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Original article

Longitudinal study of a NoGo-P3 event-related potential component following mild traumatic brain injury in adults

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ABSTRACT

Background: Event-related potentials have repeatedly revealed electrophysiological markers of cognitive dysfunction associated with Mild Traumatic Brain Injury (MTBI) and may represent a sensitive tool to guide cognitive rehabilitative interventions. We previously found patients with symptomatic MTBI characterized by smaller P300 (or P3) wave amplitudes in a NoGo-P3 subcomponent in the acute phase of the injury. The goal of this longitudinal study was to investigate whether this early NoGo-P3 subcomponent differs over time in symptomatic MTBI patients and healthy controls.
Methods: We included adults with a diagnosis of MTBI and individually matched healthy controls tested at 1 week, 3 months, and 1 year after the MTBI. Symptoms were assessed by the Rivermead Post-Concussion Symptoms Questionnaire. NoGo-P3 was collected by using a cued Go/NoGo task and the relevant subcomponent was extracted by independent component analysis.
Results: Among 53 adults with a diagnosis of MTBI and 53 controls, we included 35 with symptomatic MTBI and 35 matched healthy controls (18 females each group; mean age 34.06 ± 13.15 and 34.26 ± 12.98 years). Amplitudes for the early NoGo-P3 subcomponent were lower for symptomatic MTBI patients than controls ($P < 0.05$) at 1 week post-injury. Furthermore, mixed ANOVA revealed a significant time by group interaction ($P < 0.05$), so the effect of time differed for symptomatic MTBI patients and healthy controls. The amplitudes for MTBI patients normalized from 1 week to 3 months post-injury and were comparable to those of controls from 3 months to 1 year post-injury. However, amplitudes for 3 MTBI patients with particularly severe complaints 1 year post-injury did not normalize and were lower than those for the remaining MTBI sample ($P < 0.05$).
Conclusions: Selected event-related potentials can be used as a sensitive and objective tool to illustrate the cognitive consequences of and recovery after MTBI.

1. Introduction

Mild Traumatic Brain Injury (MTBI) is a common global health problem [1]. The pathophysiology is heterogeneous and complex, but diffuse axonal injury should play a central role across all severities of TBI [2]. Although the World Health Organization task force on MTBI concluded that symptoms after MTBI are typically

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temporary for most patients and resolve within days to a few months post-injury [3], a small proportion of patients does not fully recover and show persisting cognitive, affective and somatic symptoms [4,5]. There is a lively debate on the factors that cause or maintain these long-term problems, and different demographic, psychosocial, medical and situational predictors of prolonged symptoms after MTBI have been investigated [3]. Notably, depression is among the most common conditions after MTBI and can be a direct or indirect consequence of the injury [6].

The symptoms after MTBI are subtle, and the sensitivity of conventional neuroimaging techniques such as CT and MRI to abnormalities is rather low [7,8]. Furthermore, in terms of sensitivity and validity, addressing cognitive symptoms and cognitive recovery may be difficult with conventional neuropsychological testing [4,9]. Accordingly, there have been calls for more sensitive and objective tools for investigating symptoms after MTBI [10]. Diffusion Tensor Imaging (DTI) is among the most promising neuroimaging techniques in MTBI research [11,12], and DTI studies suggest that some longer-lasting effects of MTBI may be seen in some individuals [12]. However, at present, some major challenges include comparability across sites and protocols for determining an appropriate technique for clinical practice [11].

In recent years, electrophysiological methods have contributed considerably to our understanding of the cognitive mechanisms involved in MTBI [13]. Among these methods, Event-Related Potentials (ERPs) are particularly important because they offer a real-time measure of the neural events associated with specific cognitive processes. The functional significance of some ERP components may be further specified by applying Independent Component Analysis (ICA) [14,15]. ICA allows for analyzing waveforms of the source activities, which, overlapping both in space and time, constitute the measured multichannel signal mixtures. By assessing diverse cognitive processing capabilities, ERPs have repeatedly uncovered electrophysiological markers of covert cognitive dysfunctions associated with MTBI [10,13,16]. Furthermore, ERPs may be a sensitive tool to monitor the clinical course and guide cognitive interventions [13,17,18]. Studies with a longitudinal prospective design have been found useful for following changes in cognitive function in the context of other conditions such as sleep disorders [19].

In the context of MTBI, the most consistent ERP finding has been reduced P300 (or P3) wave amplitude. P3 is one of the most-studied ERP components and essentially constitutes a set of several P3 components that all reflect cognitive processes [20,21]. Broglio and colleagues [22] found that athletes with MTBI showed diminished oddball P3b amplitudes in a post-acute phase as compared with age-matched young adults without an MTBI history. The authors interpreted this result in terms of a reduced capacity of MTBI patients to allocate attentional resources. This finding is consistent with other studies showing comparable P3 alterations in athletes or other patients with MTBI weeks to months [23,24] or even years after the injury [25,26].

The cued Go/NoGo task is used to investigate several executive and facilitating processes [20] that typically are impaired in patients after TBI [27]. A cue signals that the subsequent (Go or NoGo) stimulus may require a response. Therefore, the task involves both the preparation of a response and, in the case of a NoGo stimulus, the abortion of the prepared response. The NoGo stimulus typically evokes the NoGo-P3 component. Using ICA, Brunner and colleagues [28] showed that this ERP component is composed of at least 2 subcomponents, and the early NoGo-P3 subcomponent should reflect the process of replacing the prepared response with an alternative response [14].

We previously showed that amplitudes for the early NoGo-P3 subcomponent were smaller for symptomatic MTBI patients than matched controls in the acute phase of the injury [29]. This finding was interpreted in terms of an impaired ability to energize the initiation of response patterns. From this observation, here we investigated whether the development of this ERP component differs over time between MTBI patients and controls and accordingly normalizes in MTBI patients.

2. Material and methods

2.1. Participants

We included 106 adults with MTBI and healthy controls individually matched for sex, age and education. Because of a technical problem, ERPs at 1 week post-injury were not available for one MTBI patient. One MTBI patient failed to appear at the third session. The patients were recruited in the emergency units of 4 hospitals in Switzerland. The injuries consisted of sports and cycling accidents (45%), falls (23%), car and motorbike casualties (19%), accidents sustained due to falling objects (9%), and other incidents (4%). Inclusion criteria were Glasgow Coma Scale score 13–15 at hospital admission, normal posttraumatic CT findings, and one or more of the following characteristics: loss of consciousness (up to 30 min), presence of altered mental state (e.g., confusion, disorientation or dizziness) at the time of the incident, post-traumatic amnesia (< 60 min), and/or retrograde amnesia (< 30 min). The exclusion criteria were a history of neurologic or psychiatric disease, neurosurgical intervention or TBI; current and past drug or alcohol abuse; and age < 17 or > 64 years. Patients with past concussions were excluded if the concussion occurred within 3 months before study intake. Both the patient and the control group included 17 smokers (one cigarette a day up to one package a day).

The main analyses involved a sample of MTBI patients who reported clinical impairments (symptomatic) within 1 week after the injury. MTBI patients reporting symptoms that were comparable in severity to those of the controls were not considered because these were not considered clinical and may not result in any brain function deficits. Assignment to symptomatic and non-symptomatic MTBI groups was based on the results of a cluster analysis of scores from the Rivermead Post Concussion Symptoms Questionnaire (RPQ; described below) and generating 2 clusters characterized by differing levels of symptom severity. Then, an exploratory analysis was conducted on a very small MTBI subsample, also determined by cluster analysis that consisted of 3 MTBI patients who reported comparatively severe clinical symptoms at 1 year post-injury. The purpose of this second analysis was to compare high-risk patients exhibiting persisting problems and the remaining MTBI patients. These 3 MTBI patients were characterized by the highest RPQ scores at 1 year after the incident and no improvement in symptoms from the acute to the chronic phase. The process of assigning subjects to the subgroups is illustrated in Fig. 1. More detailed information about the clustering is provided in the Procedure section.

The study was approved by the cantonal ethics committee of Aargau (reference no. 2009/039) and the cantonal ethics committee of Zurich (reference no. 2010-0546/4). All participants gave their written informed consent before inclusion. Loss of income due to study participation was refunded.

2.2. Procedure

This paper was written in the context of an interdisciplinary study involving the use of various questionnaires, neuropsychological tests, and neuroimaging methods (MRI and electroencephalography [EEG] techniques). This paper refers to the analysis of ERP data. For all patients, the first examination was completed

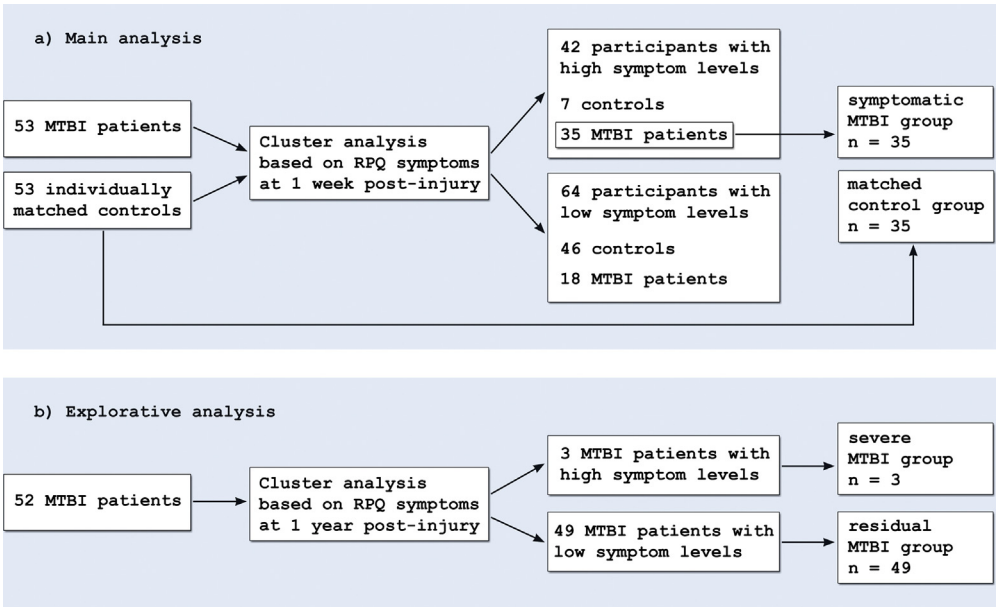

Fig. 1. Flow of participants in the study illustrating the allocation to subgroups. a) Assignment of patients to the symptomatic mild traumatic brain injury (MTBI) group. b) Assignment of MTBI patients to the severe and residual groups. One patient was not available 1 year after the injury.

within 8 days post-injury (mean 5.36 ± 1.59 days). The participants were followed longitudinally and retested at 3 months (mean 98.49 ± 5.32 days) and 12 months (mean 371.04 ± 4.76 days) post-injury.

2.3. Questionnaires

The RPQ contains 16 items that represent the most frequently reported symptoms after MTBI: cognitive (forgetfulness, poor concentration, taking longer to think), emotional (being irritable, feeling depressed, feeling frustrated, restlessness) and physical (headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, blurred vision, light sensitivity, double vision). The patients are asked to rate the degree to which post-concussion symptoms are more of a problem than before the accident. The items are rated on a 5-point scale: 0, not experienced at all; 1, no more of a problem; 2, a mild problem; 3, a moderate problem; 4, a severe problem. As recommended by King and colleagues [30], scores of 1 were combined with 0 scores for further analysis. Eyres and colleagues [31] have shown that the items "headaches", "dizziness" and "nausea" measure a construct different from all the other items. Therefore, these 3 items were excluded and the analyses were conducted with the unidimensional RPQ-13 scale.

Depression severity was assessed by the German version of the Beck Depression Inventory 2nd Edition (BDI-II) [32]. This self-reporting inventory contains 21 items rated on a 4-point scale, and the values are totalled for a sum score.

2.4. EEG

EEG for all participants was performed in the morning and involved a Mitsar 201 (Mitsar, St Petersburg, Russian Federation) with a sampling rate of 250 Hz. Nineteen tin electrodes were placed according to the International 10–20 system by using electrode caps (Electro-cap International, Eaton, OH, USA). Two reference electrodes were placed on the earlobes. Before data processing, EEG data was bandpass-filtered (0.53–50 Hz) and notch-filtered (45–55 Hz) and the montage was changed to average. Eye-blinks and horizontal eye movements were identified by using ICA decomposition and removed from EEG by zeroing the activation curves of the respective individual independent components. The remaining artifacts were excluded from further analysis by rejecting epochs of the filtered EEG with excessive amplitude (> 100 μV) and/or excessive 0 to 3 Hz and 20 to 50 Hz band frequency activities (threshold = channel z-score of 6).

2.5. ERPs

ERPs were collected by using a cued Go/NoGo task. Three categories of visual stimuli (pictures of animals, plants, and people) were presented. Stimuli were displayed on 43 cm screens (refresh rate of 60 Hz) and occupied approximately 3° of the visual field. Trials consisted of the presentation of a pair of visual stimuli and were grouped into 4 categories. In Go trials, a picture of an animal is followed by a picture of an animal. In NoGo trials, a picture of an animal is followed by a picture of a plant. Participants underwent ignore trials (picture of a plant followed by a picture of a plant) and novelty trials (picture of plant followed by picture of human being, presented along with a novel sound), but these data were not analyzed in this paper. The trials were grouped into 3 blocks. Each block consisted of unique set of 5 animals, 5 plants and 5 people stimuli and a pseudorandom presentation of 100 trials with equal probability for each trial category. Participants underwent 300 trials (75 NoGo trials). The stimulus duration was 100 ms, inter-stimulus interval 1 s, and trial duration 3.1 s. Participants were told to press a button as quickly as possible in response to all Go trials.

ERPs were decomposed into Independent Components (ICs) by applying the ICA Infomax algorithm [33] to ERPs from all 3 time measurements for all 106 participants. ICA involved use of the EEGLAB Matlab toolbox v10.2.5.6b [34]. ICA input data were the 2-D 19-scalp-locations x 318-ERP-time-series matrix. This paper addresses the early subcomponent of the NoGo-P3 wave ($P3NOGO_{early}$), so named in previous publications, and was calculated by applying ICA to the 700-ms time interval following the second stimulus in the NoGo trials. The resulting spatial filter was applied to the individual ERPs, and ERPs were back-projected to the Cz electrode.

IC $P3NOGO_{early}$ amplitudes were quantified as we previously described [29]. Baseline correction of the ERP epochs involved use

of the 100 ms pre-stimulus interval. Trials with commission errors were exempt from the averaging. IC P3NOGO$_{early}$ amplitudes were measured by identifying the positive extreme in the 260 to 380 ms latency range. Afterwards, the area under the curve in a 80 ms time window centered at the individual extremum was determined and transformed into a mean amplitude measure.

3. Statistical analysis

Statistical analyses involved use of SPSS for Windows, v23. To partition the total sample into 2 groups that differed in symptom severity, we used hierarchical cluster analysis with Ward's method and squared Euclidean distances of the 1-week RPQ-13 items for all participants (MTBI patients and controls). To obtain an equidistant scale (after combining the response categories "not experienced at all" and "no more of a problem"), we re-scored the RPQ item values to obtain the following categories: 0, not experienced at all or no more of a problem; 1, a mild problem; 2, a moderate problem; 3, a severe problem. MTBI patients belonging to the group characterized by a comparatively high degree of severity were further analyzed and compared to their matched control subjects. Unless otherwise specified, all reported analyses refer to these downsized groups. A further cluster analysis based on the 1-year RPQ-13 items for all MTBI patients and using the above-mentioned method, was used to identify an MTBI subgroup with particularly severe persisting symptoms. The corresponding MTBI subgroup is called the severe MTBI group. Group comparisons incorporating repeated-measures data involved mixed-design ANOVA. In most cases, the assumption of sphericity was not violated. Otherwise, degrees of freedom were altered by Greenhouse-Geisser correction. Paired-group comparisons of categorical demographic data involved the McNemar test. Independent-group comparisons of categorical data involved Chi^2 test. The Wilcoxon signed-rank test was used for comparing ordinal data. Interval-scaled demographic and ERP data were analyzed by paired-sample Student t test. Traditional parametric tests have assumptions underlying their use. Because these assumptions cannot be tested when the sample size is small [35], the non-parametric Mann-Whitney U-test was used for independent-group comparisons including the severe MTBI subsample ($n = 3$). $P < 0.05$ was considered statistically significant.

4. Results

We included a total of 106 participants (66 males): 53 were patients with mTBI (mean age 34.02 ± 12.48 years) and 53 were healthy controls (mean age 34.23 ± 12.21years). The main analysis involved 35 MTBI patients who reported clinical impairments within 1 week after the injury (mean age 34.06 ± 13.15 years) and 35 healthy controls (mean age 34.26 ± 12.98 years). Both cluster solutions produced clusters with consistently differing symptom levels across almost all problems. The two-cluster solution based on the RPQ values of the total sample from 1 week post-injury constituted the primary basis for the analyses and revealed one cluster with low symptom level ($n = 64$) and one with high symptom level ($n = 42$) (Fig. 1). Median RPQ item scores for these groups are in Table 1. MTBI patients assigned to the high symptom level group represent the symptomatic MTBI group ($n = 35$).

Table 1
Scores for RPQ-13 items (1 week post-injury) for study participants (with mild traumatic brain injury [MTBI] and healthy controls) with high and low symptom level.

RPQ symptoms	High symptom level ($n = 42$)	Low symptom level ($n = 64$)	P value[a]
Noise sensitivity	2 (2)	0 (0)	< 0.001
Sleep disturbance	2 (2)	0 (0)	< 0.001
Fatigue	3 (1)	0 (0)	< 0.001
Being irritable	0 (2)	0 (0)	< 0.001
Feeling depressed	0 (2)	0 (0)	< 0.001
Feeling frustrated	0 (2)	0 (0)	< 0.001
Forgetfulness	2 (2)	0 (0)	< 0.001
Poor concentration	2 (0)	0 (0)	< 0.001
Taking longer to think	2 (2)	0 (0)	< 0.001
Blurred vision	0 (2)	0 (0)	< 0.001
Light sensitivity	0 (2)	0 (0)	< 0.001
Double vision	0 (0)	0 (0)	NS
Restlessness	0 (0.5)	0 (0)	0.005

Data are median (interquartile range); NS: not significant.
[a] P values adjusted by Holm–Bonferroni sequential correction.

Table 2
Scores for RPQ-13 items (1 week post-injury) for patients with symptomatic MTBI and matched controls.

RPQ symptoms	Symptomatic MTBI ($n = 35$)	Matched controls ($n = 35$)	P value[a]
Noise sensitivity	2 (3)	0 (0)	0.001
Sleep disturbance	2 (2)	0 (0)	0.009
Fatigue	3 (1)	0 (0)	< 0.001
Being irritable	0 (2)	0 (0)	0.009
Feeling depressed	0 (2)	0 (0)	0.007
Feeling frustrated	0 (2)	0 (0)	NS
Forgetfulness	2 (2)	0 (0)	0.001
Poor concentration	2 (0)	0 (0)	< 0.001
Taking longer to think	2 (2)	0 (0)	< 0.001
Blurred vision	0 (2)	0 (0)	0.015
Light sensitivity	0 (2)	0 (0)	0.004
Double vision	0 (0)	0 (0)	NS
Restlessness	0 (0)	0 (0)	NS

Data are median (interquartile range); NS: not significant
[a] P values adjusted by Holm–Bonferroni sequential correction.

The two-cluster solution based on the RPQ values of MTBI patients from 1 year post-injury constituted the basis for the explorative analyses and revealed one small cluster with high symptom level ($n = 3$) and one with comparably low symptom level ($n = 49$). MTBI patients assigned to the first cluster represent the severe MTBI group and those assigned to the second cluster represent the residual MTBI group. Along with showing high symptom levels at 1 year, all 3 patients constituting the severe MTBI group also showed considerable RPQ-13 sum scores at 1 week (all scores > 17), and we found no amelioration of RPQ-13 sum score over time for any of the 3 patients. Median RPQ item scores for the relevant groups are in Tables 2 and 3.

Symptomatic MTBI patients and controls did not differ in gender, handedness, or age (Table 4). However, although the groups had been matched in terms of education, controls had more years of education than symptomatic MTBI patients ($P = 0.042$). Severe and residual MTBI patients did not differ in gender ($P = 0.851$), handedness ($P = 0.561$), or education ($P = 0.112$), but severe MTBI patients were older than residual MTBI patients ($P = 0.041$).

RPQ-13 and BDI-II sum scores for symptomatic MTBI and matched control groups are in Table 5.

For RPQ-13 scores, we found a significant main effect of time ($F(2, 136) = 18.293$, $P < 0.001$). Scores were lower at 3 months and 1 year post-injury ($F(1, 68) = 17.862$, $P < 0.001$, and $F(1, 68) = 31.545$, $P < 0.001$) than 1 week post-injury, with no significant effect of time between 3 months and 1 year post-injury. We found a significant main effect of group ($F(1, 68) = 32.015$, $P < 0.001$): RPQ-13 scores were higher for symptomatic MTBI patients than healthy controls. Furthermore, we found a significant interaction of time and group ($F(2, 136) = 16.372$, $P < 0.001$), which indicates reduced RPQ-13 scores over time for symptomatic MTBI patients but not controls. We found significant interactions when comparing MTBI and control scores from 1 week to 3 months post-injury ($F(1, 68) = 12.364$, $P = 0.001$), from 1 week to 1 year post-injury ($F(1, 68) = 30.343$, $P < 0.001$), and from 3 months to 1 year post-injury ($F(1, 68) = 4.064$, $P = 0.048$).

For BDI-II sum scores, we found a significant main effect of time ($F(1.81, 122.78) = 7.777$, $P = 0.001$). Scores were higher at 1 week post-injury ($F(1, 68) = 14.106$, $P < 0.001$) and 3 months post-injury ($F(1, 68) = 7.674$, $P = 0.007$) as compared with 1 year post-injury, with no significant difference between 1 week and 3 months post-injury. The significant main effect of group ($F(1, 68) = 4.499$, $P = 0.038$) indicates that symptomatic MTBI patients showed more depression symptoms than controls. We found no significant overall interaction effect of time and group ($F(1.81, 122.78) = 3.124$, $P = 0.053$). However, the BDI scores decreased in MTBI patients from 1 week to 1 year post-injury but remained stable for controls ($F(1, 68) = 4.993$, $P = 0.029$).

The activation curve of IC $P3NOGO_{early}$ was characterized by a positive deflection peaking at about 320 ms after the onset of the second stimulus, and the topography showed a central distribution. Grand average waveforms for the subgroups at the 3 measurement times are in Fig. 2.

Mean amplitudes for symptomatic MTBI patients and matched controls as well as severe and residual MTBI groups

Table 3
Scores for RPQ-13 items (1 week and 1 year post-injury) for severe and residual MTBI patients.

RPQ symptoms	One week post-injury			One year post-injury		
	Severe MTBI ($n = 3$)	Residual MTBI ($n = 49$)	P value[a]	Severe MTBI ($n = 3$)	Residual MTBI ($n = 49$)	P value[a]
Noise sensitivity	2	0 (2)	NS	2	0 (0)	0.010
Sleep disturbance	2	0 (2)	NS	3	0 (2)	0.043
Fatigue	3	2 (3)	NS	3	0 (2)	0.006
Being irritable	3	0 (0)	NS	3	0 (0)	0.009
Feeling depressed	2	0 (1)	NS	2	0 (0)	0.033
Feeling frustrated	2	0 (0)	NS	3	0 (0)	0.001
Forgetfulness	2	0 (2)	NS	3	0 (0)	0.010
Poor concentration	2	2 (2)	NS	3	0 (0)	0.008
Taking longer to think	2	0 (2)	NS	3	0 (0)	0.002
Blurred vision	3	0 (0)	0.036	2	0 (0)	0.006
Light sensitivity	0	0 (2)	NS	2	0 (0)	0.008
Double vision	0	0 (0)	NS	2	0 (0)	NS
Restlessness	2	0 (0)	NS	3	0 (0)	0.001

Data are median (interquartile range); NS: not significant.
[a] P values adjusted by Holm–Bonferroni sequential correction.

Table 4
Demographic features of patients with symptomatic MTBI and matched controls and severe and residual MTBI patients.

	Symptomatic MTBI ($n = 35$)	Matched controls ($n = 35$)	P value	Severe MTBI ($n = 3$)	Residual MTBI ($n = 49$)	P value
Gender (female/male)	18/17	18/17	NS	2/1	30/19	NS
Handedness (left/right)	4/31	6/29	NS	0/3	5/44	NS
Age	34.06 ± 13.15	34.26 ± 12.98	NS	49.33 ± 6.81	33.14 ± 12.30	0.041
Years of education	11.66 ± 2.40	12.26 ± 2.11	0.042	10.33 ± 2.08	12.53 ± 2.54	NS

Data are number or mean ± SD; NS: not significant.

Table 5
Mean RPQ and BDI-II sum scores for patients with symptomatic MTBI and matched controls.

	RPQ-13 sum scores		BDI II sum scores	
	MTBI ($n = 35$)	Controls ($n = 35$)	MTBI ($n = 35$)	Controls ($n = 35$)
One week post-injury	15.51 ± 8.04	2.23 ± 3.58	8.31 ± 7.08	4.06 ± 4.78
Three months post-injury	8.97 ± 10.57	1.63 ± 4.22	6.26 ± 6.69	4.23 ± 6.60
One year post-injury	6.69 ± 9.52	2.14 ± 4.28	4.71 ± 5.00	3.14 ± 4.48

Data are mean ± SD.

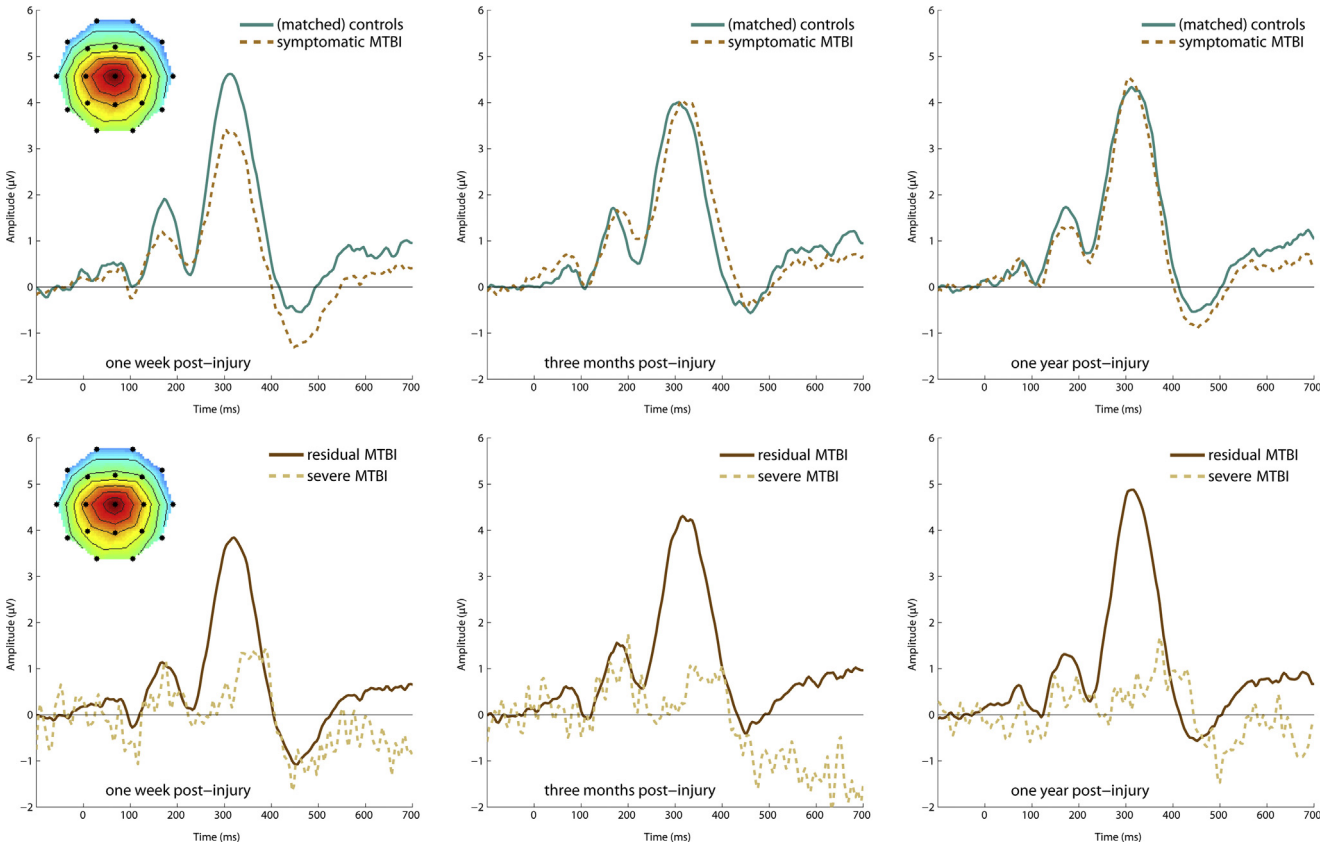

Fig. 2. Activation curves of IC P3NOGO$_{early}$, back-projected to Cz electrodes for symptomatic MTBI and matched controls (top) and severe and residual MTBI subsamples (bottom), for 1 week, 3 months and 1 year post-injury relative to the onset of stimulus 2. Top left: topography of IC P3NOGO$_{early}$.

Table 6
Mean IC P3NOGO$_{early}$ amplitudes for symptomatic MTBI patients and matched controls and severe and residual MTBI patients.

	Symptomatic MTBI ($n = 35$)	Matched controls ($n = 35$)	Severe MTBI ($n = 3$)	Residual MTBI ($n = 49$)
One week post-injury	3.32 ± 3.09	4.60 ± 2.89	1.13 ± 1.93	3.75 ± 3.38
Three months post-injury	4.06 ± 3.75	4.09 ± 2.95	0.67 ± 2.09	4.21 ± 3.76
One year post-injury	4.30 ± 3.66	4.44 ± 2.34	0.98 ± 1.72	4.66 ± 3.73

Data are mean ± SD.

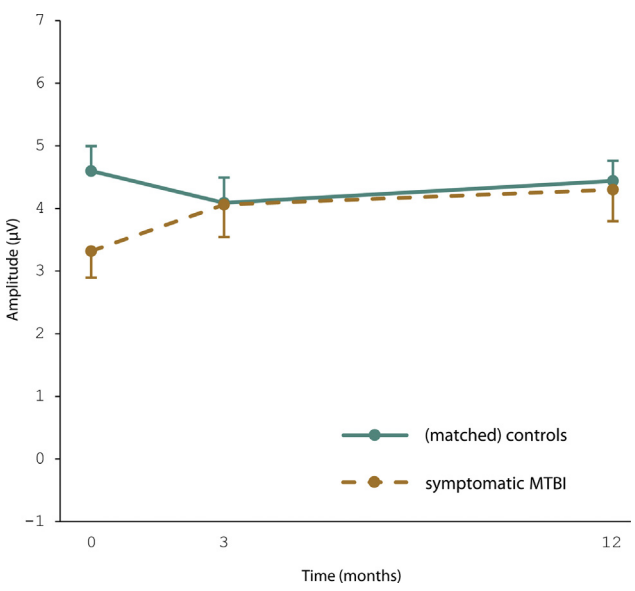

Fig. 3. Mean IC P3NOGO$_{early}$ amplitudes by time (months) for symptomatic MTBI patients and matched controls at the 3 measurement times.

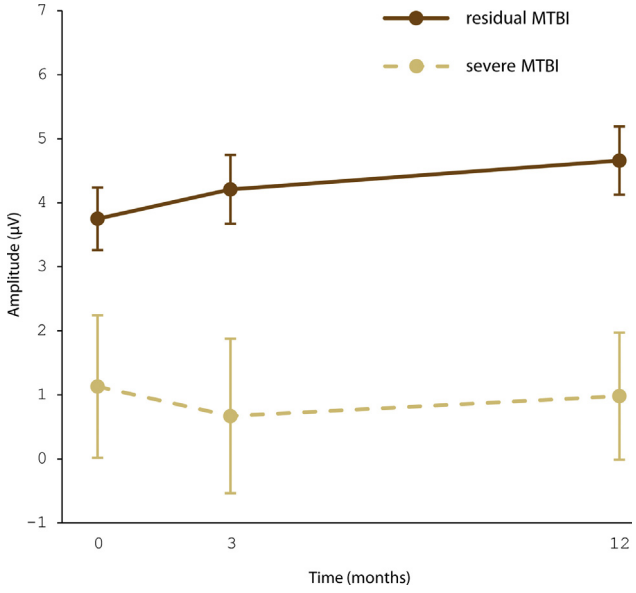

Fig. 4. Mean IC P3NOGO$_{early}$ amplitudes by time (months) for severe and residual MTBI patients at the 3 measurement times.

are in Table 6. Mixed ANOVA revealed no significant main effects on comparing symptomatic MTBI patients and matched controls, so in general, IC P3NOGO$_{early}$ amplitudes did not differ between groups and across measurement times. However, we found a significant interaction effect of time and group ($F(2, 136) = 3.916$, $P = 0.022$), so the effect of time differed in symptomatic MTBI patients and controls. The profile of mean IC P3NOGO$_{early}$ amplitudes differed between the groups from 1 week to 3 months post-injury ($F(1, 68) = 5.636$, $P = 0.020$) and from 1 week to 1 year post-injury ($F(1, 68) = 4.726$, $P = 0.033$). However, the amplitudes for MTBI patients and controls developed similarly from 3 months to 1 year post-injury (Fig. 3). Paired-sample t test follow-up analysis of the first measurement revealed a significant difference in mean amplitude between symptomatic MTBI patients and matched controls ($t(34) = 2.294$, $P = 0.028$).

Fig. 4 shows the development of mean IC P3NOGO$_{early}$ amplitudes for severe and residual MTBI patients. The amplitudes did not differ between the groups at 1 week and 3 months post-injury ($P = 0.164$, and $P = 0.078$). However, P3NOGO$_{early}$ amplitudes were significantly reduced with severe MTBI at 1 year post-injury ($P = 0.028$).

5. Discussion

The aim of this study was to investigate longitudinal changes in the well-researched ERP subcomponent P3NOGO$_{early}$ in a patient sample with MTBI. In general, the profiles of IC P3NOGO$_{early}$ mean amplitudes differed across the times measured between symptomatic MTBI patients and their matched controls. More specifically, IC P3NOGO$_{early}$ mean amplitudes were smaller for symptomatic MTBI patients than matched controls at 1 week post-injury, but the amplitudes normalized and were comparable from 3 months to 1 year post-injury. However, a small patient subsample with severe and persisting symptoms showed reduced P3NOGO$_{early}$ amplitudes at 1 year post-injury as compared with the remaining MTBI patients. This provides some indication for an incomplete or at least delayed recovery in a few MTBI patients.

First, these findings indicate impairment in a specific cognitive process in the acute phase of MTBI, namely, in the executive process of replacing the prepotent response with an alternative response. This process is suggested to be facilitated by the attentional function of energization [14], and deficient energization has been found associated with lesions in the frontal lobe [36]. This result agrees with the findings of Dall'Acqua and colleagues [37] who, by applying Diffusion Tensor Imaging (DTI) to the same MTBI patient sample, found an association between reduced connectivity strength in frontal lobe areas and high levels of self-reported post-concussion symptoms.

Second, the normalization of this process in the subacute phase of MTBI agrees with the reported reduction in symptoms over time and with the frequently observed resolution of symptoms within weeks to months after such an injury [3]. However, a recent review of the course of recovery of MTBI-related cognitive impairment indicated limited agreement on when the deficits resolve, and some evidence suggests that certain cognitive deficits may persist [38]. This suggestion agrees with our third finding, that the permanence of IC P3NOGO$_{early}$ amplitudes at a comparably low level in a particularly affected MTBI subsample indicates persisting cognitive change in a small number of MTBI patients. This finding is confirmed by results from Messé and colleagues [39], who found decreased connectivity in frontal regions in MTBI patients with post-concussion syndrome in a late phase after the injury. However, this conclusion is cautioned in view of the very small number of persistently affected patients. Particularly, low statistical power may lead to unreliable findings [40]. Of note, these patients with severe MTBI were older than residual MTBI patients, and older MTBI patients may exhibit diminished regeneration capabilities [41].

In summary, the findings show that selected ERPs can be sensitive and objective tools to illustrate the cognitive consequences after MTBI. Indeed, current diagnosis of MTBI is primarily based on self-reported symptoms, and patients may conceal, overstate or be unable to notice their problems. Furthermore, the sensitivity of conventional neuroimaging methods [8] and neuropsychological tests [4] for detecting MTBI-related abnormalities is rather unsatisfactory. Finally, financial and methodological reasons can hamper the routine use of promising techniques such as DTI [11]. Straightforward sensitive and objective indicators of status after MTBI could contribute to appropriate diagnoses and to the monitoring of rehabilitative interventions and cognitive recovery. Along with their close association to specific cognitive processes, ERPs seem to be practical candidate markers of cognitive dysfunction after MTBI.

Our study has some limitations and particularities. As mentioned previously, the small number of MTBI patients exhibiting severe symptoms 1 year post-injury affects the generalizability of the corresponding results. Cluster analysis yielded an MTBI subsample of 3 patients, about 6% of the entire MTBI sample. This percentage agrees with estimates of patients with persistent sequelae [5], but longitudinal studies with a larger number of MTBI patients are needed for formulating reliable statements about the cognitive recovery of patients with persistent complaints.

In the present study, the posttraumatic symptoms were self-assessed by use of the RPQ. Although the RPQ is considered a valid tool for assessing post-concussive symptoms [42], the corresponding score is based on only subjective perceptions of patients regarding their condition.

Persistent problems in the MTBI context can be caused or maintained by multiple factors that may also differ from brain damage [3]. For example, by using an additional comparison group of children with injuries unrelated to the head, Babikian and colleagues [43] found similar neurocognitive weaknesses in both the MTBI and the other injury groups up to 1 year post-injury. Furthermore, problems such as depressive symptoms can be direct or indirect consequences of the MTBI [6]. The same applies to IC P3NOGO$_{early}$ amplitudes, which among other things, can be affected by depressive symptoms. Hence, the presumably multifactorial cause of reduced IC P3NOGO$_{early}$ amplitudes needs further exploration.

We observed a small but distinct decline in amplitudes over time in controls, in particular from the first measurement right after the MTBI to the second measurement 3 months later. On investigating the same P3NOGO$_{early}$ component in a sample of children with attention deficit hyperactivity disorder, Kompatsiari and colleagues [44] observed a comparable trend. However, in contrast to our study, the observation involved a short-term test-retest design with the second session following the first session within a 30 min interval. Therefore, an altered attentional effort due to fatigue might not be a suitable explanation in the present context. However, the amplitude of IC P3NOGO$_{early}$ has been shown to increase when subjects are asked to invest more effort to enhance response speed [20]. Thus, healthy participants, having experienced the task at the first measurement, may be optimizing their attentional effort in terms of a more economical performance in the following examinations. Alternatively, a decrease in IC P3NOGO$_{early}$ amplitudes over time could be interpreted in the framework of P300 arousal effects that have been found to occur as a result of environmental factors [45] or stimulus features [46]. More specifically, subjects may be more involved in the task at the first measurement, and comparatively motivated subjects may exhibit increased engagement of attentional resources to the

stimuli, which would result in increased P3 amplitudes [47]. However, in MTBI patients, injury-decreased cerebral activation in attention-related circuits in the acute phase may return to normal activation patterns in the post-acute phase [12].

6. Conclusions

To the best of our knowledge, this is the first study to examine the longitudinal changes of a P3-related ERP component in patients who experienced an MTBI. With reduction 1 week after the injury and normalization at 3 months and 1 year post-injury, the investigated early NoGo-P3 subcomponent has been found a sensitive measure of characteristic cognitive impairment after MTBI. The component can readily be assessed shortly after the injury and can serve as an objective piece of the puzzle in evaluating the clinical course of MTBI.

Disclosure of interest

S.J. is principal investigator of the study. In addition, he is the medical director of the Bellikon Rehabilitation Clinic, which is owned by the Swiss National Accident Insurance Fund SUVA. P.D'A. has been financially supported by the SUVA. Yet, the opinions and views stated in this article are those of its authors and do not necessarily represent the views of the SUVA. A.M acts as a management board member for HBImed AG. The remaining authors declare that they have no competing interest.

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