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The impact of stroke on cognitive processing — A prospective event-related potential study

Leandra Stahlhut [a], Karl-Heinz Grotemeyer [a,b], Ingo-W. Husstedt [a], Stefan Evers [a,c,*]

[a] Department of Neurology, University of Münster, Germany
[b] Klinikum Winterberg, Saarbrücken, Germany
[c] Department of Neurology, Krankenhaus Lindenbrunn, Germany

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ABSTRACT

Background and purpose: Stroke is often associated with cognitive decline which can be evaluated by event-related potentials (ERP). So far, only little is known about the impact of stroke on ERP. The aim of this prospective study was to follow-up ERP latencies in stroke patients and to evaluate the influence of sex, vascular territory of stroke, reinfarction, and secondary prevention (acetylsalicylic acid versus piracetam).
Methods: Visually evoked ERP were recorded in 563 stroke patients at baseline (i.e., within four weeks after stroke), after 12 months, and after 24 months. The latencies of the P2, N2, and P3 components were assessed and compared between different subgroups.
Results: The P3 latency is initially more increased in female stroke patients, but shows a better recovery in women compared to men. A secondary prevention with piracetam leads to a significantly better recovery of ERP latencies than a treatment with acetylsalicylic acid. Data suggests a better recovery of left hemispheric infarction compared to right hemispheric infarction. Patients, who suffered another stroke during the follow-up period, showed a prolongation of P3 latency, suggesting an increased P3 latency to be associated with reinfarction.
Conclusions: Our results suggest that ERP measurement is an appropriate method for diagnosis and follow-up of cognitive changes after ischemic stroke. In particular the P3 component is an indicator for patients at risk for reinfarction.

1. Introduction

Stroke is associated with an obvious cognitive decline in many sufferers. Studies with neuropsychological testing revealed different deficits depending on the localization, size, comorbidity etc. of the infarction [1–11]. However, neuropsychological testing depends on the cooperation of the patient and is often complex, time-consuming, and exhausting. Therefore, objective alternatives such as event-related potentials (ERP) are helpful tools to evaluate cognitive impairment.

ERP are reproducible electrophysiological responses to an external stimulus, representing a brain activity associated with various cognitive processes such as selective attention, memory, or decision making [12–14]. Within its components recorded in EEG as positive or negative small-voltage deflections, it is distinguished between early, exogenous components (P100, N100, probably P200) and later occurring, endogenous components (N200 and P300), which are considered to reflect a further perceptual or cognitive processing [15,16]. Among these, the P300 (or further simply P3) component is the most widely studied ERP so far. A prolongation of P3 latency indicates a cognitive slowing and could be shown for normal ageing [17,18] and various neurological and psychiatric diseases including dementia [19–23], schizophrenia [24–27], depression [28,29], Parkinson's disease [30], and multiple sclerosis [31–33].

However, studies focussing on the measurement of ERP in ischemic stroke have shown controversial results. So far, reports have shown a prolongation of P3 latency in unilateral thalamic infarction [34], brainstem and hemispheric infarction [35] as well as in cases of multiple cerebral infarction [36] and in multiinfarct dementia [37]. Still, it has not yet been clarified, if there is any difference in P3 latency between right and left hemispheric infarction or not [35,38,39]. A couple of other studies did not find significant differences of P3 latency in stroke patients at all [40] or only in stroke patients showing cognitive deficits or dementia or stroke associated apathy [41,42]. All these studies did not evaluate in a prospective design, how the cognitive impairment caused by stroke recovers and which factors are associated with cognitive improvement after initial decline.

* Corresponding author at: Department of Neurology, University of Münster, Albert-Schweitzer-Str. 33, 48129 Münster, Germany. Tel.: +49 251 8348196; fax: +49 251 8348181.
E-mail address: everss@uni-muenster.de (S. Evers).

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The increase of P3 latency in stroke patients and its potential usefulness for prognosis or therapy of the patient after stroke has not been clarified yet. Moreover, it has not yet been studied in a prospective design, if increased latencies after stroke improve over time and which factors might influence this improvement.

With respect to these questions we have evaluated the latencies of different ERP components (P2, N2, and P3) in ischemic stroke and focussed on their changes over a prospective two year follow-up period. We analysed the data of 563 stroke patients who had participated in a prospective treatment trial [43]. The patients were divided into several subgroups, and their ERP latencies were compared with respect to sex, vascular territory of stroke, reinfarction, and impact of secondary prevention.

2. Methods

2.1. Study design

The data of this study has been collected within a follow-up study enrolling patients for a two year period after they had suffered an ischemic stroke in the past four weeks confirmed by CT or MRI scan. For detailed inclusion criteria, we refer to the original publication [43]. The study was originally designed to compare the efficacy of daily 1600 mg piracetam t.i.d. versus 200 mg acetylsalicylic acid (ASA) t.i.d. in secondary stroke prophylaxis. Patients were randomised into two parallel treatment groups in a double-blind design and received either piracetam or ASA for antithrombotic medication.

Appropriate patients were recruited from a rehabilitation centre for neurological diseases (Rhein-Ruhr-Klinik, Essen-Kettwig, Germany) and admitted to the study centre (Department of Neurology, University of Münster, Germany). Apart from regular (every three months) neurological and laboratory examinations, the ERP of the patients were measured and the P2, N2, and P3 latencies were assessed at baseline, after 12 months, and after 24 months.

The study was approved by the local Ethics Committee and carried out according to the German Drug Law, the declaration of Helsinki, and the rules of Good Clinical Practice (GCP). An informed consent was obtained from all patients, before they were enrolled into the study. As the study was complete, an audit of GCP compliance was performed by an external independent organisation.

Patients were excluded prematurely in case of compliance loss or protocol violation. In particular, reasons for study withdrawal were:

- non-compliance (e.g. no/incorrect intake of study medication)
- intake of agents not permitted by the study protocol (e.g. haemorheologically active drugs)
- adverse events unacceptable to patient and/or investigator (secondary study endpoint)
- patient's decision to withdraw informed consent

The following events were defined as primary study endpoint and efficacy parameter and also lead to premature termination of the study for the patients:

- new stroke including transient ischemic attack (TIA)
- myocardial infarction
- death due to vascular reasons.

2.2. ERP measurement

At baseline, after 12, and after 24 months, patients underwent neurological examinations and laboratory tests in the study centre. During these study visits, the ERP of all patients were investigated. The ERP were evoked by a visual oddball paradigm and recorded according to the international 10–20 system by Ag/AgCl EEG electrodes placed in centroparietal position (Pz) using an indifferent electrode above the mastoid as reference. The frequency was set at 70 Hz for the high-pass filter and at 0.1 Hz for the low-pass filter. The digital EEG response on a visual stimulus was stored starting 300 ms before and completing 1100 ms after the given stimulus. The recorded EEG phases were averaged separately for the target and for the non-target stimuli. Latencies of the endogenous P2, N2, and P3 components were evaluated according to international recommendation [44]. For the P3 latency, laboratory specific age-dependent normal values exist. Therefore, we also evaluated the percentage of normal or pathological P3 latencies.

The measurement of the ERP was performed in a standardized way, using red and white flashes as visual stimuli. In a dark, air-conditioned room, patients were seated in a distance of 150 cm in front of a 30 cm × 30 cm video screen and instructed to press a button with their dominant (or non-paretic) hand, whenever a red light (target-stimulus) appeared on the screen and to ignore a white light. In total, 400 flashes were presented in a random sequence (85% flashes of white light with 17 cd, 15% flashes of red light with 6 cd). The flashes occurred at intervals of 1800 ms lasting 100 ms each.

2.3. Statistical analysis

The statistical calculation was performed as a per-protocol analysis. The Mann–Whitney–*U*-Test was performed to compare the P2, N2, and P3 latencies measured within the different subgroups. The percentage of pathological P3 latencies was determined for each subgroup and visit and compared between the subgroups using Chi^2-test. The ERP components measured in the different subgroups at the first, second, and third visit were compared by Wilcoxon test. In the interpretation of data, probability values of $p < 0.05$ (two tailed) were considered statistically significant.

The statistical analysis was performed, using SPSS 16.0 for Windows (SPSS Inc.).

3. Results

3.1. Baseline data

We enrolled a total of 563 patients (385 male and 178 female patients) with a mean age of 58.3 years. Table 1 displays the patients' data at baseline and their study outcome status. The data reflects the typical features of stroke patients in the first weeks after qualifying event and treated in a rehabilitation centre.

3.2. ERP follow-up data

Table 2 presents the ERP latencies of all patients at the beginning of the study and at the follow-up examinations after 12 months and after 24 months. We have assessed the percentage of abnormal P3 latencies according to normal values (see Methods). Latencies measured after 12 and 24 months were compared to those determined at the baseline. The P2 latency continuously increased over the observation period with a significant difference after 24 months compared to baseline while the N2 latency showed a highly significant increase after the first 12 months of follow-up but no significant difference after 24 months compared to baseline. A significant decrease could be shown for the P3 latency after 24 months. The percentage of abnormal P3 values also significantly decreased from 51% to 43% over 24 months.

Table 3 presents the data for the intergroup comparison of ERP latencies between male and female patients. We found a significantly longer P2 latency after 12 months of follow-up in men compared to women, as well as a significant increase of P2 latency after 24 months compared to baseline in the group of male patients. There was no significant difference in the group comparison of N2 latencies. A significant increase of N2 latency after 12 months, however, was shown for both men and women. Comparing the P3 values at baseline, women showed a significantly longer P3 latency than men. 61% of the women had