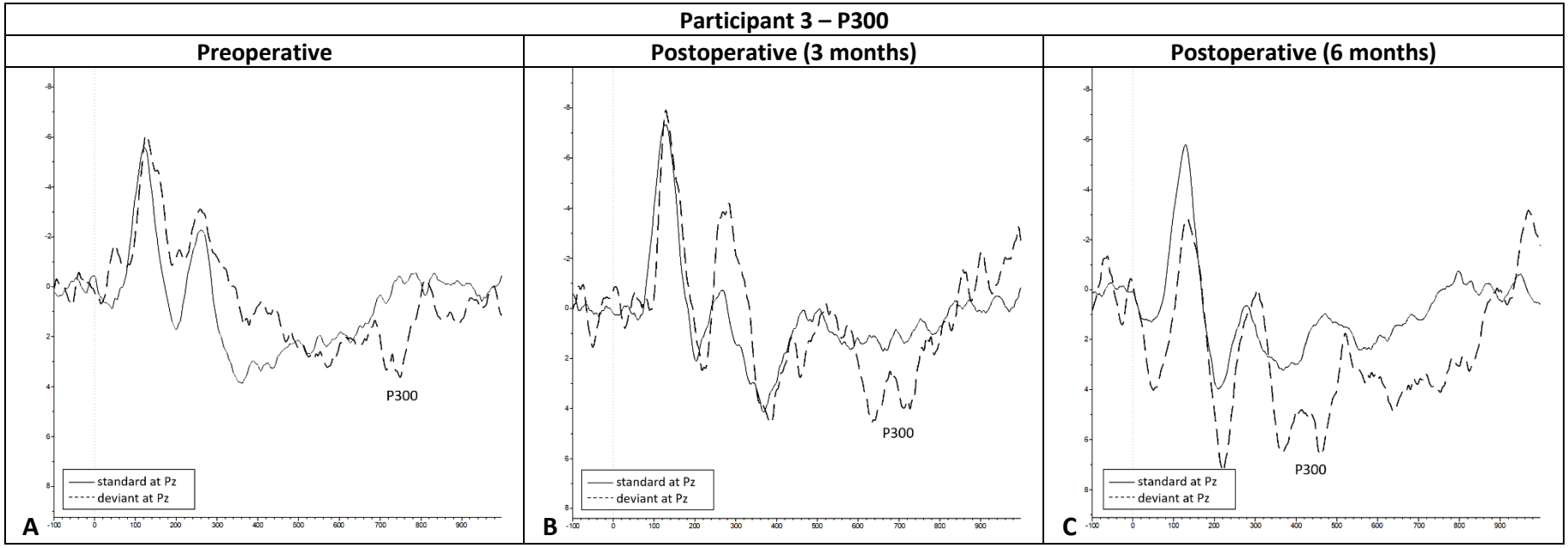

100 ms - 150 ms
150 ms - 200 ms
200 ms - 250 ms
250 ms - 300 ms
-3.22 µV
0 µV
3.22 µV
D
100 ms - 150 ms
150 ms - 200 ms
200 ms - 250 ms
250 ms - 300 ms
-2.5 µV
0 µV
2.5 µV
E
100 ms - 150 ms
150 ms - 200 ms
200 ms - 250 ms
250 ms - 300 ms
-3.57 µV
0 µV
3.57 µV
F

Figure 6. P300 results of participant 3. Standard and deviant waveform of the P300 at Pz at preoperative assessment (A), 3 months postoperative assessment (B) and 6 months postoperative assessment. Topographic distribution of the P300 difference waveform at preoperative assessment (D), 3 months postoperative assessment (E) and 6 months postoperative assessment.



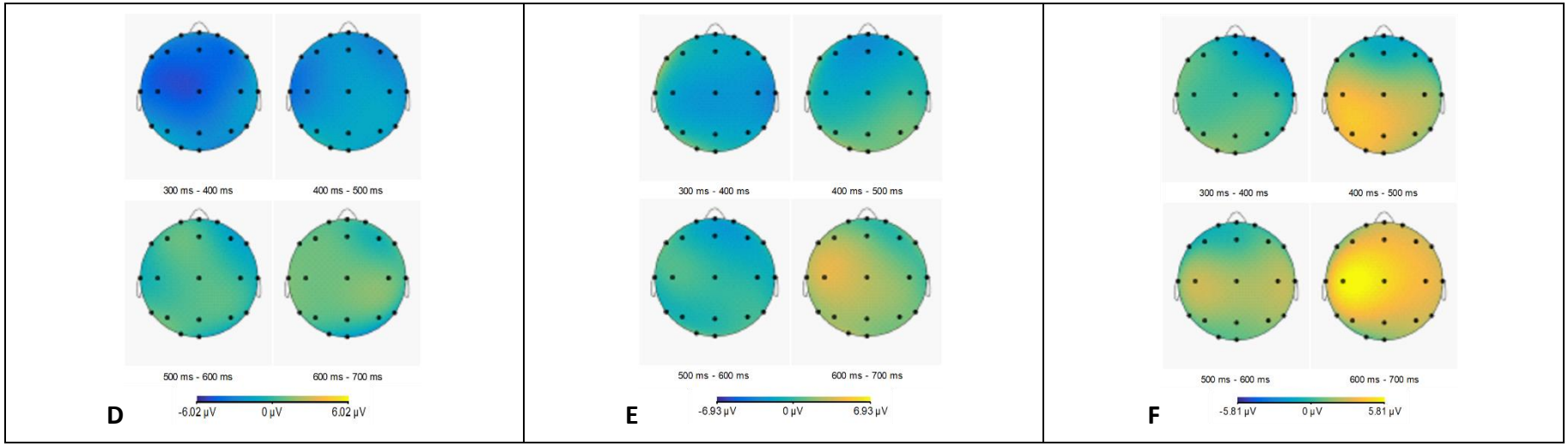

300 ms - 400 ms
400 ms - 500 ms
500 ms - 600 ms
600 ms - 700 ms
-6.02 µV
0 µV
6.02 µV
D
300 ms - 400 ms
400 ms - 500 ms
500 ms - 600 ms
600 ms - 700 ms
-6.93 µV
0 µV
6.93 µV
E
300 ms - 400 ms
400 ms - 500 ms
500 ms - 600 ms
600 ms - 700 ms
-5.81 µV
0 µV
5.81 µV
F

Figure 7. MMN results of participant 4. Difference waveform of the MMN at Fz and Cz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the MMN difference waveform at preoperative assessment (C) and postoperative assessment (D).

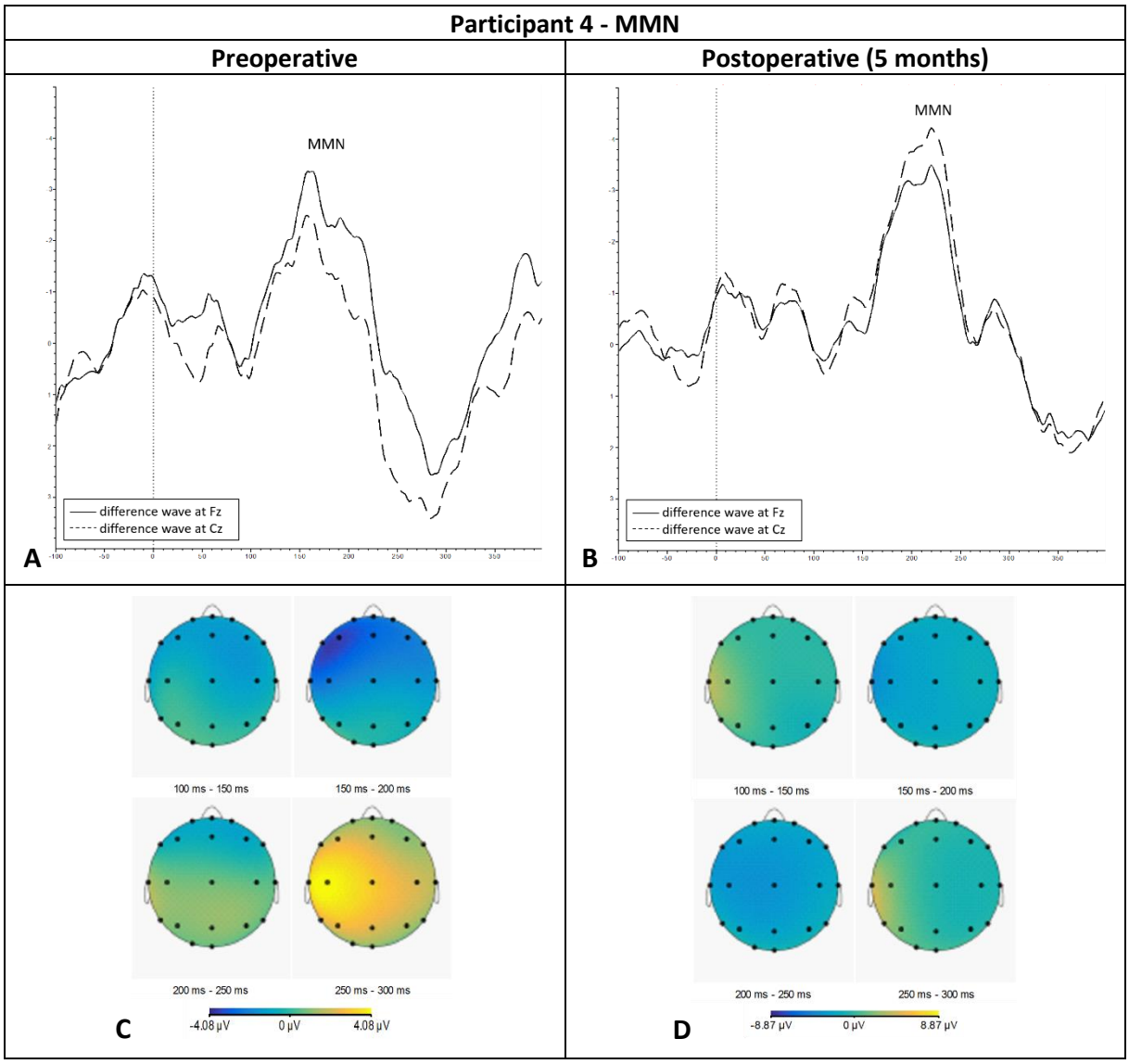


Figure 8. P300 results of participant 4. Standard and deviant waveform of the P300 at Pz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the P300 difference waveform at preoperative assessment (C) and postoperative assessment (D).

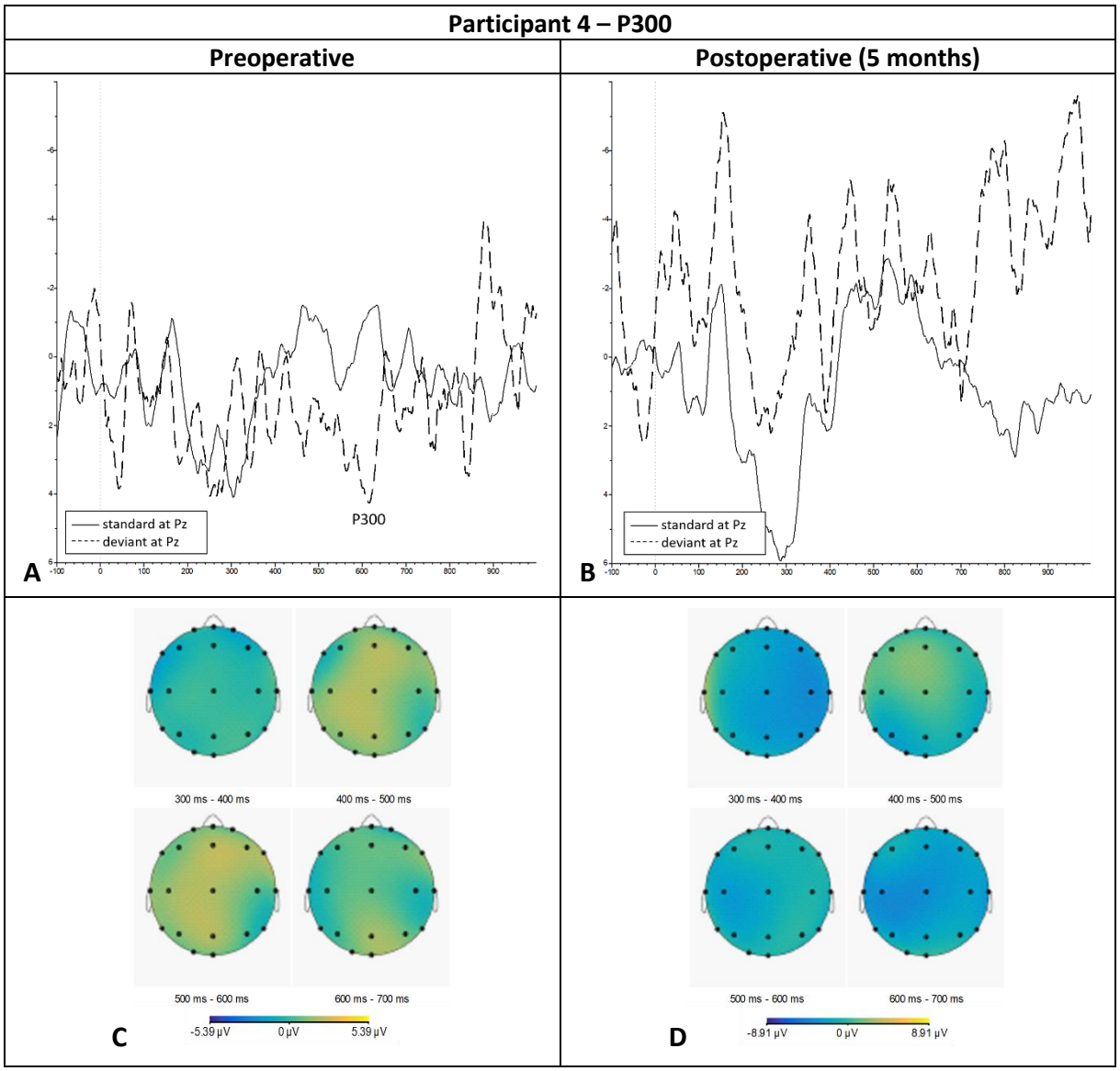


Figure 9. MMN results of participant 5. Difference waveform of the MMN at Fz and Cz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the MMN difference waveform at preoperative assessment (C) and postoperative assessment (D).

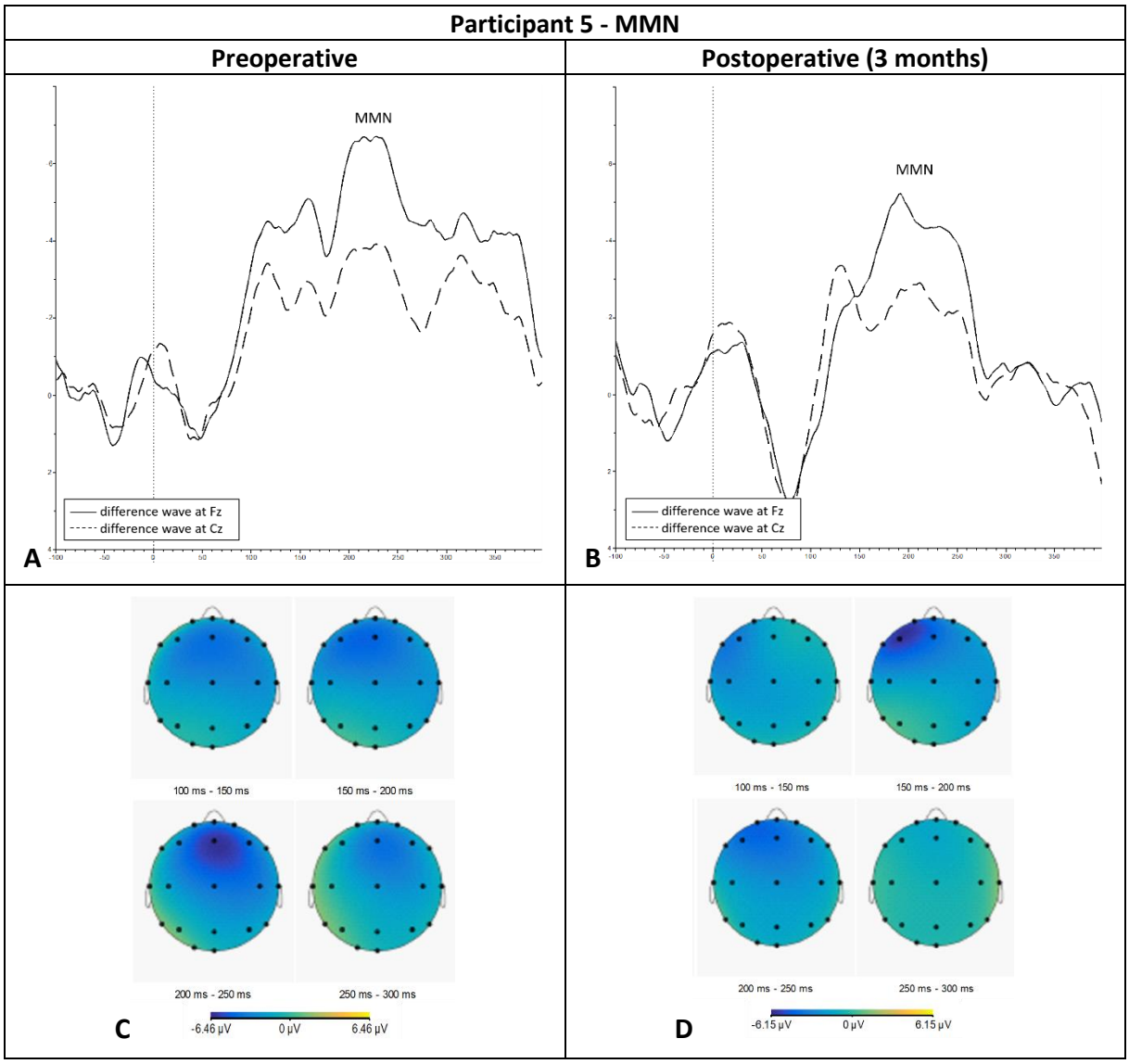


Figure 10. P300 results of participant 5. Standard and deviant waveform of the P300 at Pz at preoperative assessment (A) and postoperative assessment (B). Topographic distribution of the P300 difference waveform at preoperative assessment (C) and postoperative assessment (D).

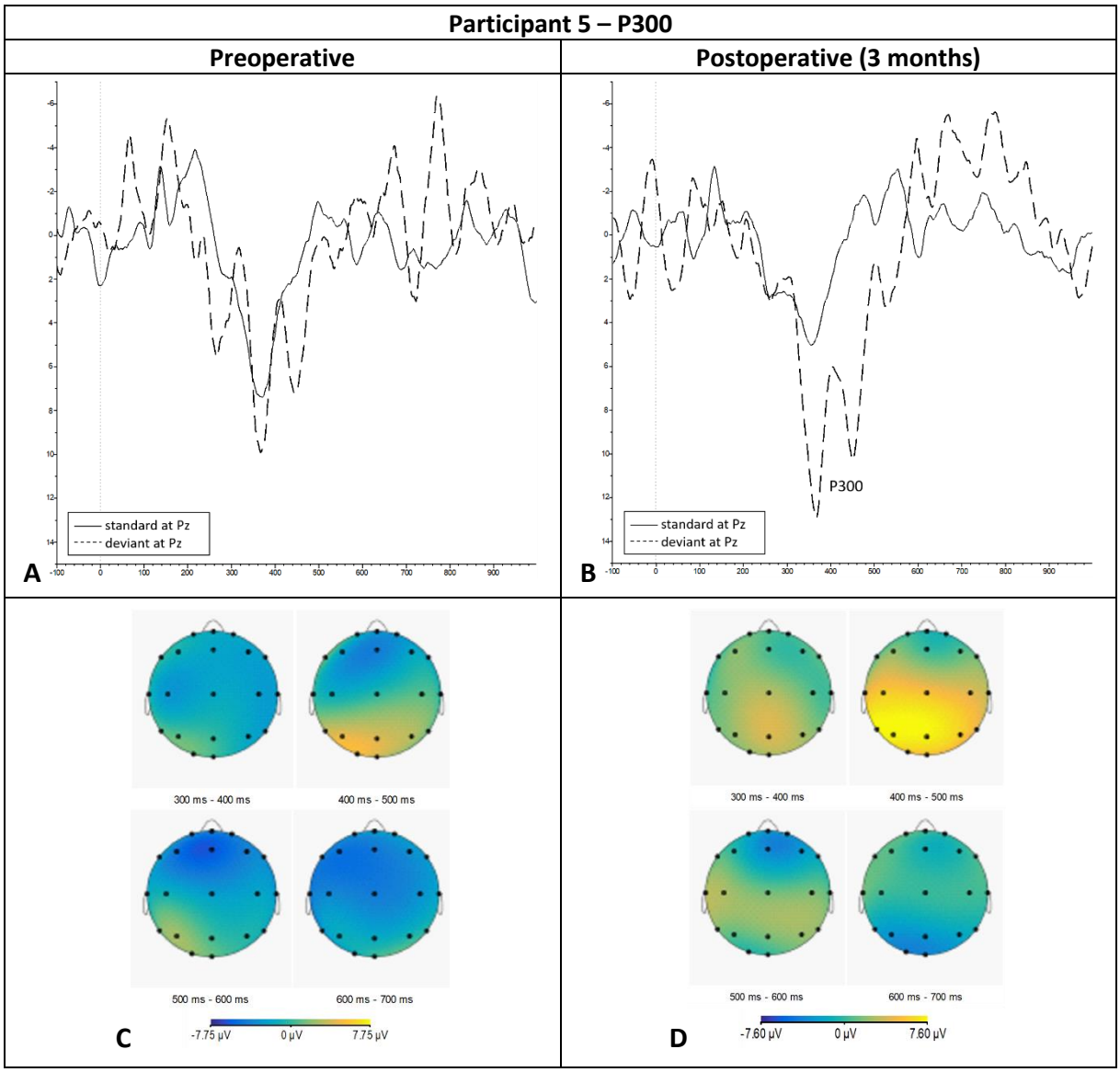
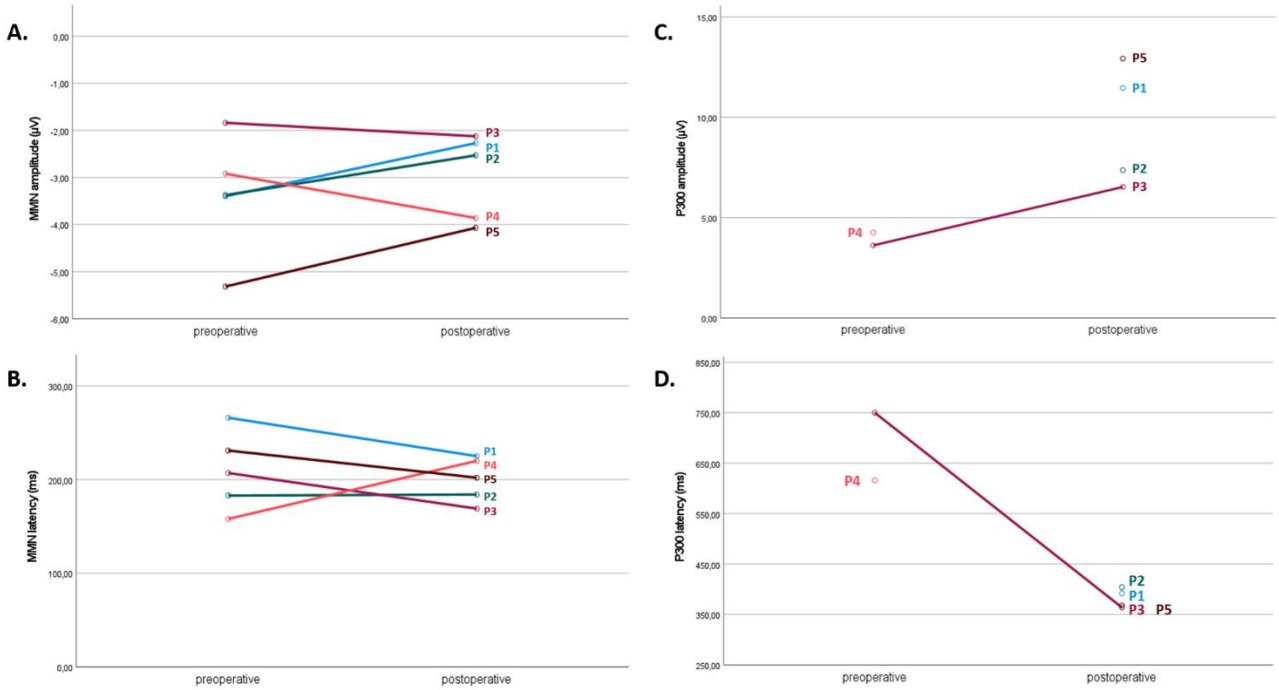


Figure 11. Line plot of MMN amplitude (A) and latency (B) outcome and P300 amplitude (C) and latency (D) outcome for each participant at preoperative and postoperative assessment.


A.
MMN amplitude (µV)
0,00
-1,00
-2,00
-3,00
-4,00
-5,00
-6,00
P3
P1
P2
P4
P5
preoperative
postoperative
B.
MMN latency (ms)
300,00
200,00
100,00
0,00
P1
P4
P5
P2
P3
preoperative
postoperative
C.
P300 amplitude (µV)
15,00
10,00
5,00
0,00
P5
P1
P2
P3
P4
preoperative
postoperative
D.
P300 latency (ms)
850,00
750,00
650,00
550,00
450,00
350,00
250,00
P4
P2
P1
P3
P5
preoperative
postoperative