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A Novel Approach to Screen for Somatosensory Evoked Potentials in Critical Care

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Abstract

Background: Somatosensory evoked potentials (SSEP) help prognostication, particularly in patients with diffuse brain injuries. However, utilization of SSEP is limited in critical care. We propose a novel, low-cost approach allowing acquisition of screening SSEP utilizing widely available ICU equipment, specifically a peripheral ‘Train Of Four’ (TOF) stimulator and standard electroencephalograph (EEG).

Methods: The median nerve was stimulated using a TOF-stimulator and a standard 21-channel EEG was recorded to generate the screening SSEP. Generation of the SSEP was supported by visual inspection, univariate event-related potentials (ERP) statistics, and a multivariate support vector machine (SVM) decoding algorithm. This approach was validated in 15 healthy volunteers and validated against standard SSEP in 10 ICU patients. The ability of this approach, to predict poor neurological outcome, defined as death, vegetative state or severe disability at 6 months was tested in an additional set of 39 ICU patients.

Results: In each of the healthy volunteers, both the univariate and the SVM methods reliably detected SSEP responses. In patients, when compared against the standard SSEP method the univariate ERP method matched in 9/10 of them (sensitivity=94%; specificity=100%) and the SVM had 100% sensitivity and specificity when compared to the standard method. For the 49 ICU patients, we performed both the univariate and the SVM methods: a bilateral absence of short latency responses (N=8) predicted poor neurological outcome with 0% FPR (sensitivity= 21 %, specificity=100%).

Conclusion: SSEPs can reliably be recorded using the proposed approach. Given the very good but slightly lower sensitivity of absent SSEPs in the proposed screening approach, confirmation of absent SSEP responses using standard SSEP recordings is advised.

Introduction

Reliable prognostication of neurological recovery is particularly challenging in unresponsive ICU patients. Somatosensory evoked potentials (SSEP) have long been used to assist in prognostication of patients with diffuse brain injuries such as cardiac arrest [1,2] and traumatic brain injury [3,4]. Several meta-analyses revealed that bilaterally absent N20 components have a predictive value close to 100% in predicting poor neurologic outcome or death in post-anoxic coma [1,2]. As a result, SSEPs have emerged as a widely recommended approach for prognostication after post anoxic brain injuries [5–9].

In the ICU, SSEPs are non-invasive, typically acquired at the patient's bedside, and generated following electrical stimulation of a peripheral nerve, such as the median nerve, from electrodes placed along the somatosensory pathway [10]. The stimulation generates a series of positive and negative potentials by time-synching to the electrical stimulus and averaging to visualize the smaller electrically evoked signals from the higher amplitude electrical background noise, such as the brain's spontaneous electrical activity. Significant operator expertise is required for acquisition and interpretation, as well as significant financial investments to obtain specialized SSEP technology. This limits broader use of this diagnostic tool [11], particularly in settings with limited resources. Two international surveys on current practices for neurological prognostication after cardiac arrest conducted in majority in Europe [12] and in USA [13] suggested that traditional SSEP were only available respectively in 36 and 50 % of the patient. Even expert visual analysis may be challenging at times given the low signal-to-noise ratio often encountered in an electrically noisy ICU environment [14,15]. However, since its introduction into the ICU in the 1980s [16,17], standard interpretation of SSEPs still relies on visual inspection of the recordings and does not make use of available statistical testing methods to add measures of certainty to the interpretations [5,8,18]. Particularly promising may be statistical approaches such as parametric and non-parametric ERPs, as well as multivariate decoding techniques and denoising methods, such as probabilistic independent component and wavelet filtering analysis. These techniques have proven extremely effective in isolating stimulus-related responses from multi-channel EEG recordings in a research setting [19–23], but have yet to be successfully employed in a clinical context.

Fundamentally, conventional SSEP require specialized systems that in comparison to standard EEG systems have three main additional characteristics; (i) an electrical peripheral nerve stimulator synchronized with the EEG, (ii) a higher sampling rate, and (iii) online algorithms to average and reject artifact contaminated trials [24]. Here we aimed to develop a novel methodology to acquire median nerve SSEPs using widely available technology (i.e., routine digital EEG, peripheral 'Train Of Four' [TOF]-stimulator) supported by a semiautomated analysis approach, utilizing a signal and statistics computer toolbox (Brainstorm, an open-source Matlab ® toolbox, with both parametric event related potentials (ERPs) and support vector machine (SVM) analyses [23,25–27].

Methods

Subjects

We included 15 healthy volunteers and we prospectively included 49 ICU patients with acute brain injury, and a Glasgow Coma Scale score of 8 or below that were admitted to the neurological intensive care unit at Columbia University Irving Medical Center. The study was approved for both patients and healthy volunteers by the local institutional review board ([Consciousness Recovery Project with Outcomes] IRB-AAAR3191 approval (12/07/2017). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. Written informed consent was obtained from patient surrogates and from the healthy volunteers, respectively; all patients who recovered consciousness were given the opportunity to withdraw from the study. At the time of SSEP assessment the coma recovery scale revised (CRS-r) was evaluated [28]. Functional outcome was assessed with the Glasgow Outcome Scale–Extended (GOS-E; levels range from 1 (death) to 8 (good recovery) with data obtained in a structured telephone interview at 6 months after the injury. Poor neurological outcome was defined as death, vegetative state or severe disability (GOS-E < 4) at 6 months. **Both ICU clinicians in charge of the patients and the interviewer who performed the outcome assessments were unaware of the SSEP categorization.**

SSEP Acquisition

In the new '*screening method*', SSEP were acquired during EEG continuous monitoring. 19 electrodes were applied following the International 10–20 System (Fp1,

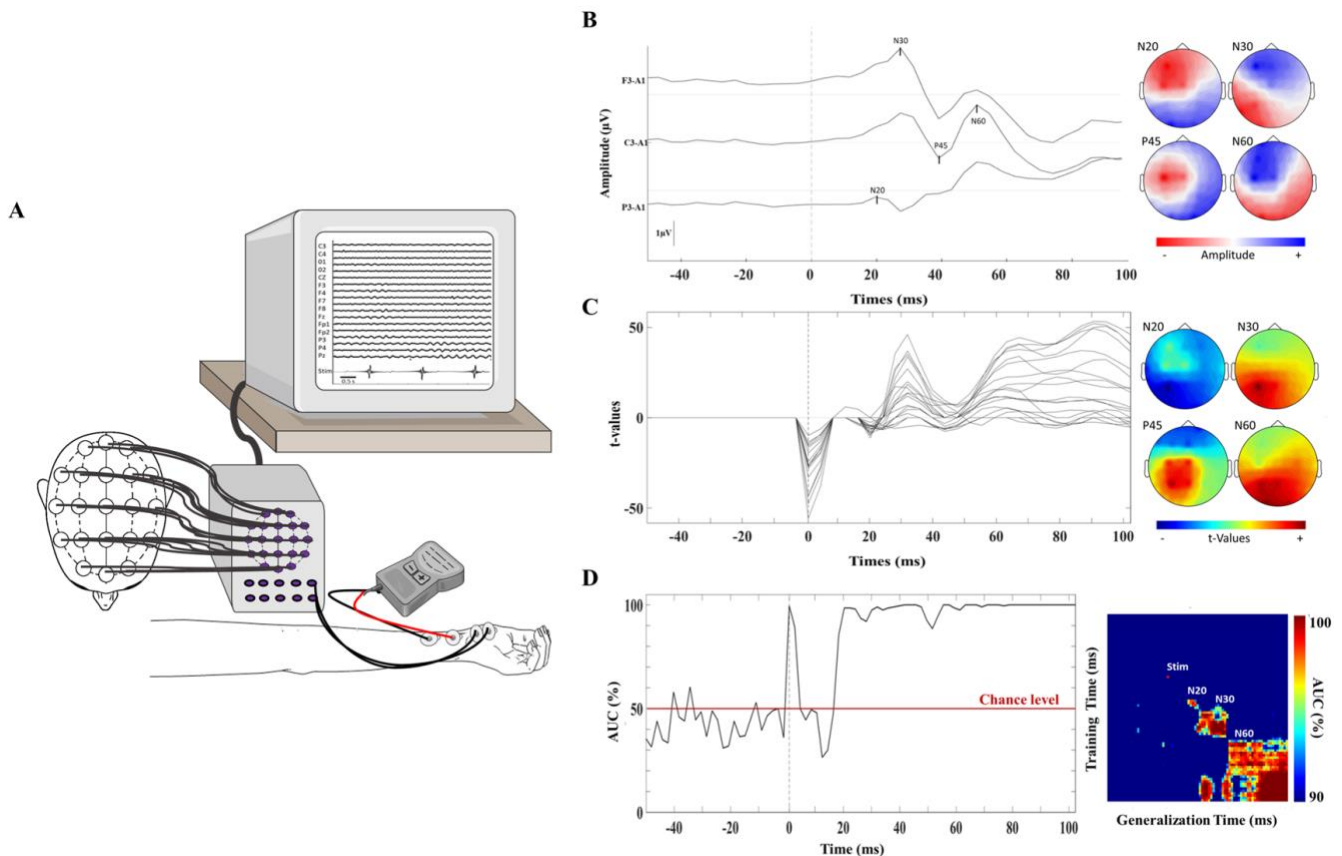


Fig 1. Schematic illustration of the proposed 'screening method. **A)** Stimulation electrodes are placed over the median nerve and connected to the peripheral nerve stimulator. The nerve stimulator is set to a train of four over 10 minutes on each side. Two additional electrodes are placed over the left and right thenar eminence, respectively for left and right median nerve stimulation, respectively and connected to two free channels in the EEG headbox. Stimulation of the median nerve can be verified visually by thenar muscle contraction and on the EEG monitor detecting the stimulation artefact. EEG electrodes using the standard 21-channel montage are connected to the standard EEG headbox. **B)** Average waveforms and topographic maps of mean voltage. Scalp SSEP recorded after right sided median nerve stimulation in one of the 15 healthy volunteers. Potentials were identified on the basis of latency, polarity and scalp distribution in the 10–20 system. Recordings at F3, C3, and P3 electrodes are shown in details. **C)** Univariate statistics based on a sample-by-sample *t*-test against the baseline After right sided stimulations each channel significantly different from base line is plotted and represented with topographic maps. ($p < 0.05$, after correction for multiple comparison by the FDR in time and channels dimension) The color scaling was adapted for each map (positive *t*-values: red, negative *t*-values: blue). **D)** Multivariate decoding algorithms. SSEP responses in the short and middle latency temporal window were decoded from the baseline after right sided stimulation with an area under the curve (AUC) above chance level (50%). Pairwise curve at the left part and temporal generalization matrix at the right side. Temporal decoding matrices revealed a diagonal-shaped form suggestive of a serial chain of distinct neural generators.

Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, FZ, CZ, PZ,) and referenced to the vertex. Two additional electrodes were placed on the left and right thenar eminences to detect the stimulation artefact (Fig.1.A). A tutorial and a checklist related to patient preparation, stimulation parameters, data collection and data analysis is provided in [Supplementary data](#) and in Table 1.

EEG was recorded using a digital video EEG bedside monitoring system (Xltek-Natus, ON, Canada; sampling rate of 256 Hz (10 volunteers and 3 patients), or 512Hz (15 volunteers and 7 patients)). Electrode impedance was maintained below 10 k Ω . Stimulating

bipolar surface electrodes were placed over the median nerve trunk, just proximal to the wrist (cathode proximally). Square wave pulses of 0.2-msec duration were applied at a rate of 1 pulses/sec with a standard train of four (TOF) (SunStim nerve stimulator, Sunmed medical™, USA) during 10 minutes. All patients underwent right followed by left median nerve stimulation.

Among the 15 healthy subjects, 6 were stimulated on each side as for patients, and 9 were stimulated on the right median nerve only. We collected 400 to 600 sweeps for each stimulated side per patient.

Patient factors	
✓	Exclude patients with severe peripheral neuropathy, medullar or brainstem lesions (eg : critical illness polyneuropathy, Guillain Barre Syndrome, Brachial plexopathy after prone positioning, post traumatic or vascular medullar and brainstem infractions...)
✓	Vitals, body temperature and sedation are noted for interpretation
✓	In case of excessive patient movement consider muscle relaxants if deemed safe by the attending intensivist
Stimulation parameters	
✓	Place stimulator over the median nerve trunk, proximal to the wrist, cathode proximally
✓	Intensity: at the motor threshold value, able to trigger a distal twitch of the thumb
✓	Stimulation frequency: 1-3 Hz (1-3 times per second)
Data collection	
✓	EEG electrode impedances should be below 10 k Ω and raw EEG data signal quality should be good
✓	EMG electrodes are placed over thenar eminence, connected to headbox, and channel must be visible on EEG recording montage
✓	EMG stimulation artefact does not contaminate EEG data recorded from the scalp.
Data analysis	
✓	Confirm that EEG data quality is good
✓	When present, left and right SSEP are not only differentiated from the baseline but are lateralized

Table 1. Procedure checklist

In the ‘standard method’, SSEP were acquired following standard SSEP guidelines [8,10], similarly to [29]. Platinum needle electrodes were applied to the central scalp electrodes (C3’ and C4’) 2 cm posterior to their 10-20-position of C3 and C4. Scalp electrodes were referenced to the midforehead electrode (Fz). A sodium chloride-soaked cuff was attached to the upper arm as a ground-reference. Electrode impedance was maintained below 5 k Ω . Square-wave pulses of 0.1-msec duration were applied at a rate of 5 pulses/sec. Two averages of sweeps were obtained in the 0.1-sec post stimulus epoch and plotted with an on-line system (Mistral, Medelec International, Surrey, UK) using a bandpass from 1 to 1500 Hz (sampling frequency 10 kHz per channel; artifact threshold adjusted at $\pm 50\mu\text{V}$).

SSEP Extraction

Data analysis was performed with Brainstorm, which is documented and freely available for download online under the GNU general public license (<http://neuroimage.usc.edu/brainstorm>) [30]. In order to synchronize EEG recordings with SSEP stimulations, artefacts were detected respectively from the left and right wrist channels, using an amplitude threshold. In order to analyze short and middle latency SSEP components, we segmented epochs spanning from -50ms to 100ms locked to each single stimulus artifact and used a 1 Hz high-pass filter. In order to analyze long latency SSEP components, we used a different epoching spanning from -200 to -600ms locked to each stimulus artifact and applied a 0.5-45Hz band-pass filter.

SSEP analysis

SSEP results were interpreted using visual inspection (Fig.1.B), univariate statistics (Fig.1.C), and a multivariate decoding algorithm (Fig.1.D). These approaches of interpreting the recorded signal are complementary and outlined in more detail below:

Visual inspection. The sequence of expected and usual SSEP peaks was visually inspected. Each peak was labelled according to its morphology, latency, and topography on at least two distinct averaged waveforms of 200 trials: N20 and N30 for short latency components (on parietal and contra-central channel), P45 and N60 for middle latency components (on central and frontal channels), and N100, and P300 for long latency potentials (on central and frontal channels)[8,31,32].

Univariate statistics: For all patients, the voltage recorded at each time-sample was compared to the baseline distribution (-200 to 0 ms for long latency and -50 to 0 ms for short and middle latencies). We used the corresponding predefined time-window for each component: 18 to 40 ms for short-latency, 40 to 100 ms for middle latency, and 100 to 300 ms for late latency components. In order to extract ubiquitous subcortical components from cortical responses that typically appear as bilateral and symmetric responses due to their midline generators, left and right trials were also compared in dedicated tests. We used both parametric tests (sample-by-sample Student t-test corrected for multiple comparisons in time and channel dimension

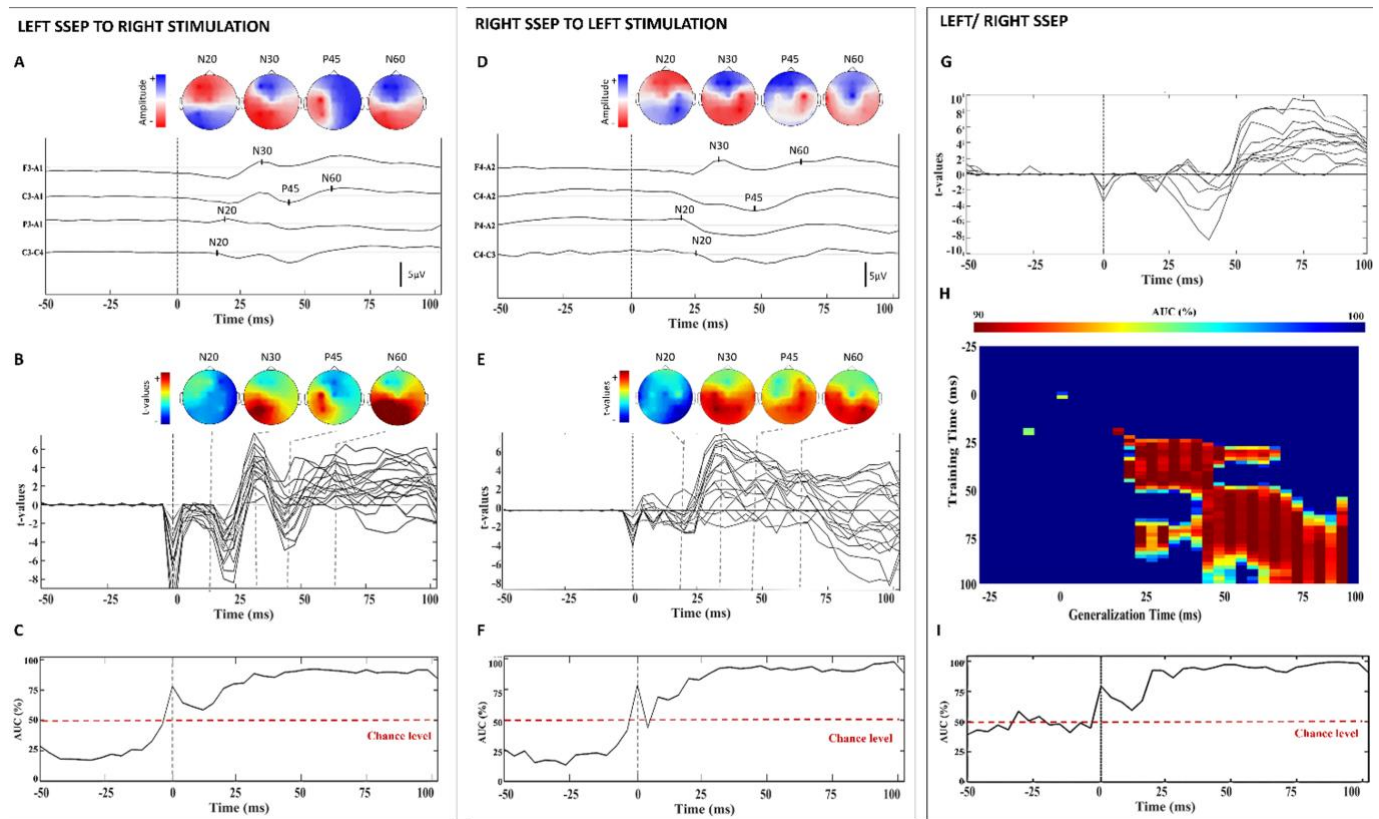


Fig 2. Short and middle latency grand averaged SSEPs in healthy volunteers. In healthy controls, short (N20, N30) and middle (P45, N60) SSEP waveforms were reliably detected:

- Visual inspection of average waveforms and topographic maps of mean voltage after right sided median nerve stimulation ((A), $n = 15$) and left ((D), $n = 6$). The color scaling was adapted for each map (positive voltage: red, negative voltage: blue).
- Univariate statistics: Based on a sample-by-sample t -test against the baseline after right (B) and left (E) sided stimulations. Each channel significantly different from base line is plotted and represented with topographic maps. ($p < 0.05$, after correction for multiple comparison by the FDR in time and channels dimension) The color scaling was adapted for each map (positive t -values: red, negative t -values: blue).
- Multivariate decoding algorithms: SSEP responses in the short and middle latency temporal window were decoded from the baseline after right (C) and left (F) sided stimulation with an area under the curve (AUC) above chance level (50%). In order to extract ubiquitous subcortical components from cortical responses that typically appear as bilateral and symmetric responses due to their midline generators, left and right sided trials were also compared with univariate statistics tests (G) and multivariate decoding algorithms (temporal generalization matrix (H) and pairwise curve (I)). Temporal decoding matrices revealed a diagonal-shaped form suggestive of a serial chain of distinct neural generators.

[21,33]) and non-parametric tests (permutation tests with cluster-based correction for multiple comparison[22]).

Multivariate decoding algorithm: Similarly to [34] at each time point across the whole 19 cephalic channels a classifier was applied based on a linear support vector machines (SVMs; libsvm: [35], 5 k folds, 100 permutations). Decoding performance was measured as the area under the receiver operating characteristic curve (AUC). In addition to applying a different classifier at each time point, we computed temporal generalization matrices. The classifier that was identified at time t recurred at time t' to evaluate the persistence of neural representations over time [36]. To demonstrate that the technique was also be translatable

to EEG montages using a limited montage used in certain ICU [8], we downsampled the number of electrodes to 8 channels (O1, O2, C3, C4, P3, P4, F3, F4) and replicated the analyses.

The Standards for Reporting Diagnostic Accuracy was followed thoroughly [37].

Results

Visual inspection

In each of the 15 healthy controls, short (N20, N30), middle (P45, N60) and long (N100, P300) latency SSEP were detected by visual inspection (Fig.2 A, D, Fig.3. A). Mean latency (\pm SEM) were N20: 20.1 ± 3.5 ms,

	Standard Method	Screening Method					
	Short Latency	Short Latency			Middle Latency		
	Visual Inspection	Visual Inspection	Univariate statistical analysis	Multivariate decoding	Visual Inspection	Univariate statistical analysis	Multivariate decoding
Patient 1	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 2	-/-	-/-	-/-	-/-	-/-	-/-	-/-
Patient 3	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 4	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Patient 5	+/+	+/+	+/+	+/+	+/-	+/-	+/-
Patient 6	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 7	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 8	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 9	-/+	-/+	-/+	-/+	-/+	-/+	-/+
Patient 10	+/+	+/+	-/-	+/+	+/+	+/+	+/+

Table 2. Interpretation of SSEP in 10 ICU patients acquired both with a standard conventional method and the proposed screening method, and interpreted following various and complementary approaches, including visual inspection, univariate statistics, and multivariate decoding algorithm.

N30: 31.6 ± 2.5 ms, P45: 42.0 ± 3.0 ms, N60: 62.2 ± 7.0 ms, N100 : 103.0 ± 10.5 ms, P300: 293.0 ± 31.8 ms. In 10 of the 49 ICU patients, SSEPs were acquired both with the proposed screening method, and with a standard conventional/or reference method. Mean time interval between the two sessions was 3 days (± 6 ; median = 1; IQR=0). Based on visual inspection, both acquisition methods showed the same performance in detecting the presence of a cortical response (see Table.2). Representative individual data of patients with bilaterally and unilaterally absent SSEP responses are presented in Fig.4.

Univariate analysis

For each of the 15 healthy volunteers SSEP responses were identified at short (18-40 ms), middle (40-100 ms), and late latencies (100- 300 ms; FDR corrected $p < 0.05$, see Fig.2 B, E and l Fig.3 B). Moreover, left stimulation trials differed significantly from right stimulation trials (Fig.2 G), enabling the distinction between non-lateralized scalp recorded subcortical responses and lateralized cortical responses [8]. In 9 of 10 ICU patients (see Patient 10 in Table 2), a perfect match was observed between the new quantified approach and the conventional method (Se=94%; Sp=100%, VPN=75%,

VPP=100%, Youden index=0.94). When a cortical response was identified with the reference method, the new quantified approach (i) confirmed the significance of short latency components against baseline, and (ii) identified a significant left/right difference (see Table.2 and Fig.4).

Downsampling the EEG from 21 to 8 electrodes did not affect the results significantly, suggesting that our new approach could be efficient with a limited EEG montage. Note however that non-parametric tests against baseline (permutation tests with cluster-based correction for multiple comparisons) have few significant effects both in healthy volunteers and ICU patients when applied on the 8-electrodes sub-sampled dataset (Table.3).

Multivariate decoding methods

In all healthy volunteers, SVM classifiers decoded SSEP responses in the short latency window trials against the baseline mean (median AUC = 90 %, min= 63 %, max=90 %, Fig.2 C, F). Trials obtained after left sided stimulation were reliably decoded from right

stimulation trials (median AUC = 95 %, min=77%, max=100%, Fig.2.H, I). Middle and late components

right SSEPs (median AUC 91% [min=80%; max=100%], median Z score from baseline 3.5 [min= 2,

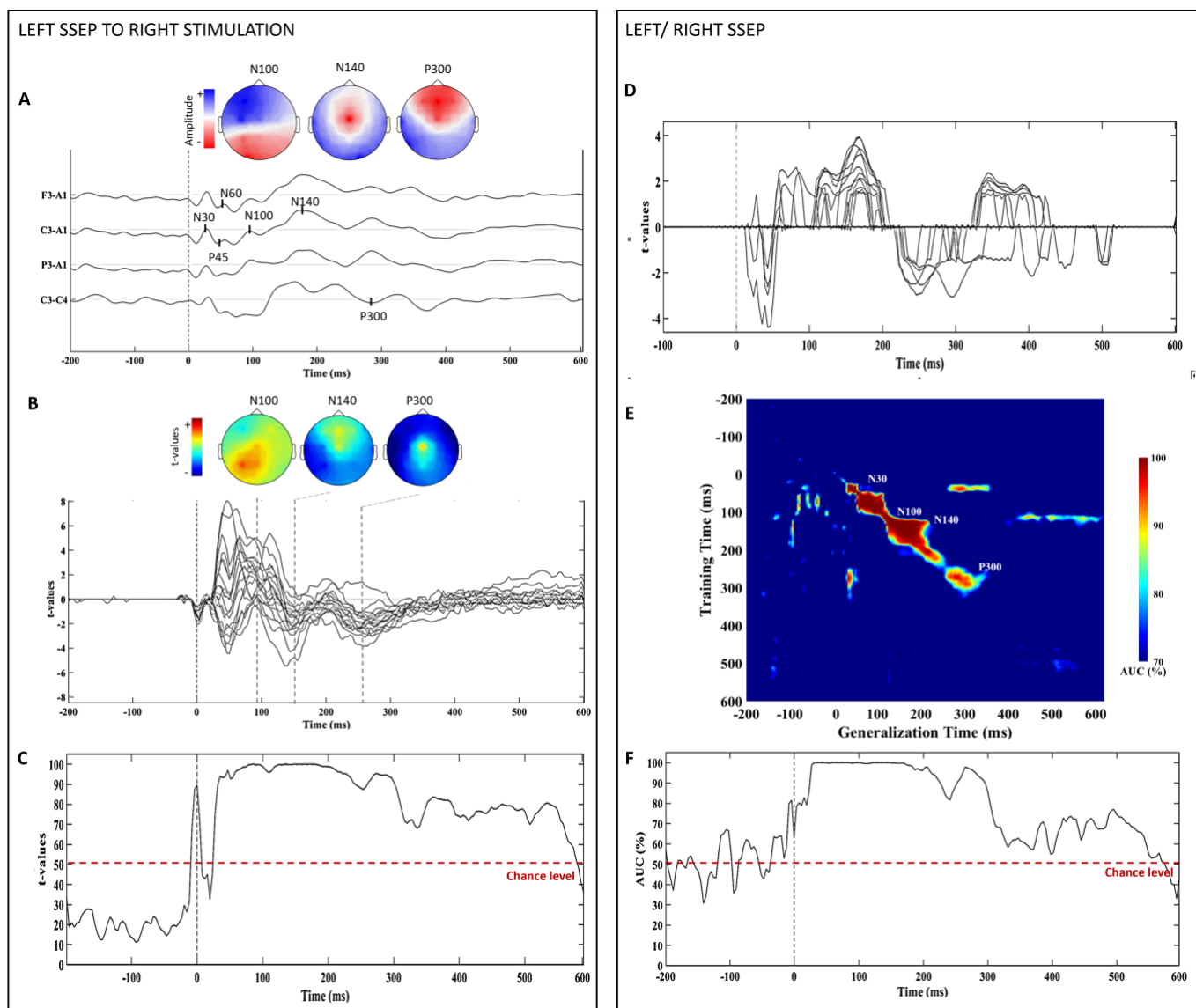


Figure 3. Long latency grand averaged SSEPs in healthy volunteers. In healthy controls long (N100, P300) latency SSEP were reliably detected:

- Visual inspection of average waveforms and topographic maps of mean voltage recorded after right sided median nerve stimulation (A). The color scaling was adapted for each map (positive voltage: red, negative voltage: blue).
- Univariate statistics: Based on a sample-by-sample t -test against the baseline after right sided stimulations (B). Each channel significantly different from the baseline is plotted and represented with topographic maps. ($p < 0.05$, after correction for multiple comparison by the FDR in time and channels dimension) The color scaling was adapted for each map (positive t -values: red, negative t -values: blue).
- Multivariate decoding algorithms: SSEP responses in the long latency temporal window were decoded from the baseline (C) with an area under the curve (AUC) above chance level (50%).
- In order to extract ubiquitous subcortical components from cortical responses that typically appear as bilateral and symmetric responses due to their midline generators, left and right sided stimulation trials were also compared with univariate statistics (D) and multivariate decoding algorithms (temporal generalization matrix (E) and pairwise curve (F).

were similarly decoded above chance-level (Fig.3.C, H, I).

In the 9 patients with at least unilaterally present short latency SSEP responses identified with the standard method, left SSEP responses were discriminated from

max= 6.8], Fig.4, Table.2). In the only patient with bilaterally absent responses according to the standard reference method, AUC values after stimulation did not differ from an additional control condition consisting in computing an AUC in the baseline (i.e.: before

	Standard Method	Screening Method					
	Short Latency	Short Latency			Middle Latency		
	Visual Inspection	Visual Inspection	Univariate statistical analysis	Multivariate decoding	Visual Inspection	Univariate statistical analysis	Multivariate decoding
Patient 1	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 2	-/-	-/-	-/-	-/-	-/-	-/-	-/-
Patient 3	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 4	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Patient 5	+/+	+/+	+/+	+/+	+/-	+/-	+/-
Patient 6	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 7	+/+	+/+	+/+	+/+	+/+	+/+	+/+
Patient 8	+/+	+/+	+/+	+/-	+/+	+/+	+/+
Patient 9	-/+	-/+	-/+	-/+	-/+	-/+	-/+
Patient 10	+/+	+/+	-/-	+/+	+/+	+/+	+/+

Table 3. Interpretation of SSEP in 10 ICU patients acquired both with a standard conventional method and the proposed screening method with 8 EEG channels, and interpreted following various and complementary approaches, including visual inspection, univariate statistics, and multivariate decoding algorithm. The detection or absence of a significant neural response are represented with plus and minus signs (1 symbol: unilateral response, 2: bilateral responses, red: discordant results).

stimulation): AUC=62%; Z score=0.04 (Fig.4). When SSEP responses were present according to the standard reference method, temporal decoding matrices revealed a diagonal-shaped form suggestive of a serial chain of distinct neural generators [36]. In sharp contrast, such a decoding matrix pattern was absent when SSEP responses were absent according to the standard reference method (Fig. 5).

After comparing left and right SSEP responses, we then studied SSEP separately on each side. The multivariate decoding method was able to distinguish lateralized left and right SSEP from baseline with a median AUC of 78% (min=56%, max=100%). By contrast, when SSEP responses were not detected by the standard method, SVM decoding also failed to distinguish left from right trials with a mean AUC of 44% (min = 33%, max=48%). As a conclusion, the standard method and

decoding matched perfectly for all patients (Se=100%, Sp=100%, VPN=100%, VPP=100%, Youden index=1) (Table. 2).

Finally, downsampling the EEG from 19 to 8 electrodes, affected the decoding results for one patient: patient 8, who had bilateral cortical responses according to the standard method, was decoded as showing only unilateral left responses (see Table.3).

Prognostic performances

In 49 ICU patients (median age =58.5 with interquartile range (IQR) = 52–65); 32 male patients, Table.4) the ability to predict outcomes using the proposed SSEP approach was tested. At the time of SSEP assessment 20 patients were in a comatose state (41%, median CRS-r =1, (IQR = 0-1), 15 in a VS/UWS state (31%, median CRS-r =3 (IQR = 1.5-4), and 14 patients were MCS

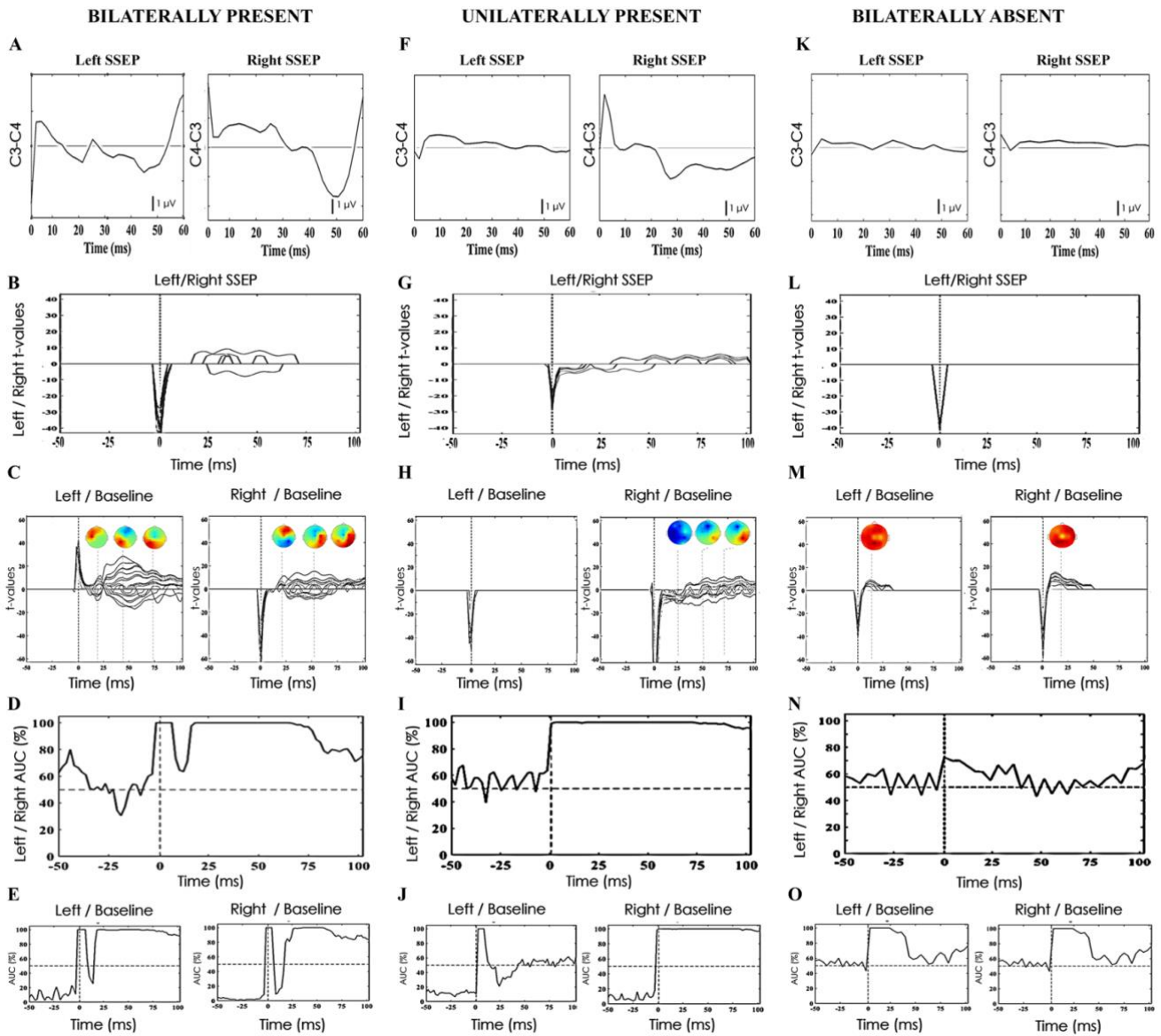


Fig 4. Representative individual data of ICU patients with bilaterally present, bilaterally absent, and unilaterally absent SSEP. (A-E) In a patient with bilaterally present responses visualised on average waveforms (A), not only are left SSEP distinguishable from the right SSEP (B-D), but also both left and right SSEP can be distinguished from baseline (C-E) by statistical testing (B-C) and SVM approaches (D-E). (F-J) In a patient with unilateral response visualised on average waveforms (K), left SSEP are distinguishable from the right SSEP (G-I), but only one side SSEP (right in this example) can be distinguished from baseline (H-J) by statistical testing (G-H) and SVM approaches (I-J). (K-O) In a patient with bilaterally absent responses visualised on average waveforms (K), left and right SSEP cannot be distinguished either with statistical testing (L), and SVM approaches (N). Note that in the case of preservation of subcortical responses, widely recorded other the scalp from 14 to 60 ms, even in the absence of cortical responses, the post stimulation period is different from baseline (M-O). However, because responses are not lateralized, they are suppressed by a Left/ Right comparison.

(29%, median CRS-r =6.5 (IQR = 4.3-7.8). Patients in the sample were admitted for intracranial hemorrhage (N=22; 45 %), cardiac arrest with anoxic-ischemic encephalopathy (N=7 ; 14%) subarachnoid hemorrhage (N=12; 25%), traumatic brain injury (N=3; 6%), acute ischemic stroke (N=3; 6%), and other lesions (N=2 ; 4%). Median time to perform SSEPs was 7 days (IQR = 5–15) after onset of brain lesion. Visual inspection and multivariate decoding were congruent in all 49 patients to identify the presence or absence of short latency

cortical SSEP components. Short latency cortical responses were bilaterally absent in 8 patients, unilaterally present in 12 and bilaterally present in 29 patients. Bilaterally absent short latency SSEP responses (8 patients) predicted poor neurological outcomes (GOS-E < 4 at 6 months) with perfect specificity and positive predictive value (Sp=100%, 95% CI [72-100], PPV=100%) and with a weak sensitivity (Se=21%, 95% CI [10-37]) and negative predictive value (NPV=27%, 95% CI [24-30]). More specifically, bilaterally present cortical responses

(n=29) predicted a good neurological outcome with a low specificity (Sp=47 %, 95% CI [31-64]) and positive predictive value (PPV=31%, 95% CI [23-40]) and a high sensitivity Se=82%, 95% CI [48-97]) and negative predictive value (NPV=90%, 95% CI [71-97]). Among patients with cortical responses (n=41), unilateral responses (n=12) predicted a poor neurological outcome with a high specificity (Sp=83 %, 95% CI [52-98]) and positive predictive value (PPV=82%, 95% CI [53-95]) and a low sensitivity Se=31%, 95% CI [15-51]) and negative predictive value (NPV=33%, 95% CI [26-42]). Prognostic value of bilateral absence of short latency SSEP for each aetiology is provided in [Supplementary Table 1](#).

Discussion

In this paper we developed a novel and simple quantified approach to screen for cortical SSEP responses using standard EEG recordings combined with a widely available and inexpensive peripheral nerve stimulators. We first demonstrated that SSEPs can be reliably identified in healthy volunteers (N=15), using (i) visual inspection, (ii) parametric and non-parametric univariate ERPs analyses, and (iii) multivariate SVM decoding. We then established that in ICU patients with acute brain injury (N=10), the novel approach reliably classified SSEP responses based on

visual inspection as well as statistical analysis when compare to the standard method. Initial downsampling experiments (19 to 8 electrodes), support the notion that the novel method is able to generate reliable results even with a limited montage. Finally, we tested the performance value of this new approach in 49 ICU patients and confirmed very high specificity to predict poor neurological outcome, despite low sensitivity (27%). This further confirms the strong value of this new method as a screening test easier to implement than gold-standard SSEP confirmatory test that has to be performed in patients with a bilateral absence of short latency cortical responses.

Strengths and potential of this novel approach. Building on existing technology should allow for ICU teams to quickly adopt this new technique since they are already familiar with the equipment. The potential to fully automatize SSEP generation by building on a pipeline of data processing that includes artefact rejection and statistical testing of hypotheses may allow probing for SSEP responses in a more reproducible way. It is conceivable that remote verification would

suffice as long as recording standards are met. The present data provide proof-of-concept support for a clinical application in the ICU as a screening tool. Considering the enormous number of ICU patients with unclear prognoses [38–40] and the fact that the majority are managed outside of centers with access to neurophysiological expertise, there may be a role for SSEP screening methods. Capitalizing on the recent achievements in the automatization of processing of resting state EEG [41,42] combined (or not) with EEG recordings during the ‘odd-ball’ paradigm (‘local global task’[42,43]) to accurately classify the patients’ conscious state and possibly predict recovery, one can predict that a similar development for SSEP has the potential to improve diagnoses and prognoses of unconscious patients. Indeed SSEPs, are recommended in many prognostication guidelines [6]. While EEG monitoring is not yet accessible to all ICUs [12,13], such findings may motivate the more widespread integration of EEG as a diagnostic and prognostic tool in ICUs for patients with or without brain injury. Moreover, during continuous EEG monitoring, it is possible to repeat SSEP acquisition sessions and thus to follow the evolution of patients. The introduction of quantitative statistics (both univariate and SVM) as compared to the exclusively visual inspection will allow patients that do not have easy access to expert neurophysiologists the option of being screened for the presence of this important prognostic finding. Moreover, this approach may provide additional reassurance to expert neurophysiologists confronted with difficult cases. In the future, the implementation of an automated analysis software based on these analysis techniques might allow intensivists to easily obtain interpretations. Importantly, SVM tools in particular can reveal new patterns that typically escape to human visual expertise (e.g.: stability of one SSEP type versus succession of distinct neural codes assessed with the temporal generalization method [36]). The significance of these novel observations is yet to be determined but opens new opportunities for a well-established technique.

Lastly, this new method incorporates EEG spatial sampling from 21 electrodes unlike the usual 2 to 3 EEG electrodes (including a reference) used in traditional SSEP recordings that are used in clinical practice. This additional spatial information provides more detailed scalp topographies of each SSEP component and could turn out to be particularly valuable when assessing late SSEP components distant from primary somato-sensory cortices and more related to the conscious state than

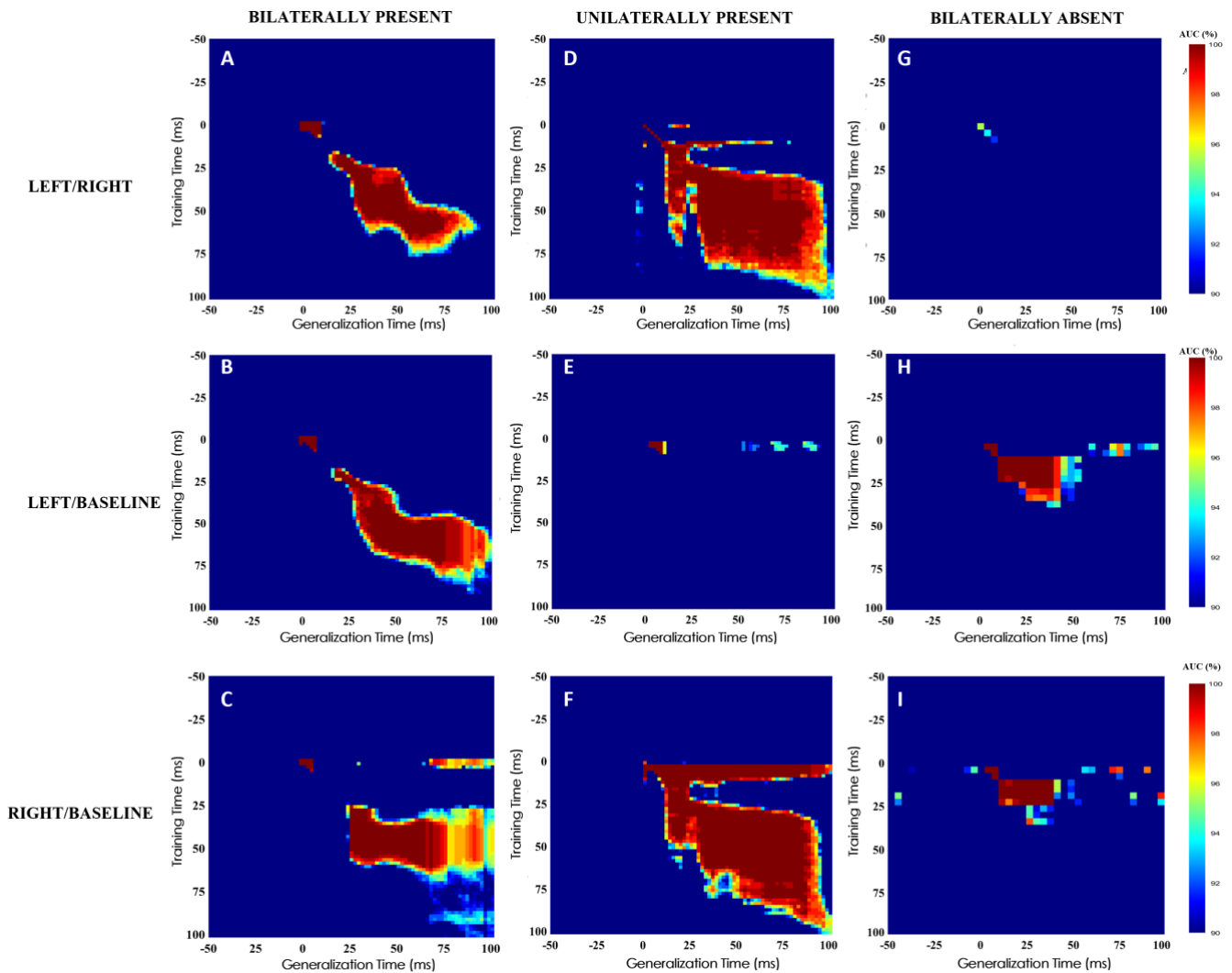


Fig 5. Representative individual temporal generalization matrices of ICU patients with bilaterally present, bilaterally absent, and unilaterally absent SSEP. When SSEP responses were present according to the standard reference method, temporal decoding matrices revealed a diagonal-shaped form suggestive of a serial chain of distinct neural generators (A, B, C, D, F). In sharp contrast, such a decoding matrix pattern was absent when SSEP responses were absent according to the standard reference method (E, G, H, I).

earlier local components such as the N20 [43–45]. While N20 generator is localized to primary somatosensory cortex contralateral to stimulation [46–48], middle-latency components are localized in contralateral fronto-central region (N60) and in bilateral temporal cortex (N70)[49,50] and late components are generated in a largely distributed frontoparietal network [51,52].

Limits of the novel approach. Limitations of the proposed approach include, that the sampling rate of most standard EEG devices ranges from 128Hz to 512Hz, whereas the fine distinction of subcortical SSEP as the P14 requires much higher values (i.e.: around 10kHz). This clear limitation made it necessary to define gross time-windows of interest (early/middle/late) rather than probing each individual SSEP component. Secondly, our basic clinical EEG

setting did not include electrodes that would enable us to diagnose abnormalities of somatosensory conduction at the peripheral nervous system, plexus, spinal cord or brainstem levels (eg : critical illness polyneuropathy, Guillain Barre Syndrome, Brachial plexopathy after prone positioning, post traumatic or vascular medullar and brainstem infractions...). Furthermore, if the signal noise ratio is too low interpretation of the SSEP cannot be done reliably. Even with such a semi-automatized procedure, checking the quality of the recording requires—knowledge of EEG analysis. Given these limitations, the proposed new approach to record SSEPs is in its current form is most useful as a screening method. In presence of clear cortical SSEP components (the vast majority of explored clinical cases in ICU), there is no need to complete this exploration with standard SSEP methodology. The absence of cortical

SSEPs diagnosed with this new approach—must trigger the acquisition of traditional SSEPs in order to confirm a negative result. However, because of limited resource, restricting the use of traditional SSEP only for those patients should represent a gain of cost and delay. Lastly, stimulus onset detection used in this study derived from the automatic measurement of electrical stimulation artefacts in the EEG traces and not from a digital signal (i.e.: TTL signal sent from the stimulator device to the amps). The fixed latency between the stimuli onset and the stimulation artefact allowed to easily remove it, but this procedure may impair the precise estimation of SSEP latencies. Note also that the TOF stimulator used a fixed periodicity, whereas the insertion of random jittering in stimulation onsets enables the distinction between genuine SSEPs and unrelated physiological or artefactual signals.

These limitations could rather easily be overcome, by using a higher sampling-rate, by adding the few critical electrodes on peripheral nervous system conduction points (ipsilateral Erb's point, C2 and C5), and by using a dedicated stimulation box (see for instance: [42]), including a temporal jitter between trials. Finally, even when the technique is automated, SSEP acquisition and interpretation require a certain level of expertise and users need to be aware of potential pitfalls (eg: signal to noise ratio, etiology and delay of brain lesions, confounding medications such as high doses of barbiturates). SSEP should never be considered individually but rather always be integrated into a multimodal prognostication algorithm, including clinical examination, neuroimaging, biomarkers such as Neuron-Specific-Enolase and other neurophysiologic tools such as EEG.

Conclusion

In this pilot study, SSEPs were reliably detected using a simple, peripheral nerve stimulator and clinical EEG recordings in healthy volunteers as well as in as in ICU patients. This inexpensive and easy to implement screening approach may dramatically increase availability of SSEPs in the ICU, including in settings with limited resources. Clinical performance of this screening method remains to be studied in a larger cohort of patients.

Conflict of interest

The authors declare that they have no competing interests.

Ethical approval/informed consent

The study was approved for both patients and healthy volunteers by the local institutional review board (Consciousness Recovery Project with Outcomes IRB-AAAR3191 approval [12/07/2017]). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. Written informed consent was obtained from patient surrogates and from the healthy volunteers, respectively; all patients who recovered consciousness were given the opportunity to withdraw from the study.

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Patient	Stade	Sex, Age	Etiology	Delay	CRS-r	N20	GOS-E
1	COMA	F,62	CA	13	1	B	1#
2	COMA	M,58	ICH	7	1	U	1#
3	COMA	M,39	TBI	17	2	B	4
4	COMA	M,65	ICH	1	1	-	1
5	COMA	M,58	SAH	8	2	B	2
6	COMA	M,66	SAH	20	0	-	1
7	COMA	F,30	ICH	3	0	B	8
8	COMA	M,66	SAH	7	0	B	2
9	COMA	F,51	ICH	5	2	B	3
10	COMA	F,75	ICH	14	0	U	1#
11	COMA	F,72	ICH	6	0	-	1
12	COMA	F,59	ICH	2	0	U	2
13	COMA	F,84	Other	9	1	-	1
14	COMA	M,66	CA	5	0	B	1
15	COMA	M,70	Isch Stroke	14	0	B	2
16	COMA	M,44	Isch Stroke	55	1	-	2
17	COMA	M,34	ICH	25	1	B	2
18	COMA	M,55	CA	22	0	B	3
19	COMA	M,84	ICH	3	3	B	1
20	COMA	M,59	CA	5	1	-	1
21	VS/UWS	F,57	SAH	27	6	B	6
22	VS/UWS	M,54	CA	15	1	B	4
23	VS/UWS	F,73	ICH	1	4	U	1#
24	VS/UWS	M,49	ICH	3	3	U	1#
25	VS/UWS	M,79	SAH	20	3	B	5
26	VS/UWS	M,49	ICH	5	1	B	4
27	VS/UWS	F,74	ICH	4	3	B	1#
28	VS/UWS	F,85	CA	2	2	-	1#
29	VS/UWS	M,77	SAH	15	5	B	1#
30	VS/UWS	F,59	ICH	18	4	U	3
31	VS/UWS	M,76	TBI	16	1	B	1#
32	VS/UWS	M,55	ICH	13	1	U	1
33	VS/UWS	M,59	ICH	4	3	-	1#
34	VS/UWS	F,70	CA	13	3	B	1
35	VS/UWS	M,77	ICH	114	4	U	1
36	MCS	M,54	Isch Stroke	14	7	B	4
37	MCS	F,59	SAH	6	8	B	1
38	MCS	M,44	SAH	7	6	B	4
39	MCS	M,65	TBI	2	7	B	3
40	MCS	M,63	SAH	16	6	B	1#
41	MCS	M,23	ICH	2	4	U	1#
42	MCS	M,88	Other	22	10	B	1#
43	MCS	M,37	ICH	7	5	U	5
44	MCS	M,52	ICH	29	4	U	3
45	MCS	M,59	SAH	9	7	B	3
46	MCS	F,76	ICH	7	16	U	4
47	MCS	F,61	ICH	6	3	B	4
48	MCS	M,71	SAH	5	4	B	3
49	MCS	F,95	SAH	6	13	B	3

Table 4. Patient characteristics Sex, Age, Aetiology, Delay of DoC in days, CRS-r, and 6 months outcome, Abbreviations: CA: cardiac arrest; GOS-E, Glasgow outcome scale extended; ICH: intracerebral hemorrhage; Isch Stroke : ischemic stroke; MCS, minimally conscious state; SAH, subarachnoid haemorrhage; TBI, traumatic brain injury; UWS, unresponsive wakefulness syndrome, VS :vegetative state, # withdrawal of life sustaining therapies

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