PREDICTION OF CONSCIOUSNESS RECOVERY IN UNRESPONSIVE WAKEFULNESS SYNDROME BY A VIBROTACTILE P300-BCI

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ABSTRACT: The clinical evaluation of the disorders of consciousness (DOC) is challenging, leading to a high rate of misdiagnosis. Herein, we aimed to evaluate somatosensory responsiveness in Unresponsive Wakefulness Syndrome (UWS) patients using a vibrotactile P300-based BCI and explore its predictive role on consciousness recovery.
Methods: 10 UWS patients were enrolled and participated in a BCI session including two vibrotactile paradigms (i.e. VT2 and VT3). All patients were followed up for six months after the BCI assessment. A correlation analysis was used to evaluate whether the VT2 and VT3 Accuracy rates were associated with the clinical outcome.
Results: Four UWS patients showed clear responsiveness at the vibrotactile paradigms. Accuracy rates showed no correlation with clinical variables.
At 6-months follow-up, the clinical outcome expressed as Coma Recovery Scale-Revised (CRS-R) scores, strongly correlated with the VT2 and VT3 Accuracy rates.
Conclusions: somatosensory discrimination can be detected in UWS patients and might play a predictive role in the recovery of consciousness.

INTRODUCTION

In the clinical practice, the Disorders of Consciousness (DOC) are assessed by the bedside administration of behavioral tools, aiming to collect verbal or motor responsiveness to the environment. Unresponsive Wakefulness Syndrome (UWS) is a disorder of consciousness characterized by spontaneous eye opening without consistent behavioral responses to external stimuli. When reproducible signs of awareness are detected, the clinical condition is defined as Minimally Conscious State (MCS). However, the behavioral assessment of awareness has objective limitations, leading to up to 30-40% of diagnostic errors[1]. In the last decades, several EEG-based protocols have been applied to the detection of consciousness, with the aim of increase the diagnostic accuracy of the DOC. These approaches included BCIs, mostly based on auditory evoked potentials[2]. The Event-related potentials evoked by the violation of local and global auditory regularity have been proposed as a marker of consciousness[3].

In preliminary studies, a vibrotactile P300-based BCI was used to detect command following, and to allow communication in healthy subjects and patients with locked-in syndrome/complete locked-in syndrome (LIS/CLIS),[4,5].

In the present research, we used two different vibrotactile BCI paradigms to explore awareness in UWS patients, and evaluate the predictive role of somatosensory discrimination on the recovery of consciousness.

MATERALS AND METHODS

Participants

We enrolled 10 patients (8 males, 2 females) affected by UWS (Coma Recovery Scale-Revised [CRS-R] $\leq$ 6). Three patients had a traumatic brain injury, seven a non-traumatic disease (Table 1). Mean age was 53.3 years (SD= 25.1), median disease's duration was 62 (IQR 45-260) days since disease's onset. Clinical characteristics of the patients are shown in Table 1. Behavioral responsiveness was repeatedly assessed using CRS-R. Written informed consent was obtained from the legal guardians of the patients. All procedures were approved by our Ethics Committee.

Hardware

The mindBEAGLE system® (g.tec, Austria) provided the hardware and software platform for all recordings, stimulus presentation and real-time data analysis. It has been validated for assessment of consciousness and communication on healthy subjects, DOC patients, and locked-in patients[6]. The system includes a laptop with installed software, three vibrotactile stimulators, two in-ear headphones, one g.USBamp biosignal amplifier with 16 channels and 24 Bit ADC resolution and one EEG cap with 16 g.LADYbird active electrodes. The EEG is sampled with 256 Hz and filtered between 0.1-

30 Hz. Data were recorded from Fz, C3, Cz, C4, CP1, CPz, CP2, PZ for the P300 paradigms.

Experimental procedure
All the experiments were performed in the ward by a trained physician, with the patients lying in bed.
To prepare each session, the experimenter mounted first the electrode cap on the participant's head according to the International 10-20 system. A small amount of electrode gel was then placed under each electrode to establish a good connection between each electrode and the corresponding scalp region (for scalp electrodes) or earlobe (for the earlobe clip electrodes).
One earbud in each of the participant's ears, as well as one vibrotactile stimulator on each of three locations: the left wrist, right wrist, and the right ankle.
A system check was performed to ensure that the electrodes were providing high quality data and that the earbuds and stimulators were both operating correctly. Then, the experimenter provided the instruction to the patient in the subject's mother tongue.

Assessment
This study presents two of mindBEAGLE's assessment paradigms for evoking potentials (EP) like the P3 response:

Vibro-tactile stimulation with two tactors (VT2): In this paradigm, the left and right wrist are randomly stimulated with a vibrotactile stimulator for 100 ms each. One stimulator delivers 87,5% of the stimuli which are used for distraction. The other stimulator delivers 12,5% of the stimulation thereby evoking a P300 response. The subject is verbally instructed to count the stimuli silently on the hand that receives the less probable target stimuli. Afterward, 480 trials are presented to the subject in a random order where 12.5% of all trials (60 trials) are stimulation on the target hand. During each run, the subject performs this task four times whereby the location of the target hand is selected in a random order.

Vibro-tactile stimulation with three tactors (VT3): A third tactor was added to the VT2 paradigm whereby the number of 480 trails presented to the subject stayed the same. The positions were on the left, right wrist and one tactor placed on the foot or the back as an additional distractor. The distractor receives 75.% of the stimuli (360 trials) while the left and right wrist each receives 12,5% (120 trials, 60 trials per hand) of the stimuli. The subject is instructed through earplugs to count stimuli to the target hand which is either the left or right wrist. Afterward, 120 trials are presented to the subject in a random order where 12.5% of all trials are stimuli on the target hand, 12.5% of all trials are stimuli on the non-target hand, and 75% of all stimuli are on the distractor. During each run, the subject performs this task four times whereby the location of the target hand is selected in a random order.

Table 1 | Clinical Characteristics and Classification Accuracy results of the patients.

Patient	Gender	Age	Diagnosis	Disease Duration (days)	VT2 Classification Accuracy	VT3 Classification Accuracy
1	M	19	TBI	360	80	80
2	M	19	TBI	300	30	10
3	F	36	TBI	60	45	10
4	M	34	HBI	240	20	30
5	M	91	STROKE	49	30	0
6	M	82	SDH	64	20	0
7	M	61	HBI	45	50	60
8	M	66	STROKE	180		
9	F	65	ME	35	50	50
10	M	60	HBI	45	0	15

TBI: Traumatic Brain Injury, HBI: Hemorrage Brain Injury, ME: meningoencefalitis

Signal Processing and Classification

The raw EEG data and the stimulation time points are recorded during each run with a sample rate of 256. The EEG data is filtered between 0.1 and 30 Hz. Data segments from -100 ms to 600 ms from each stimulation point are created. The data are classified using linear discriminant analysis (LDA). To evaluate the classification, a classification accuracy is created ranging from 0% to 100% averaged over 30 trials.

To calculate the classification accuracy, the following procedure is repeated ten times and the results are averaged over 30 trials: The target and nontarget trials are randomly assigned into two equal sized pools. One pool is used to train a classifier, and the other pool is used to test the classifier. The classifier is tested on an increasing number of averaged stimuli out of the test pool. At first, it is tested on only one target and seven nontarget stimuli. If the classifier detected the target stimulus correctly, the resulting accuracy is 100 %; otherwise, it is 0 %. This process is repeated for two averaged target stimuli and 14 averaged nontarget stimuli, for three nontarget stimuli and 21 target stimuli, and so on until the full test pool is used. This produces 30 single values (for 30 target stimuli in the test pool), each one either 100 % or 0 %. The averaging of 10 single results in values ranging from 0 % to 100 %. Increasing the number of averaged stimuli will increase the accuracy if the subject follows the task, because this averaging reduces random noise in the data. An accuracy significantly beyond the chance level of 12.5 % shows that the subject can direct attention to the task of counting target stimuli for most or all of a run.

For the calculation of the EPs, the system compares the data segments from -100 ms to 600 ms from the target and non-target stimuli. The data are extracted, baseline corrected and averaged. Trials with an amplitude above 100 μV are rejected. A Kruskal-Wallis-Test was performed that presents areas under the curve with significant differences between targets and non-targets as green-shaded (p<0.05). An example for such an elicited Evoked Potential response can be seen in Figure 1. Results from Patient 1 and Patient 9 are shown.

Data Analysis and Statistics
We divided the patients into two groups according to the Accuracy rates. Patients with an Accuracy rate equal or greater than 4 x class probability (4 x 12.5 % = 50) were considered responsive, while patients with lower Accuracy rates were dubbed as unresponsive. Continuous variables were compared using the Mann–

Whitney U test. The Spearman rank correlation coefficient was used to evaluate if the neural correlates of somatosensory discrimination were associated with the behavioral assessment of consciousness, expressed as CRS-R scores, at six months following the investigation.

RESULTS

Patients n. 1, 7 and 9 showed responsiveness at both VT2 and VT3 paradigms, patient n. 8 obtained a positive score only at VT2.
Overall, the patients obtained higher Accuracy rates at VT2 than VT3 (p 0.018 T-Test Paired).
Responsive patients didn't differ from unresponsive patients in age (Mann-Whitney U Test [MWUT], VT2: p=0.9, VT3: p= 0.6), disease's duration (MWUT, VT2: p=0.9, VT3: p=0.6) and CRS-R (MWUT, VT2: p= 0.4, VT3: p=0.18).
At 6-months follow-up, Patients n. 2 and 5 had died. Patients n. 1 and 7 evolved to an MCS, whereas Patient 9 recovered full consciousness. Correlation analysis showed a strong association between the VT2 and VT3 Accuracy rates and the 6-months CRS-R scores (VT2: rs = 0.77, p 0.004, VT3: rs = 0.85, p 0.01) but not with age (rs =0.23, p 0.5) and disease's duration (rs =0,1, p 0.7).

DISCUSSION

We aimed to detect neural signatures of consciousness in UWS patients using two vibrotactile P300-based BCI paradigms. Results demonstrated that a considerable proportion of UWS patients shows neural signatures of volitional behavior. The two paradigms allowed us to explore discrimination of an infrequent stimulus along a regular stimulation (VT2) and left/right somatosensory localization and suppression of irrelevant stimuli (VT3). Overall the patients obtained higher scores at VT2 than VT3, as a consequence of the different complexity of the mental tasks.
However, six-months follow-up showed that the Accuracy levels at both VT2 and VT3 paradigms correlate with the recovery of detectable behavioral responses.
This evidence fosters the importance of integrating neurophysiological approaches into clinical evaluation of the DOC. EEG-based quantitative measures of cortical responsiveness represent a non-invasive and easily repeatable diagnostic tool, which provides also prognostic information.

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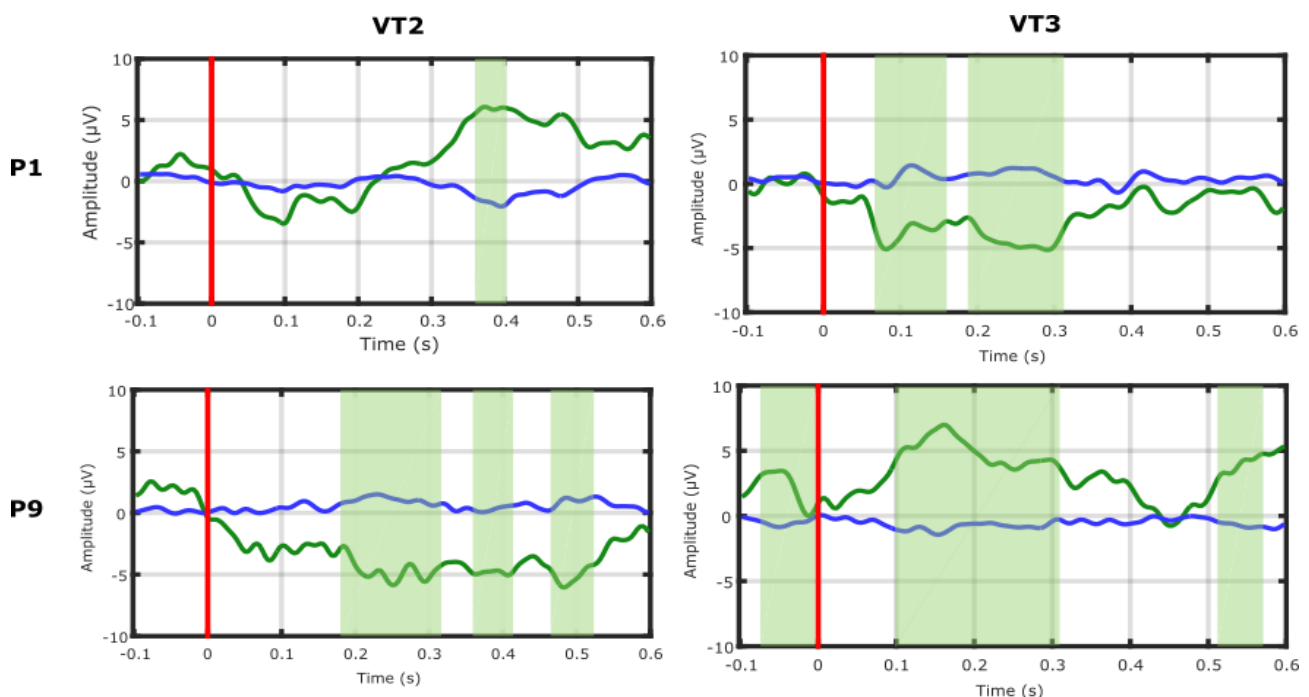
Figure 1:| The elicited Evoked Potential responses from Patient P1 and P9 from the Cz electrode position. In the left column the EPs from the vibro-tactile 2 paradigm (VT2) can be seen, in the right column the Eps elicited from the vibro-tactile 3 paradigm (VT3) can be seen.