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THE AUDITORY P300-BASED SSBCI: A DOOR TO MINIMALLY CONSCIOUS PATIENTS?*

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Abstract— **In this study we report on the evaluation of a novel auditory single-switch BCI in nine patients diagnosed with MCS. The task included a simple and a complex oddball paradigm, the latter uses the tone stream segregation phenomenon. In all patients a significant difference between deviant and frequent tones could be observed in EEG. However, in some cases the deviant tones produce a significant negative peak and in some a very late positive peak. These preliminary findings are relevant in order to address future customization of this auditory ssBCI-based paradigm for unresponsive patients.**

I. INTRODUCTION

Minimally conscious state (MCS) is a disorder of consciousness (DOC) clinically identified on the basis of behavioral assessment that shows the presence of non-reflexive responses to visual and/or auditory stimulation (i.e. visual tracking, manipulation of objects [1], [2]). The possible concurrence in these patients of severe motor impairment might, however, prevent the disclosure of such behavior even during a carefully repeated examination. Traditional means of assistive technologies (AT), such as button or joystick-based systems rely on residual motor signals from the patient. In contrast, the Brain-Computer Interface (BCI) is a technology that utilizes neurophysiological signals from the brain to control external devices bypassing the natural muscular output [3]. Currently, the electroencephalography (EEG)-based BCI systems provide severely motor disabled people with a new output channel to voluntarily control applications for communication and environmental interaction purposes [4], [5], [6], [7], [8], [9]. Recently, different protocols based on neuroimaging and electrophysiological techniques have revealed that unresponsive patients diagnosed with MCS may produce specific neural responses to verbal commands. Such responses are considered a sign of awareness otherwise undetectable [10], [11]. Based on these considerations, the EEG-based BCI systems may offer a unique opportunity in supporting the bedside clinical assessment of these unresponsive patients to eventually provide them with a binary (yes/no) communication device at home.

II. APPROACH

When considering the application of BCIs to unresponsive patients for communication purposes, system development must aim to implement simple and robust devices. A BCI system based on only one reliably detectable pattern is called single-switch BCIs (ssBCIs). Such an ssBCI comply with both needs. In fact, it is possible to control any kind of assistive technology (AT) applications by using yes/no commands conveyed by means of a ssBCI [12], [13], [14]. While the auditory pathway is usually preserved in unresponsive patients, the visual ability can be often functionally not sufficient to sustain stimulation. To this regard, Murguialday and colleagues [15] have recently reported on a patient in a completely locked-in state due to a progressive neurodegenerative disease (amyotrophic lateral sclerosis) who had lost all afferent pathways except for the auditory system. Previous findings have already highlighted the suitability of an auditory paradigm based on the stream tone segregation phenomenon in the BCI framework [16], [17]. These studies showed promising results but exclusively in healthy participants.

In this study we report on the evaluation of a novel auditory ssBCI in a sample of patients diagnosed with MCS.

III. EXPERIMENTS

Nine patients (2 female, 7 male, aged between 21 and 66 years) diagnosed as minimally conscious were enrolled in the study. The clinical status persisted from a minimum of 5 month to a maximum of 10.75 years. The patients were behaviorally assessed by means of the Coma Recovery Scale Revised [1] within 24 hours prior to or after EEG measurements. Their CRS-R varied between 7 and 21. The study was approved by the local ethics committee at the Medical University of Graz (Austria), the Medical Faculty of the University of Würzburg (Germany), and at the Fondazione Santa Lucia (Italy). Written informed consent was obtained by the patient's legal representatives. Four patients are currently hospitalized in a special unit for non-responsive patients at Albert-Schweitzer Klinik Graz. Two patients are admitted at the Fondazione Santa Lucia for rehabilitation program. Three patients are hospitalized in a rehabilitation clinic specialized in care for non-responsive patients (Intensiv-Pflegeklinik Schwaig). The EEG was recorded using a g.USBAmp [Guger Technologies OG, Graz, Austria] together with a g.GAMMAsys active electrode system at nine electrode positions (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4, according to the international 10-20 system) with a sampling

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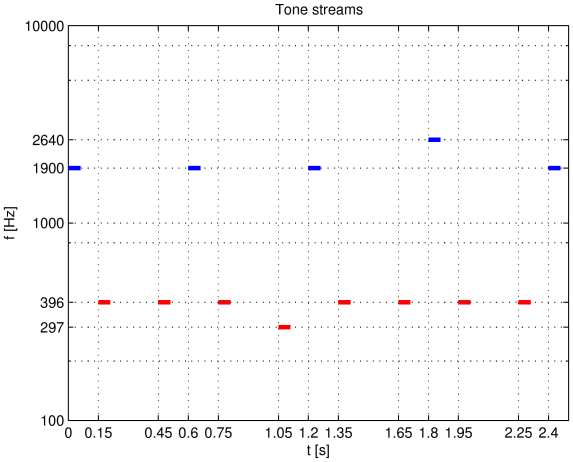

Fig. 1. Intermixed tone streams. Pattern showing the high tone stream (1900 Hz) and low tone stream (396 Hz) consisting of short beep tones. Infrequently appearing deviant tones were placed at random positions.

rate of 512 Hz. The ground electrode was attached to the right mastoid; the left earlobe was used as reference. The EEG measurements were done in a silent room in clinical environment. The patients were either lying in bed with their upper part of the body slightly elevated or sitting in a wheelchair. Tone streams were used as auditory stimuli and were presented binaurally using in-ear headphones. Instructions were given both, auditory (standardized via headphones and orally by the experimenter at the beginning of each single trial) and visually by means of a laptop screen positioned in front of the patient's head.

A. *Stimulus description: tone streams*

Two different tone streams with infrequently appearing deviant tones at random positions were used in this work (Figure 1). The low tone stream (LTS) consisted of a series of short beep tones (duration 60 ms, rise/fall time 7.5 ms) with an inter-stimulus interval (ISI) of 300 ms. The regular tones had a frequency of 396 Hz, whereas the deviant tones had a frequency of 297 Hz. During one trial (lasting for 33 s), 100 low tones were played in total, with 10 deviant tones randomly distributed in the tone stream. At least 5 and at most 13 regular low tones (uniform distribution, 9 tones on average) were always placed between two deviants. The high tone stream (HTS) also consisted of a series of short beep tones (same parameters as above) with an ISI of 600 ms. The regular tones had a frequency of 1900 Hz, whereas the deviant tones had a frequency of 2640 Hz. During one trial, 50 high tones were played in total, with 10 deviant tones randomly distributed in the tone stream. At least 2 and at most 6 regular high tones (uniform distribution, 4 tones on average) were always placed between two deviants. In order to ensure that all beep tones were perceived equally loud the loudness of the beep tones of both tone streams was adjusted according to the normal equal-loudness-level contours [ISO 226:2003].

B. *Paradigm Description*

Each session started with a simple auditory oddball paradigm [18], i.e. either the LTS or the HTS tone stream was presented. This paradigm was included as a kind of screening with the hypothesis that the presence of a P300 in the simple paradigm is related to the presence of a P300 in the more complex paradigm. Moreover, patients got accustomed to the experimental condition. At the beginning of each trial, 5 (in case of the HTS) or 10 (in case of the LTS) additional beep tones were played without any deviant tones. The patients were instructed to listen to the tone stream and to count the deviant tones. This instruction was given in order to facilitate the focusing in the following complex paradigm. Four runs (5 trials each) were recorded with random breaks between all trials (between 8 and 12 s). Longer breaks were taken between the runs according to the patient's needs. After the simple paradigm, a complex paradigm based on the auditory stream segregation phenomenon [17] was used. Both, the LTS and HTS, were intermixed (with 150 ms offset) and simultaneously presented to the patient resulting in a stream pattern of LHL_LHL_... ('_' = silent gap) [18]. Since the frequency separation between LTS and HTS was sufficiently large two separate streams can be perceived and it should be possible to shift attention from one stream to the other. It is known, that a rare event in a series of e.g. auditory stimuli elicits a P300 whose amplitude is modulated by attention, e.g. by having subjects count the occurrence of the rare event. The amplitude of the P300 following a rare event can then be used to assess whether the subject paid attention to this event [18]. First five trials in a row with LTS and then with HTS as target were recorded (when the LTS was used in the simple paradigm, vice versa otherwise). Between all trials, breaks were taken according to the patient's needs. When the patient's condition allowed it, a second turn with five trials each (LTS and HTS) was repeated.

C. *Data Analysis*

A first visual inspection of traces was performed to reject all trials contaminated by EMG and EOG artifacts. Then, the remaining data were low-pass filtered with a 3^{rd} order Butterworth filter with a cut-off frequency at 10 Hz. Trials containing amplitudes exceeding 70 mV were removed as artifacts. Baseline correction was defined from -250 ms to 0 ms. Data segments from 0 to 1.2 s after all beep tones were extracted and averaged according to stimulus type and task. For the simple paradigm, this procedure resulted in two averaged activation patterns (deviant vs. frequent). For the complex paradigm this procedure resulted in four patterns (low frequent, low deviant, high frequent, high deviant) per task (focus low vs. focus high). Those segments were again averaged so that two curves for both targets were inspected for P300 potentials or any significant difference between targets (deviant tones in target stream the patient was asked to attend) and non-targets (deviant tones in alternative stream) using a t-test with 5% significance level. For this purpose, NPX Lab 2012 [19] was used. Target and non-target amplitudes were measured at the same latency. Latency

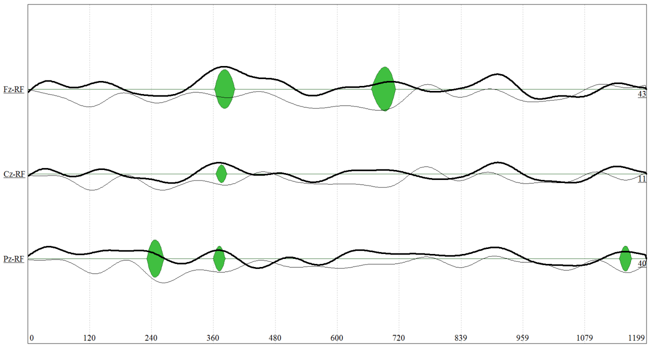

Fig. 2. Patient 2, Session 1: High deviant tones (= target, thick line) vs. low deviant tones (= non-target, thin line) while focusing on HTS.

was defined as the period between stimulus onset and the time when the maximal significant difference between target and non-target occurred. Target amplitude was defined as the voltage difference (μV, positive amplitudes in targets indicate a positive peak whereas negative amplitudes display a negative peak) between the reference line (zero line) and the positive or negative peak in the maximal significant area. At the same latency non-target amplitude was measured as the voltage difference (μV) between the reference line (zero line) and the positive or negative peak. The crucial difference should be, that while attending e.g. the low tone stream, a P300 or similar response to the low deviant tones should differ significantly from the response to a high deviant and vice versa.

D. Results

In Table 1 any significant difference (5 % significance level, t-test) between deviant and frequent tones that could be found at Fz, Cz or Pz between 250 and 900 ms is reported. Here a comparison between deviant tones and frequent tones within one tone stream was done, e.g. in the high tone stream high deviants were compared to high frequent tones and vice versa.”P” indicates a significant positive peak and ”N” a significant negative peak, the approximate latency (in ms) is defined as the period between stimulus onset and the time when the significant peak occurred. The complex paradigm was analysed more in detail. In Table 2 any significant difference (5 % significance level, t-test) between target (deviant tone in focused stream) and non-target (deviant tone in alternative stream) between 230 and 900 ms after stimulus onset at CZ is reported. Note, positive amplitudes in targets indicate a positive peak whereas negative amplitudes display a negative peak. In Figure 2 and 3 averaged data segments are presented for one patient. The marked areas show significant ($p<0.05$) differences between targets and non-targets at Fz, Cz and Pz. This image was created using NPX Lab 2012 [19].

IV. DISCUSSION

These preliminary results show the presence of significant differences between deviant target tones and deviant non target tones in all nine patients. These significant differences were not always present in both tone streams, e.g., in Patient 1 no significant differences were found in the high tone stream in the first session, but in the low tone stream; in the second session it was vice versa, no significant differences were found in the low tone stream, but in the high tone stream. For BCI communication significant differences between deviants in the focused stream and deviants in the alternative stream are necessary in both streams. Table 2 shows that there are often more significant differences between deviants in the focused and alternative stream. This phenomenon might result from an overlap due to a short inter-stimulus interval. It is not yet clear if these significant differences are really P300 potentials since sometimes the polarity is inversed and the occurrence is very much delayed. Perrin et al. [20] and Schnakers et al. [21] report P300 potentials with latencies between 600 and 800 ms in MCS patients. They conclude that MCS patients might have a slower processing speed than healthy comparatives, a result

TABLE I

SIGNIFICANT DIFFERENCES BETWEEN DEVIANT AND FREQUENT TONES FOR THE SIMPLE TASK (ST) AND THE COMPLEX TASK (CT) SHOWN FOR PATIENTS/SESSION (PAT/S).

pat/S	CRS	ST	CT LTS	CT HTS
1/1	18	N850	N350, P700	N450, P820
1/2	18	P480, N840	N640	P360
2/1	14	N320, P720, P840	N280	N280
2/2	15	N280, P680, P720	P700	N360, N520, P860
3/1	13	N400, P740	N260	N400, P840
3/2	12	P700	P750	-
4/1	8	P400, P660	N480, N660	P560, N820
4/2	8	P270, P570, N840	N750	N630, N720, P870
5/1	20	P300, N740, N840	P500	N300
6/1	18	P820	-	P820
7/1	9	N440, P840	P360	N260, P780, P880
8/1	7	-	P340	P400
9/1	21	N250, P350 P630, P840	P370, N500, P720, N870	P310, N480, P590, P810

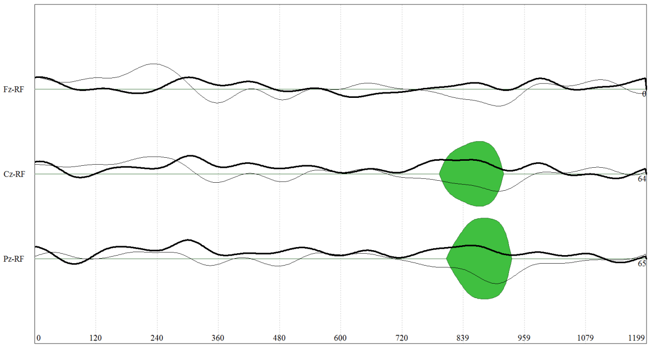

Fig. 3. Patient 2, Session 1: Low deviant tones (= target, thick line) vs. high deviant tones (= non-target, thin line) while focusing on LTS.

TABLE II

COMPLEX PARADIGM: SIGNIFICANT DIFFERENCES BETWEEN DEVIANT TONES IN TARGET AND NON-TARGET TONE STREAM AT CZ IS SHOWN FOR PATIENTS/SESSION (PAT/S). FURTHER COLUMNS SHOW THE LATENCY (L), AMPLITUDES OF TARGET (T) AND NON-TARGET (NT) RESPONSES, AND THE DIFFERENCE (D).

Pat/S	Stream	Latency (ms)	T (μV)	NT (μV)	D (μV)
1/1	LTS	270	-2,25	5,53	7,78
1/1	LTS	580	-4,78	2,43	7,21
1/1	LTS	900	-4,27	4,26	8,53
1/2	HTS	490	1,53	-4,01	5,54
2/1	HTS	370	1,99	-2,03	4,02
2/1	LTS	860	-2,24	2,62	4,86
2/2	LTS	620	-2,12	2,43	4,55
3/2	HTS	740	3,15	-0,27	3,42
4/1	HTS	470	-2,12	2,39	4,51
5/1	HTS	790	1,28	-4,57	5,85
5/1	LTS	405	5,17	-2,33	7,50
6/1	HTS	245	3,63	-2,01	5,64
6/1	HTS	245	3,63	-2,01	5,64
6/1	HTS	480	5,76	-0,61	5,15
6/1	HTS	725	5,10	0,35	4,75
6/1	LTS	235	-5,56	0,08	5,64
6/1	LTS	360	-2,05	4,62	6,67
6/1	LTS	470	-4,75	0,19	4,94
6/1	LTS	730	0,93	6,38	5,45
7/1	HTS	430	-2,32	2,54	4,86
7/1	HTS	495	3,87	-1,89	5,76
7/1	HTS	670	1,13	-3,37	4,50
7/1	HTS	750	-5,52	-0,87	4,65
7/1	LTS	290	-2,58	2,15	4,73
8/1	HTS	700	-6,09	4,94	11,03
8/1	HTS	890	-6,11	6,28	12,39
9/1	LTS	250	-2,57	0,88	3,45
9/1	LTS	725	-1,83	1,30	3,13

that is also in line with Kotchoubey et al. [11]. Several considerations have to be taken into account, in order to better interpret these patient data. Some patients might not have been able to understand or correctly follow the instructions. More analyses and more patient measurements will be required before any conclusions about the usability for patients of this paradigm can be drawn. In future studies, before using a complex BCI paradigm like the one presented here patients might first be checked for showing a reliable P3 or MMN by already standardized P300 paradigms. It might also be beneficial to study different inter-stimulus intervals in order to investigate their effect on the kind and time of reactions of the brain. By doing so, the issue of overlapping effects can be addressed. Another improvement could be to include EOG electrodes to facilitate artifact reduction. EOG artifacts are usually time locked to stimulus presentation and might be frequent in DOC patients.

In conclusion, these results are very encouraging, though further investigations and improvements are necessary.

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