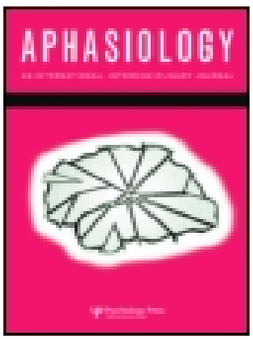

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The phonological Mismatch Negativity and P300 as diagnostic tools in stroke-related aphasia recovery: a longitudinal multiple case study

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ABSTRACT

Background: Recovery from stroke-related aphasia follows different stages, evolving from the acute and subacute phase (< 6 months post stroke) into the chronic phase (> 6 months post stroke). In general, phonology remains tenaciously disturbed, making it a relevant language marker to assess in every stage of recovery. The classical behavioural evaluation of phonological abilities in patients with aphasia can be extended with a registration of event-related potentials (ERPs), for example, the Mismatch Negativity (MMN) and the P300. ERPs have been suggested (1) to contain indications towards the language recovery progress (Nolfe et al. 2006. The role of P300 in the recovery of post-stroke global aphasia. *European Journal of Neurology, 13*(4), 377–384. https://doi.org/10.1111/j.1468-1331.2006.01237.x) and (2) to provide additional and (more) sensitive information along with the behavioural results (Aerts, Batens et al. 2015. Aphasia therapy early after stroke: Behavioural and neurophysiological changes in the acute and post-acute phases. *Aphasiology, 29*(7), 845–871. https://doi.org/10.1080/02687038.2014.996520). In this longitudinal study, we aimed to corroborate these previous findings.

Methods and procedures: In four patients with aphasia after a first-ever stroke, we administered behavioural language tasks as well as phonological ERPs in the (sub)acute and in the chronic stage of recovery.

Outcomes and results: The results demonstrate that the early presence of a P300 could be considered as an indicator of better recovery of language comprehension over time. For the MMN, such an indicative value remains to be confirmed. Moreover, abnormal ERP amplitudes or latencies accompanied behavioural ceiling effects in the chronic stage, suggesting a sensitivity of phonological ERPs for subtle language deficits that could not be detected by the established behavioural instruments.

Conclusions: The added values of phonological ERPs advocate their implementation in aphasia rehabilitation.

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Supplemental data for this article can be accessed here.

Introduction

Aphasia recovery follows different stages, evolving from the acute and subacute phase into the chronic phase. Through these stages, aphasia recovery is influenced by several factors, which are classified as intrinsic and extrinsic factors. Intrinsic variables are inter-individually different and include lesion localization, severity of aphasia, personality traits and domain-general cognitive functions (Pedersen et al., 1995; Watila & Balarabe, 2015). Extrinsic variables are related to stimulation and depend on the intensity and the content of rehabilitation or they refer to extrinsic psychosocial variables such as the participation in social activities (Cocquyt et al., 2017; Watila & Balarabe, 2015). The three stages of recovery are each characterised by specific neurophysiological and metabolic processes as well as by distinct language lateralization patterns. The acute phase is determined by dynamic changes depending on edema, excitotoxicity, diaschisis and perilesional perfusion (penumbra) (Hillis & Heidler, 2002) and is therefore estimated from a few days up to 2 weeks post-stroke (Kiran, 2012). In the subacute phase, lasting from about 2 weeks to 6 months post stroke (Kiran, 2012), edema is resolved and synaptogenesis results in new connections allowing functional reorganization (Hillis & Heidler, 2002; Kiran et al., 2019). In the chronic phase, synaptic sprouting continues (Kiran et al., 2019), especially depending on environmental stimulation such as language therapy (Crinion & Leff, 2007, 2015; Meinzer & Breitenstein, 2008). The chronic stage may span from 6 months to several years post-stroke (Kiran, 2012). Along with the metabolic processes after a stroke, the language dominant and non-dominant hemisphere are activated in an asymmetric way. In the acute stage of aphasia (< 1 week post stroke), a global reduction of ipsilesional (left) language-related activation has been observed in patients with frontal or/and temporo-parietal lesions (Saur et al., 2006; Stockert et al., 2020). In the subacute stage (1–2 weeks post stroke), all patients showed an upregulation of spared tissue in the (left) lesioned hemisphere as well as in bilateral domain-general networks. A significant activation of homologous areas in the contralateral (right) hemisphere was present only in patients with frontal lesions (Stockert et al., 2020). In the chronic stage (> 6 months post stroke), a re-shift of peak activation to the left hemispheric language regions took place (Saur et al., 2006; Stockert et al., 2020).

Depending on the type and the severity of the affected networks, language modalities are known to recover in a different way. In the study of El Hachioui et al. (2013), semantic and syntactic processing improved until 6 weeks after stroke, whereas phonology showed the longest recovery period. In general, phonological processing remains tenaciously disturbed, characterizing the residual aphasia in the chronic stage. This phenomenon is probably related to the central function of phonology at all stages of language development, with phonological encoding subserving both lexico-semantic and grammatical processing (Levelt, 1989). Since the current study focuses on the recovery of language in the different stages after stroke, phonology seems to be a relevant language marker to investigate at each stage of recovery.

Phonological abilities can be examined at the behavioural as well as at the electrophysiological level. At the behavioural level, multiple language test batteries include subtests in order to investigate the phonological skills of an individual patient. For example, phoneme discrimination is specifically targeted in two subtests of the PALPA (Psycholinguistic Assessment of Language Processing in Aphasia; Bastiaanse et al., 1995).

More precisely, subjects have to judge whether pairs of pseudowords (PALPA 1) or minimal pairs of words (PALPA 2) are different or not. Regarding electrophysiology, brain potentials reflecting phonological processing can be elicited by well-designed paradigms, focusing on phoneme discrimination for example (Aerts et al., 2013; Näätänen & Escera, 2000). Such language paradigms can be presented without (pre-attentive Mismatch Negativity (MMN)) or with active participation (attentive P300) of the patients (Bashore & van der Molen, 1991; Näätänen & Alho, 1997; Sutton et al., 1965). Compared to age-matched healthy individuals, patients with aphasia (PWA) often show reduced phonological MMN amplitudes and delayed latencies (Aaltonen et al., 1993; Csepe et al., 2001; Ilvonen et al., 2004). As for the P300, results in PWA are more heterogeneous in the sense that both normal (Korpelainen et al., 2000; Onofrj et al., 1992; Trinka et al., 2000) and reduced amplitudes (Aerts, van Mierlo et al., 2015; Dejanovic et al., 2015) as well as normal (Gummow et al., 1986) and delayed latencies (Aerts, van Mierlo, 2015; Dejanovic et al., 2015; Korpelainen et al., 2000; Onofrj et al., 1992; Trinka et al., 2000) have been reported. Interestingly, behavioural and electrophysiological results can be considered as "synergetic" measures because of the correlation between behavioural recovery and amplitude changes of several ERP-components (Barbancho et al., 2015; Mohr et al., 2016; Pulvermuller et al., 2005). For example, Ilvonen et al. (2003) found that a bilateral amplitude enhancement of the MMN correlated with the improvement of language comprehension abilities and, hence, indicated that the MMN is an index of auditory discrimination recovery. Although this synergetic relationship holds true for multiple patients, ERPs can provide more information than classical behavioural measures for those individuals who are at the ends of the aphasia severity spectrum. More in detail, patients with a severe global aphasia, for whom participation in classical behavioural testing is often impossible or very difficult, can still be evaluated with ERPs (Luck, 2014). In this context, the pre-attentive tasks (e.g., MMN) remain useful and can be applied even in patients with pronounced comprehension and production deficits. Furthermore, patients with only very mild aphasic symptoms often reach ceiling effects at behavioural language test batteries, hindering the objectification of the remaining deficits. In this case, amplitudes and/or latencies of ERPs can still be deviant and provide important insights to guide (adjustments of) therapeutic interventions (e.g., the use of constraint-induced aphasia therapy or not). In Aerts, Batens, et al. (2015) for example, a decline after a therapy-free period was only shown by the electrophysiological measures (MMN, P300 and N400), whereas maximum scores remained for the behavioural testing. Replication and confirmation of this early finding is needed, but a high sensitivity of electrophysiological registrations in order to detect subtle linguistic deficits is suggested.

Considering the abovementioned advantages of ERPs, an electrophysiological registration can be recommended as a relevant tool for the diagnostic follow-up of PWA, in addition to the behavioural testing. Preferably, future studies include patients who are already examined in the (sub)acute stage since ERP characteristics might yield predictive insights concerning the expected language recovery pattern. For example, Nolfe et al. (2006) examined the correlation between changes in the P300 component and the recovery of language comprehension in patients with global aphasia during the first six months post stroke. In more detail, patients were evaluated every month by means of an auditory oddball paradigm (P300) and the comprehension subtests of the Aachen Aphasia Test (AAT). The authors considered the early presence of a P300 response to auditory deviations (pitch) as a positive sign

for better language comprehension recovery. However, more research is needed to sustain this finding.

The main goal of this study is to obtain an estimation of the value of phonological ERPs in the diagnosis and follow-up of stroke-related aphasia recovery. A longitudinal multiple-case approach was used, first of all, in order to reproduce and extend the findings of Nolfe et al. (2006). More precisely, we aimed to explore if measures of both the (pre-attentive) MMN and the (attentive) P300 in the early stage provide indications towards the extent of language recovery. Second, we intended to examine whether phonological MMN and P300 measures are more sensitive than the behaviourally sampled data in order to support or attenuate the findings of the single-case study of Aerts, Batens, et al. (2015).

Methods

Patients

Four male individuals with aphasia, due to a first ischemic or hemorrhagic stroke in the left hemisphere, participated in this study. All patients were native Dutch speakers, right-handed and without any history of developmental or neurological disorders prior to the stroke. None of them reported severe hearing deficits. In each patient, both an extensive behavioural language assessment and an electrophysiological evaluation of phonological discrimination were administered at two evaluation moments (T1 and T2). Between T1 and T2, all patients received conventional impairment-based language therapy with a maximum of two therapy sessions of 30 minutes a week. The therapy sessions were provided by speech and language therapists in a rehabilitation clinic or at home. The first evaluation moment (T1) was in the (sub) acute stage of recovery (mean 1 week post stroke, range 0.7–1.4 weeks post stroke) whereas the second evaluation (T2) took place in the chronic stage of recovery (mean 29.8 weeks post stroke, range 20.1–48.9 weeks post stroke). The patient characteristics regarding etiology of stroke, lesion localization, age, time (weeks) post stroke and type of aphasia at T1 and at T2 can be found in Table 1.

This study was conducted in accordance with the Declaration of Helsinki, and the protocol and its amendments were approved by the Ethics Committee of the University Hospital Ghent. An informed consent was obtained from all the patients.

Behavioural language assessment

In all four patients, language abilities were investigated by means of five subtests of the Aachen Aphasia Test (AAT), including the Token Test, Repetition, Naming, Written Language and Language Comprehension (Graetz et al., 1991). In three patients (P1, P2, P4), several subtests of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Bastiaanse et al., 1995) were administered as well, namely phoneme discrimination in pseudowords (PALPA 1), phoneme discrimination in real words (PALPA 2) and auditory lexical decision (PALPA 5). For PALPA 1 and 2, only the first columns were used, conform Bastiaanse et al. (1995).

Table 1. Demographic information of the four patients with aphasia.

Patient number	Gender	Handedness	Etiology of stroke	Lesion localization (left hemisphere)	T1				T2			
					Weeks post stroke	Recovery stage	Age (years)	Aphasia type	Weeks post stroke		Age (years)	Recovery stage
1.	male	right	H	Posterior temporal	0.7	(sub)acute	71.4	Wernicke	26.1	chronic	71.9	Amnestic
2.	male	right	I	Parietal, insula, caudate nucleus, globus pallidus	1.0	(sub)acute	46.6	Wernicke	48.9	chronic	47.6	Amnestic
3.	male	right	I	Parieto-temporal	1.0	(sub)acute	63.1	Wernicke	24.0	chronic	63.5	UC
4.	male	right	I	Parieto-temporal	1.4	(sub)acute	62.4	Wernicke	20.1	chronic	62.8	Amnestic

T1 = evaluation moment 1; T2 = evaluation moment 2; H = hemorrhagic; I = ischemic; UC = unclassified.

Electrophysiological registration, paradigms and analysis

Registration

The EEG-data were recorded, using the Neuron-Spectrum-5 (EPM) registration software (Neurosoft, Moscow, Russia) and a Haube-S2 electrode cap including 20 Ag/AgCl-electrodes, namely Cz, Fz, Fpz, Pz, Oz, C3, C4, T3, T4, F3, F4, F7, F8, P3, P4, T5, T6, Fp1, Fp2 and O1. The electrodes were placed on the scalp according to the international 10–20 system. An online linked ears-reference and a ground electrode on the forehead were used. In order to keep the electrode-impedance below 5 kΩ, an impedance-reducing gel (Electro-Gel TM, Electro-Cap International, Inc.) was applied. We used a SynAmp (Neuroscan) amplifier and the data were digitised at a sampling rate of 500 Hz.

Paradigms

Two phoneme discrimination tasks were presented as an oddball paradigm. Both tasks have been previously developed and standardised by our research group (Aerts et al., 2013). The sequence of tasks was counterbalanced across the patients and the stimuli were presented binaurally with Apple Inc. earphones, at a listening level of 70 dB. In both paradigms, the stimulus probability was 0.20 for the deviant stimulus and 0.80 for the standard stimulus. Auditory phoneme discrimination was evaluated during an unattentive condition (MMN) in which patients had to watch a silent movie and ignore the stimuli, and during an attentive condition (P300) in which patients were instructed to push a button when hearing the deviant stimulus. The experimental attentive phoneme discrimination trials were preceded by a practice block in order to assure that the task instruction was understood. The MMN and P300 paradigms consisted of 750 trials and 150 trials, respectively. The stimuli (recorded by a female native speaker of Dutch) differed in terms of the phonemic contrast "place of articulation" (standard [bə], deviant [gə]) and had a duration of 250 ms. In both paradigms, the stimuli were randomly presented and two or more deviants could never succeed each other. An interstimulus interval (ISI) of 500 msec was used in the MMN paradigm and an ISI of 2000 msec was adopted in the P300 paradigm.

Analysis

The EEG-analyses were performed using BrainVision Analyzer 2.1 (Brain Products, Munich, Germany). First, a band-pass filter from 0.5 Hz (slope 12 dB/octave) to 30 Hz (slope 48 dB/octave) with a notch at 50 Hz was applied. In all patients, independent component analysis (ICA) was performed in order to detect and remove artefacts caused by eye-blinks and horizontal eye-movements. Next, standard and deviant trials were evaluated separately during segmentation. The EEG was segmented in 500 and 1100 ms long epochs, for the MMN and P300 paradigm respectively. All epochs contained a baseline-period of 100 msec pre-stimulus, that was used for baseline correction. Data exceeding ±100 μV in the baseline-corrected epochs were semi-automatically rejected from further analysis. For every patient, the average of standard trials on the one hand and deviant trials on the other hand was created. For unattentive phoneme discrimination, the extraction of amplitude and latency measures was performed on the difference waves (created by subtracting the standard trials from the deviant trials). For the attentive phoneme discrimination, amplitudes and latencies were extracted from the averaged

deviant trials. Peak latencies and amplitudes were calculated semi-automatically in a component-specific time window. The measurement windows for the MMN and P300 were chosen based on a visual inspection of the data averaged across participants (Luck, 2014), namely 100–300 ms (MMN) and 300–700 ms (P300). Moreover, we focused on the electrode positions for which normative data in healthy individuals (Aerts et al., 2013) are available (MMN: Cz and Fz; P300: Pz).

Statistical analyses

Behavioural measures

Between T1 and T2, the behavioural results at the five subtests of the AAT and the PALPA tasks were compared by means of effect sizes based on the changes of raw scores, which were classified according to Robey et al. (1999) namely 2.6 = small effect, 3.9 = medium effect and 5.8 = large effect.

Electrophysiological measures

Neurophysiological values of all four patients were compared to the normative data previously developed in our research group (Aerts et al., 2013). More precisely, both peak amplitudes and latencies of the MMN and the P300 at T1 and T2 were examined relative to the corresponding age-dependent normative values. Values that were larger/smaller than the mean ± 2 standard deviations were considered to be outside of the normative range.

Results

Behavioural results

The behavioural results for the AAT subtests and the PALPA assessments in the subacute (T1) and in the chronic stage (T2) can be found in Table 2. At T1, all four patients were diagnosed with Wernicke's aphasia characterised by a moderate to high severity in general, as measured with the Token Test (Cohen et al., 1976). More specifically, moderate to severe repetition deficits and mild to moderate impairments on the naming, written language and language comprehension subtests were revealed. Multiple PALPA-tests were administered in three out of four patients (P1, P2 and P4). For phoneme discrimination (PALPA 1 and 2), P1 reached the maximum scores, whereas P2 and P4 showed deficiencies (score 26/36). On the auditory lexical decision task (PALPA 5), all three patients showed moderate to severe impairments.

At T2, a notable progress at the subtests of the AAT and the PALPA was present as shown by the effect sizes between T1 and T2 (Table 2). In all four patients, an anomic aphasia remained which was characterised by a minimal to mild severity and minimal to mild repetition, naming, written language and language comprehension disorders. One remarkable difference between patients 1 and 3 on the one hand and patients 2 and 4 on the other hand was a relatively less pronounced recovery of language comprehension in the latter, as reflected by smaller effect sizes for the Token Test and Language Comprehension subtest. In general, however, high scores were reached on the AAT subtests and on the PALPA tasks 1, 2 and 5 with ceiling effects (percentiles equal to or

Table 2. Overview of the behavioral results (raw scores and percentiles) on five AAT subtests (Token Test, Repetition, Naming, Written Language and Language Comprehension), PALPA 1, 2 and 5 at both evaluation moments as well as off the effect sizes between the two evaluation moments in patients 1–4.

AAT-subtests	Max.	Patient 1			Patient 2			Patient 3			Patient 4		
		T1	T2	T1-T2 (d)	T1	T2	T1-T2 (d)	T1	T2	T1-T2 (d)	T1	T2	T1-T2 (d)
Token Test (severity score)	0	41 (32)	7 (90)	−12.36***	43 (27)	22 (67)	−7.63***	46 (18)	8 (88)	−13.81***	23 (65)	14 (79)	−3.27*
Repetition	150	52 (15)	136 (83)	10.41**	75 (25)	139 (85)	7.93**	115 (58)	148 (98)	4.09**	75 (25)	134 (80)	7.31**
Naming	120	93 (70)	119 (100)	3.09*	82 (55)	112 (98)	3.56*	92 (69)	114 (99)	2.61*	82 (55)	108 (92)	3.09*
Written language	90	58 (57)	87 (95)	3.80*	64 (63)	90 (100)	3.41*	71 (70)	90 (100)	2.49	64 (63)	88 (97)	3.15*
Language comprehension	120	87 (55)	119 (100)	3.13*	91 (64)	115 (99)	2.34	83 (48)	116 (99)	3.22*	91 (64)	114 (98)	2.54
Phoneme discrimination pseudowords (PALPA 1)	36[a]	36	36	0	26	34	9.70***	/	/	/	26	34	9.70***
Phoneme discrimination real words (PALPA 2)	36[a]	35	36	1.33*	28	35	9.31***	/	/	/	28	35	9.31***
Auditory lexical decision (PALPA 5)	160	141	160	8.37***	126	154	12.33***	/	/	/	126	153	11.89***

Max.: maximum raw score; T1: evaluation moment 1; T2: evaluation moment 2; T1-T2 (d): Robey's d' effect size of behavioral changes between T1 and T2; * small effect size > 2.60; ** medium effect size > 3.90; *** large effect size > 5.80; pc = percentile; [a] Aerts et al. (2012). Flemish normative data of the first column PALPA 1 and PALPA 2 (unpublished data);/ : missing value.

above 95 (Graetz et al., 1991) observed for Naming, Written Language and Language Comprehension in all four patients, as well as for Repetition in P3. Moreover, P1 reached the maximum scores for phoneme discrimination (PALPA 1 and 2) and auditory lexical decision (PALPA 5).

Electrophysiological results

The neurophysiological results for the phonological MMN and P300 at both evaluation moments can be found in Table 3. At T1, amplitude values of the MMN and P300 were in accordance with age-related normative values (Aerts et al., 2013) in P1, P3 and P4, with the latter two patients showing increased P300 latencies (although very slight in P3). P2, on the other hand, showed normal MMN-values but a reduced P300-amplitude. The grand averages of the MMN and the P300 of the 4 patients are displayed in Figures 1 and 2 respectively. The individual waveforms of all patients can be found in Appendix 1a (MMN) and Appendix 1b (P300), indicated in color black.

At T2, P1 showed a decrease of the P300 amplitude and an increase of the P300 latency, reaching aberrant values as compared to age-related normative data. In P3, the P300 amplitude remained stable and the (slightly) increased P300 latency was normalised, but a latency increase of the MMN was detected. In P2 and P4, the reduced P300-amplitude (P2) and increased P300 latency (P4) present at T1, were normalised by reaching values within the age-related normative range again (Aerts et al., 2013). The grand averages of the MMN and the P300 of the 4 patients at T2 are displayed in Figures 3 and 4 respectively. The individual waveforms of all patients can be found in Appendix 1a (MMN) and Appendix 1b (P300), indicated in color red.

Table 3. Overview of the peak amplitude and latency values of the MMN (electrode positions Cz+Fz/2) and P300 (electrode position Pz) at both evaluation moments (T1 and T2). A comparison with the normative data (Aerts et al., 2013) is made, values larger/smaller than the mean +/- 2 standard deviations are considered to be outside of the normative range.

Patient (age group)		**ERP measures**	**Normative data Mean (SD)** (Aerts et al., 2013)	**T1**	**T2**
Patient 1 (70+)	**MMN**	Amplitude (μV)	-3.64 (1.17)	-2.77 (0)	-5.16 (0)
		Latency (ms)	172 (33.97)	164 (0)	143 (0)
	P300	Amplitude (μV)	11.45 (3.10)	9.71 (0)	5.20 (↓)
		Latency (ms)	479 (77.52)	510 (0)	694 (↑)
Patient 2 (40-49)	**MMN**	Amplitude (μV)	-3.22 (2.43)	-1.23 (0)	-0.95 (0)
		Latency (ms)	171 (27.28)	118 (0)	136 (0)
	P300	Amplitude (μV)	13.09 (4.00)	4.35 (↓)	6.39 (0)
		Latency (ms)	403 (60.04)	348 (0)	320 (0)
Patient 3 (60-69)	**MMN**	Amplitude (μV)	-3.53 (1.60)	-2.22 (0)	-2.11 (0)
		Latency (ms)	171 (24.09)	118 (↓)	259 (↑)
	P300	Amplitude (μV)	11.58 (3.46)	6.39 (0)	5.24 (0)
		Latency (ms)	417 (40.36)	504 (↑)	480 (0)
Patient 4 (60-69)	**MMN**	Amplitude (μV)	-3.53 (1.60)	-1.80 (0)	-2.85 (0)
		Latency (ms)	171 (24.09)	180 (0)	157 (0)
	P300	Amplitude (μV)	11.58 (3.46)	8.95 (0)	7.94 (0)
		Latency (ms)	417 (40.36)	598 (↑)	474 (0)

ERP = event-related potential; T1 = evaluation moment 1; T2 = evaluation moment 2; MMN = Mismatch Negativity; μV = microvolt; ms = milliseconds; 0 = within normative range; ↓ = reduced relative to normative range; (↑) = increased relative to normative range.

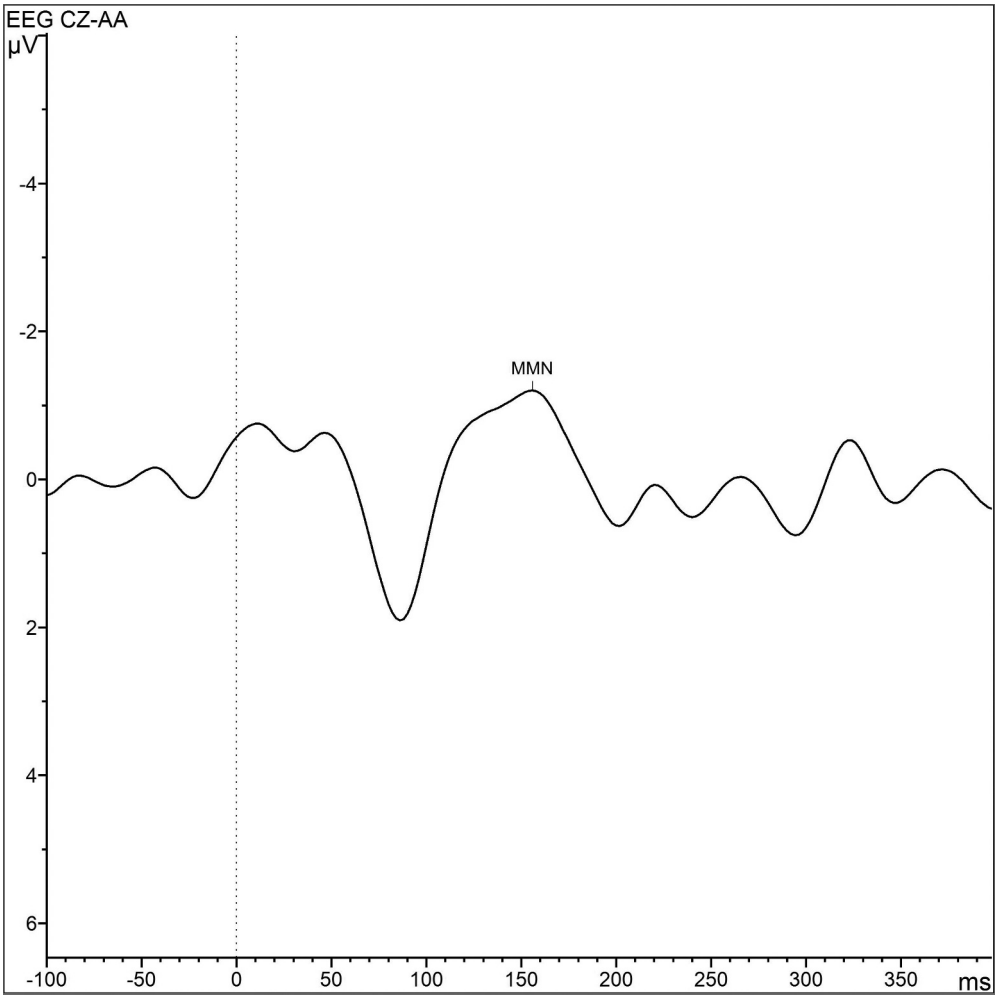

Figure 1. Grand average of the MMN of the 4 patients in the (sub)acute stage (T1) – electrode position Cz.

Summary

The four patients (P1, P2, P3 and P4), who were evaluated in the (sub)acute stage (T1) and in the chronic stage (T2), showed a good recovery of language abilities as they evolved from a severe Wernicke aphasia to a minimal/mild anomic aphasia. All patients reached behavioural ceiling effects at the Naming, Written Language and Language Comprehension subtests of the AAT. Interestingly, all patients showed intact MMN amplitudes and latencies at the initial evaluation moment (T1). Moreover, the patients with P300 amplitudes within the age-related normative range (P1 and P3) at T1 showed a more pronounced recovery of language comprehension over time. Finally, two different neurophysiological patterns could be retained between T1 and T2. In P2, P3 and P4, the aberrant P300 amplitude (P2) and latency (P3 and P4) at T1 were normalised at T2. In P1 and P3, the P300

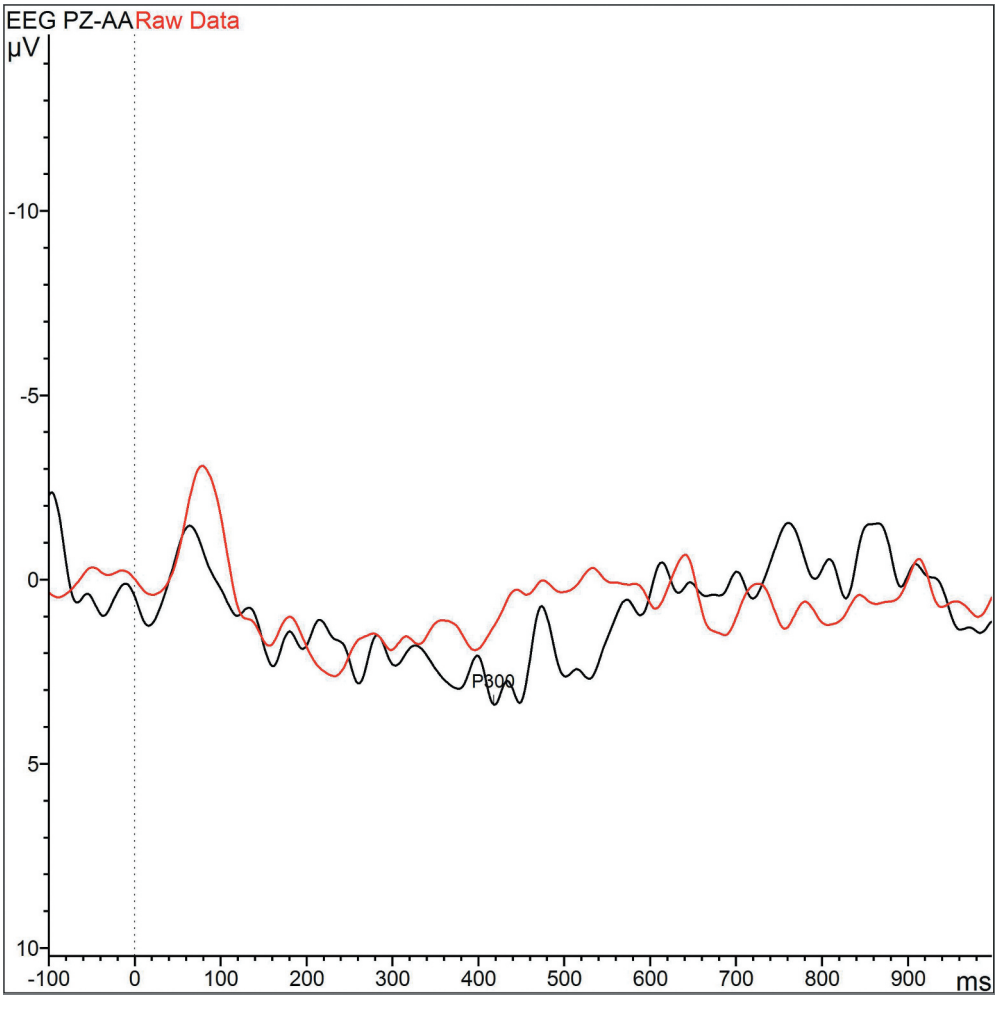

Figure 2. Grand average of the P300 of the 4 patients in the (sub)acute stage (T1) – electrode position Pz - red: standard stimuli, black: deviant stimuli.

amplitude and latency (P1) and the MMN latency (P3), which were within the normative range at T1, became aberrant at T2.

Discussion

In this longitudinal multiple case study, we aimed to estimate the value of the phonological MMN and P300 in the diagnosis and follow-up of language recovery in the different stages after stroke. Therefore, four patients with moderate to severe aphasia severity were examined with a behavioural examination (AAT subtests – Token Test, Repetition, Naming, Written Language and Language Comprehension – and PALPA 1, 2 and 5) as well as with a phonological MMN and P300 in the (sub) acute and in the chronic stage. In general, the results demonstrate that the early presence of phonological ERPs could be considered as an indicator for a good

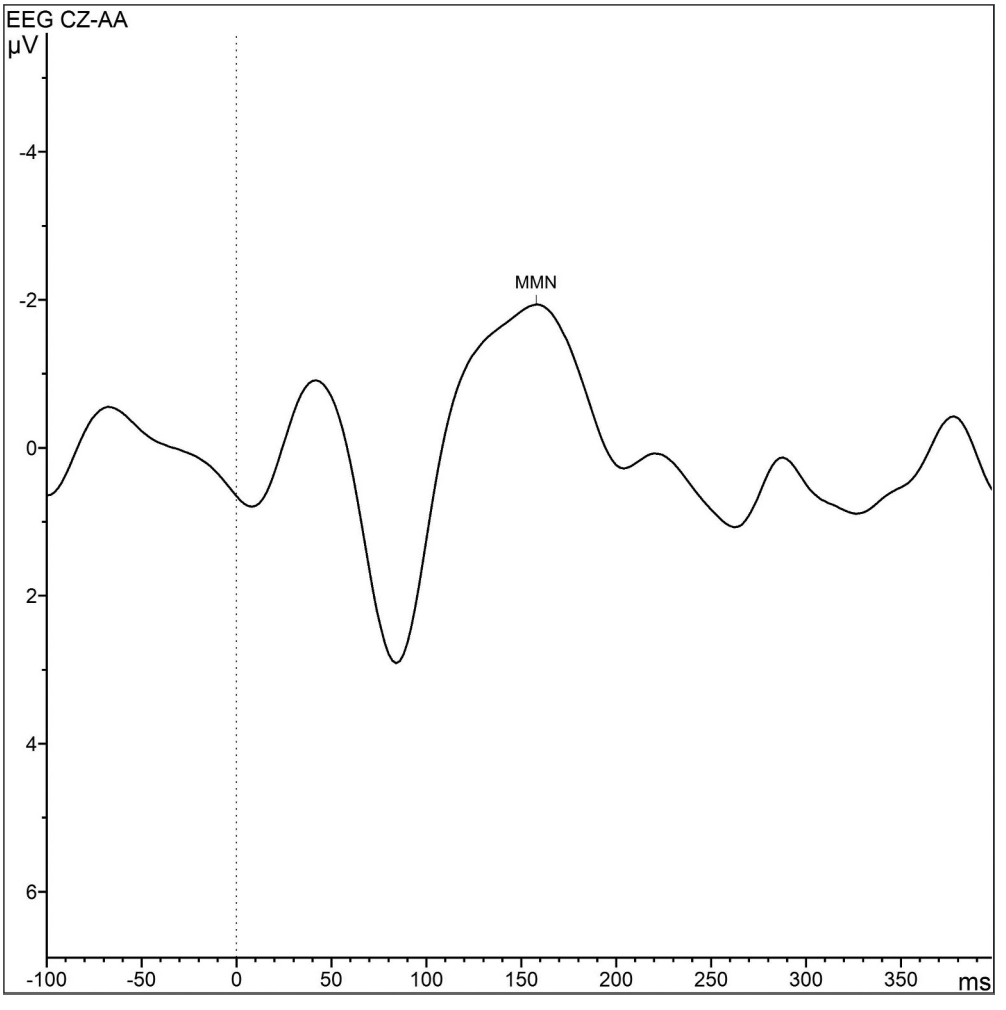

Figure 3. Grand average of the MMN of P1-P4 in the chronic stage (T2) – electrode position Cz.

recovery of language abilities over time. Moreover, abnormal electrophysiological activation (amplitudes and/or latencies) accompanied ceiling effects on the behavioural language tasks, possibly suggesting a higher sensitivity for the phonological MMN and P300 in comparison to the behavioural investigation. Both results will be discussed in the context of aphasia rehabilitation.

The indicative value of the phonological MMN and P300 regarding aphasia recovery

A good recovery of language abilities was shown in all four patients, who evolved from a moderate to severe Wernicke's aphasia to an anomic aphasia with minimal to mild severity. The successful recovery process was emphasised by the behavioural ceiling effects on the Naming, Written Language and Language Comprehension subtests of the AAT, measured in the chronic stage. Remarkably, all four individuals demonstrated

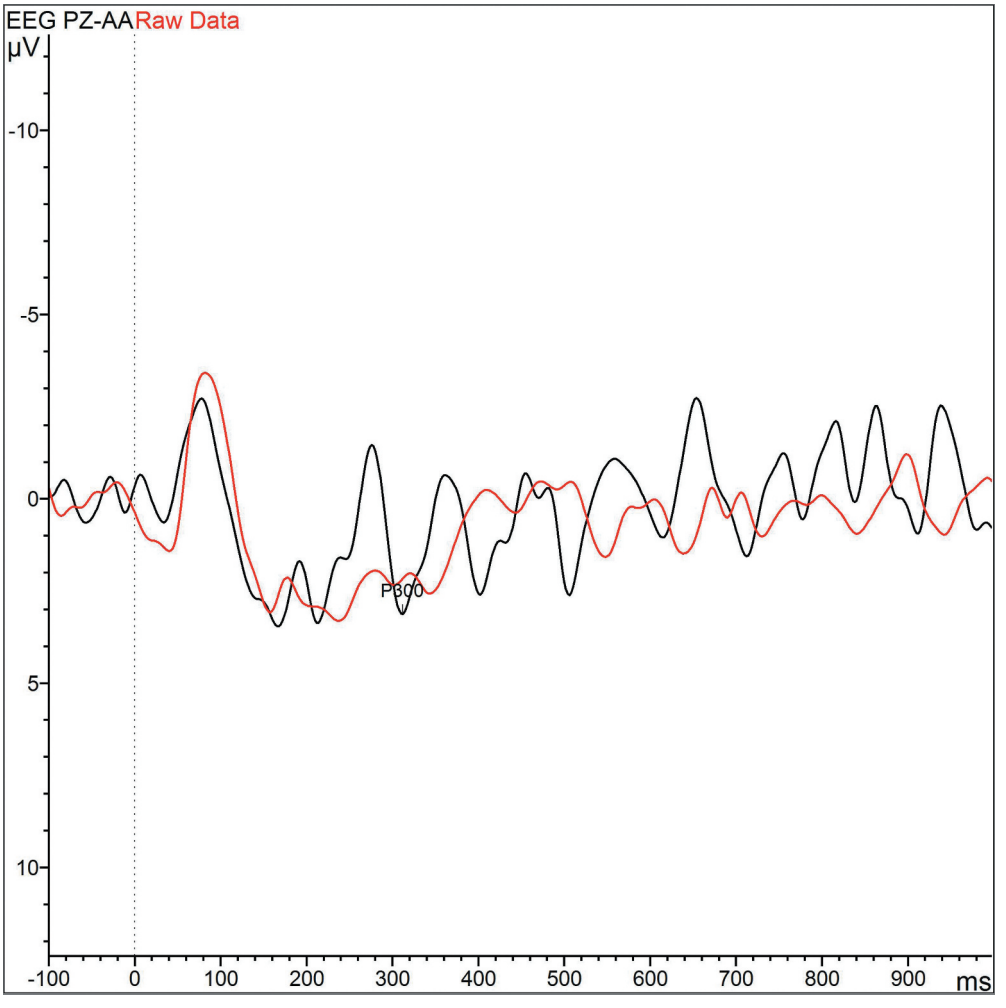

Figure 4. Grand average of the P300 of P1-P4 in the chronic stage (T2) – electrode position Pz – red: standard stimuli, black: deviant stimuli.

a phonological MMN with amplitude and latency values within the age-related normative range (Aerts et al., 2013) at the initial evaluation moment in the (sub)acute stage. One could speculate that the presence of a phonological MMN in the early stage is linked to the degree of further language recovery over time. Nonetheless, the lack of patients with deviating MMN amplitude and/or latency values in the (sub)acute stage prevents a comparison of recovery patterns and hinders the confirmation of this hypothesis. Hence, similar longitudinal research with preferably larger sample sizes is recommended in order to shed more clarity. In contrast to the lack of research on the indicative value of the MMN regarding aphasia recovery, Nolfe et al. (2006) found that global aphasic patients who presented with a P300 at the baseline registration (one month after stroke) showed the best outcome for the Language Comprehension AAT-subtest at the follow-up evaluation (six months post stroke). We were able to replicate these findings in our study.

More precisely, patients 1 and 3, who showed intact P300 amplitudes (and normal (P1) or slightly increased latencies (P3)) at the initial evaluation showed a more pronounced recovery of language comprehension than patients 2 and 4, who displayed a decreased amplitude and an obviously increased latency of the P300 respectively. Our findings expand those of Nolfe et al. (2006) by using phonemes (/b/and/g/) instead of pure tones in order to evoke the P300 component. Since PWA often show reduced responses for speech sounds, but relatively stable responses for nonverbal deviants (e.g., tones) (Aaltonen et al., 1993; Csepe et al., 2001; Ilvonen et al., 2004), the implementation of phonological ERPs in a diagnostic follow-up protocol could be useful in order to estimate the prognosis of language recovery.

Altogether, the indicative value of a phonological MMN in the (sub)acute stage towards the recovery process needs to be confirmed by future research. Moreover, we were able to confirm the early findings of Nolfe et al. (2006) and showed that the early presence of a phonological P300 accompanied a better recovery of language comprehension.

The sensitivity of the phonological MMN and P300 in aphasia recovery

The sensitivity of linguistic ERPs can be demonstrated by comparing the ceiling effects on behavioural tasks with the ERP characteristics (amplitudes and latencies). In the chronic stage, ceiling effects were observed on the Naming, Written Language and Language Comprehension subtests of the AAT in all patients. Although these linguistic competences were estimated to be relatively intact by the behavioural measures, the electrophysiological parameters of the MMN or P300 were deviant, in comparison to age-related normative values (Aerts et al., 2013) in patients 1 (P1) and 3 (P3). More precisely, P1 showed a reduced P300 amplitude and an increased P300 latency, whereas P3 showed an increased MMN latency. The latter ERP alterations are likely an expression of suboptimal neural reorganization patterns and correspond to the experience that many patients subjectively report remaining mild (comprehension) deficits, that are not detected by classic language batteries. Consequently, aphasia therapy would be considered as almost completed according to the behavioural results, while the reduced amplitudes and prolonged latencies in the electrophysiological tests suggest the possibility of further improvement through therapeutic efforts. Hence, ERP characteristics seem to be more sensitive for subtle linguistic deficits than the established behavioural measures and, therefore, therapeutic guidelines should take into account amplitude and latency deviations of ERPs as well. Importantly, whether or not to concern about the combination of behavioural ceiling effects and deviant ERP values largely depends, to our opinion, on the subjective presence of remaining (subtle) language deficits in the aphasic patients. In this context, there might be no need to return to ERP-values within the normative range for patients without such complaints. The exact reason why P1 and P3, the patients who showed more recovery of language comprehension at the behavioural level, demonstrated deviating values in the chronic stage remains unclear. In this context, Nolfe et al. (2006) reported that "latencies and amplitudes of the P300 changed in an unpredictable way" during the first six months after stroke, which is possibly due to

individual differences in spontaneous recovery (Lendrem & Lincoln, 1985; Lomas & Kertesz, 1978). This finding stresses the need for more research towards the intrinsic and extrinsic factors that influence the ERP characteristics (e.g., time post stroke, lesion localization, personality traits, therapy content and intensity, etc.). Ideally, longer periods of follow-up measurements are incorporated in order to eliminate individual differences in spontaneous recovery as a confounding factor.

Limitations of the study and suggestions for future research

The results of this study provide useful information on the neurophysiological correlates of aphasia recovery. Although our results are preliminary due to a small sample size (n = 4), the current findings provide directions for future research regarding this topic. For example, the observation of ERP differences in the (sub)acute stage between patients with a more and less pronounced recovery of language comprehension can be substantiated by means of prognostic studies with valid study-designs (Mak & Kum, 2005; Moons et al., 2009). In addition, more refined behavioural language tasks, e.g., PALPA 1 and 2, should be used in all patients under investigation in order to compare these behavioural results with the phonological ERP values. Finally, future research should address other than phonological ERP components in order to gain insights in (the indicative/predictive value and sensitivity of) the neurophysiological correlates of spectro-temporal analysis, lexico-semantic processing and grammatical processing. Finally, therapeutic guidelines, based upon (ab)normal ERP-parameters, should be developed and validated before an implementation in clinical practice is possible.

Conclusion

The results from this longitudinal multiple case study suggest an indicative value of the phonological P300 in the (sub)acute stage towards the recovery of language comprehension over time. A similar added value of the phonological MMN could not be confirmed in the present study and awaits future research. Moreover, phonological ERPs seem to be sensitive to subtle linguistic deficits that are not detected by the established behavioural measures. Hence, an implementation of linguistic ERPs in the diagnostic evaluation and follow-up of patients with aphasia would be beneficial. Our results highlight the usefulness of an integration of results from classical behavioural measures and ERPs in order to set up logopedic therapy protocols.

Disclosure statement

No potential conflict of interest was reported by the authors.

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