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The Diagnostic Value of Visual Evoked Potentials in Chronic Disorders of Consciousness

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Keywords: cluster analysis | consciousness | disorders of consciousness | ERPs | evoked potentials | f-VEPs

ABSTRACT

Objective: In chronic disorders of consciousness (DOCs), the distinction between vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS) is as crucial as it is challenging. Evoked potentials (EPs) and event-related potentials (ERPs) are helpful, but some limitations prevent their consistent use in the routine diagnostic process. This study investigated the value of EPs and ERPs in 146 adult chronic DOC patients (82 VS/UWS and 64 MCS).

Methods: All the patients underwent multimodal neurophysiological assessments, including flash-visual evoked potentials (f-VEPs), somatosensory EPs (SEPs), auditory EPs (AEPs), auditory ERPs, as well as a behavioral assessment using the Coma Recovery Scale-revised (CRS-r). We classified EPs and ERPs for the presence/absence of cortical responses, and then we performed an unsupervised cluster analysis to identify recurrent patterns. We then explored their occurrence in VS/UWS and MCS patients.

Results: VS/UWS patients showed fewer cortical responses to all modalities than MCS. Cluster analysis revealed groups 1, 2, and 3, which included patients without detectable cortical responses to ERPs and f-VEPs, patients with cortical responses to f-VEPs but not to ERPs, and patients with ERPs, respectively. Groups 2 and 3 had similar demographics and CRS-r scores, which were higher than those of patients in group 1.

Abbreviations: ABI, anoxic brain injury; AGNES, agglomerative nesting; a-SVP, auditory-slow vertex potentials; AU, arbitrary units; AUD, category of cortical response to auditory stimuli (0 = absent; 1 = present); BAEPs, brainstem auditory evoked potentials; COG, category of cortical response to event-related potentials (0 = absent; 1 = present); CRS-r, Coma Recovery Scale-revised; DIANA, divisive analysis clustering; DMN, default mode network; DOCs, disorders of consciousness; EEG, electroencephalogram; EPs, evoked potentials; ERG, electroretinogram; ERPs, event-related potentials; f-VEPs, flash-visual evoked potentials; IFCN, International Federation of Clinical Neurophysiology; KM, K means; MCS, minimally conscious state; MMN, mismatch negativity; MRI, magnetic resonance imaging; OTHER, group of brain-injured patients with etiologies different from anoxic and traumatic; PAC, proportion of ambiguous clustering; PAM, partitioning around medoids; SEPs, somatosensory evoked potentials; SOM, category of cortical response to somatosensory stimuli (0 = absent; 1 = present); TBI, traumatic brain injury; VIS, category of cortical response to visual stimuli (0 = absent; 1 = present); VS/UWS, vegetative state/unresponsive wakefulness syndrome; WSS, weighted sum of squares.

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Interpretation: Our data suggest that f-VEPs may be as effective as ERPs for diagnosing MCS. This is a significant finding, as f-VEPs likely reflect brain injury of a lesser extent and the conservation of cortical areas pivotal for consciousness, highlighting the prominence of f-VEPs for identifying MCS in chronic DOC patients.

1 | Introduction

In the last decades, the role of neurophysiology has largely grown in importance in the disorders of consciousness (DOCs) [1]. A global agreement on its crucial role in the diagnostic work-up for assessing acute, subacute, and chronic DOCs has been achieved among experts working in this field [2, 3]. The (regained) centrality of clinical neurophysiology has been fully established by the latest American [4] and European [5] guidelines on DOCs, albeit with some slight differences between them, in a conceptual framework highlighting the importance of multimodal assessment for the diagnosis of DOCs [6].

However, the most advanced neurophysiological techniques are not readily applicable everywhere, primarily due to the lack of trained personnel [3] and the inhomogeneous application of existing methods of analysis, which show high variability in single cases and need to be further validated in larger samples [7]. Hence, in a comprehensive review of International Federation of Clinical Neurophysiology (IFCN)-endorsed experts in the field [1], the authors proposed a multimodal graded assessment for prolonged and chronic DOCs where the operational stepwise workflow included several steps with increasing complexity, starting from conventional electroencephalogram (EEG) and evoked potentials (EPs) to event-related potentials (ERPs), and finally advanced approaches that can be performed only in third level centers having expensive devices and dedicated staff, as well as vast expertise to perform complicated analyses and understand the results' clinical implications.

EPs (with EEG) are probably the most used diagnostic tool to assess DOCs worldwide [3]; they are easy to perform even in small first-level centers that do not have significant resources since they are inexpensive, repeatable, non-invasive, and applicable at the patient's bedside. Among EPs, Somatosensory EPs (SEPs) are pivotal for the prognosis of acute DOCs since the bilateral absence of the N20 component yields 100% and 87%–99% predictive specificity for a poor outcome in hypoxic–ischemic (anoxic brain injury, ABI) [8, 9], vascular, and post-traumatic (traumatic brain injury, TBI) [9, 10] comatose patients, respectively. On the other hand, the SEPs show limited diagnostic power in prolonged and chronic DOCs since the preservation of cortical responses is more frequent in minimally conscious state (MCS) patients [11, 12], but not specific to this condition since it can also be frequently found in vegetative state/unresponsive wakefulness syndrome (VS/UWS) patients [12, 13]. Thus, ERPs are an effective tool for assessing awareness in chronic DOCs. Still, neither passive (e.g., paradigms inducing the mismatch negativity, MMN) [12, 14] nor active (e.g., paradigms inducing P300) [12, 15] auditory paradigms can distinguish between VS/UWS and MCS patients in single cases. The primary limits affecting the use of ERPs are: poor reproducibility, lack of normative values, large variability of the response, and the profound impact of arousal fluctuations on cognitive performance in brain-injured patients [16]. Thus, MMN and P300 are used in clinical practice for the significant positive, but not negative, early predictive value of good outcome in comatose patients [17–19].

In this patchy and contradictory picture, literature still lacks large-sample studies on DOCs evaluating the responses arising from the cortex to light stimulation, the so-called flash-visual evoked potentials (f-VEPs), even considering the importance of visual responses and visually related behaviors in assessing chronic DOCs [20, 21]. f-VEPs are easily detectable and generally stable over time, and they can be recorded even in patients unwilling or unable to cooperate, making them suitable for assessing DOCs [22]. In this line, f-VEPs reflect the global functioning of the visual pathways, including the occipital cortex, and can be used in the differential diagnosis of chronic DOCs patients.

In this study, we aimed to characterize recurring patterns derived from a multimodal EPs-ERPs assessment, including visual, somatosensory, and acoustic stimulation, in a large sample of chronic DOCs patients by means of an unsupervised analysis based on clustering, which does not rely on predefined diagnostic labels; instead, it aims at individuating patterns emerging from the experimental sample.

Second, we extracted the rules dividing the population into the individuated clusters to provide a useful set of criteria to be employed in the clinical setting; concurrently, we described the relationship between such patterns and the most relevant clinical features.

2 | Materials and Methods

2.1 | Patient Population, Diagnosis, and Behavioral Assessment

We consecutively enrolled 153 Italian native-speaker DOCs patients from the 1 January 2019 to the 31 December 2023, admitted to the Fondazione IRCCS Istituto Neurologico Carlo Besta of Milan for a re-evaluation of their clinical conditions and residual cognitive level in a third-level center.

The patients suffered from prolonged or chronic DOCs after severe acquired brain injury from different etiologies, and they were hospitalized in long-term care structures and rehabilitative centers; all the patients were classified as VS/UWS [23] and MCS [24, 25] based on clinical and behavioral assessment. Exclusion criteria were severe psychiatric or neurological diseases affecting the central nervous system before the brain injury.

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The patients included in the study took a combination of antiepileptic, sedative, and other drugs, depending on their clinical needs, and they underwent rehabilitative treatment to prevent complications and reduce motor disability.

One week after the enrolment, all the patients underwent an assessment, including the Italian version [26] of the Coma Recovery Scale-revised (CRS-r) [27]. CRS-r was administered three times, at different hours when the patients were awake, by trained and expert neuropsychologists (F.B., M.C., C.I., and F.G.M.).

For each patient, we collected information concerning sex, age, diagnosis (VS/UWS vs. MCS), etiology (ABI vs. TBI vs. other etiologies, including mixed etiology, OTHER), disease duration, and the CRS-r total and subscores representative of the patients' best performances. Group comparisons by diagnosis (VS/UWS vs. MCS) were performed using chi-squared tests and the Kruskal–Wallis test depending on whether the variables of interest were categorical or continuous (significance was set at $p < 0.01$).

The local ethics committee approved this study (ethics committee of the Fondazione IRCCS Istituto Neurologico Carlo Besta of Milan, 51/2018). Patients' legal representatives signed the written informed consent form before enrolment in the study.

2.2 | Neurophysiological Assessment: Evoked and Event-Related Potentials

For each enrolled patient, multimodal EPs and auditory ERPs were recorded using the Galileo Mizar System (EBNeuro, Florence, Italy) and standard laboratory procedures, including multiple trials for each test.

Brainstem auditory evoked potentials (BAEP), SEPs from the upper limbs, auditory-slow vertex potentials (a-SVPs), and fVEPs-electroretinogram (ERG) were performed, and the main cortical components were measured following the IFCN-recommended standards [28, 29]. The ERPs, namely auditory MMN and P300, were performed and evaluated as described in the guidelines [30] (see the Supplementary Information S1 for further details on EPs/ERPs parameters).

Importantly, ERPs were recorded three times on the same day at three different time points, and we considered the best responses (i.e., highest signal-to-noise ratio, maximum amplitude, and lowest latency) from these trials. Prior to each trial of the ERPs assessment, we gently stimulated the patients by touch to ensure they were arousable, and we performed a 5-min EEG to check for the alertness and vigilance level.

Patients showing a bilateral absence of a peripheral response to SEPs, the V component to BAEPs, or the retinal response to ERG were excluded from the analysis.

The auditory (AUD), somatosensory (SOM), and visual (VIS) responses that emerged from a-SVP, SEPs, and fVEPs, respectively, were dichotomously scored as follows:

- 0 = absence of cortical responses from both stimulated limbs, ears, or eyes.
- 1 = presence of a somatosensory, auditory, or visual cortical response(s), independently if normal or abnormal from at least one stimulated limb, ear, or eye.

Also, MMN and P300 were preliminary scored as 0 = absent and 1 = present, but considering the large variability of the ERPs in single cases and the quick fluctuations of attention in MCS patients, we pooled MMN and P300 in a "cognitive" (COG) category dichotomously scored as follows:

- 0 = absence of both auditory MMN and P300 responses.
- 1 = presence of MMN and/or P300 response(s).

AUD, SOM, and VIS represent the conservation of at least partial integrity of the auditory, somatosensory, and visual central pathways from the periphery to the cortex. The COG category represents the presence of endogenous responses related to later stages of information processing and to the cognitive feature of the task in which the stimulus is embedded.

An expert clinical neurophysiologist (D.R.S.) and two expert technicians (E.S. and L.G.) analyzed and categorized the EPs and ERPs responses, ensuring the accuracy and reliability of the results.

We compared VS/UWS and MCS groups of patients for the absence/presence (0/1) of the auditory, somatosensory, visual, and cognitive responses (AUD, SOM, VIS, and COG) with chi-squared tests (significance was set at $p < 0.01$). p-values were adjusted with Bonferroni correction.

2.3 | Cluster Analysis-Unsupervised Clustering

To identify recurring patterns in DOC patients we resorted to clustering which, being an unsupervised method, does not rely on predefined diagnostic labels; instead, it aims at individuating patterns emerging from the experimental sample.

For better stability [31], the clusters were individuated and validated via consensus clustering: this approach allowed pooling results across subsamples of the datasets, algorithms, and clusters' numbers. We considered four clustering algorithms suitable for categorical data: hierarchical agglomerative, hierarchical divisive, partitioning around medoids, and k-means. We employed the respective R implementations: agglomerative nesting (AGNES), divisive analysis clustering (DIANA), partitioning around medoids (PAM) from the cluster R-library [32], and K MEANS (KM) [33]. In all cases, we exploited the Gower's distance [34], which previously showed to return optimal results for categorical data [35]. Consensus clustering was performed using bootstrapping on five replicates, using 80% resampling, using the diceR R-library [36].

The number of clusters K was not a priori defined; instead, it was empirically determined by minimizing the proportion of ambiguous clustering (PAC) score and optimizing the trade-off between the silhouette coefficient and the weighted sum of squares (WSS) [37, 38].

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Each patient was assigned to a cluster following a majority voting criterion based on the results of the whole set of algorithms via consensus clustering. The final clustering underwent a significance analysis via Statistical Significance of Clustering (SIGCLUST) [39] (p values <0.01 were considered significant). p-values were adjusted with Bonferroni correction.

Finally, in order to extract the rules dividing the population into clusters, we fed the persistence data alongside the obtained clusters to a Random Forest trained with fivefold cross-validation optimizing for accuracy [40] via the classification and regression Training (CARET) R library [41]. The importance of the splitting variables was quantified via the Gini index and measured in arbitrary units (AU) depending on the Gini index itself and the sample size of the considered dataset [42]. Finally, we assessed the relationship between the clusters diagnosis (VS/UWS or MCS) and etiology (ABI vs. TBI vs. OTHER) with the chi-squared test (p values <0.01 were considered significant). p-values are adjusted with Bonferroni correction.

All the analyses were performed with R (version 4.3.2, R Core Team, Wien, Austria, available at {HYPERLINK: "http://www.R-project.org"}).

3 | Results

3.1 | Demographic and Clinical Features

Four patients were excluded from the subsequent analyses because they showed a bilateral absence of the peripheral responses to BAEPs ($n=1$) and SEPs ($n=3$), while two patients were excluded because the presence of artifacts polluting the traces made it impossible to correctly assess the presence of cortical responses to the EPs and ERPs; finally, one patient was excluded because the clinical evaluation demonstrated that he had emerged from MCS. Therefore, 146 (52 females, mean age 50.3 ± 14.1 years) of the 153 patients enrolled in the study underwent the statistical analysis.

The upper part of Table 1 summarizes the demographic and clinical features of the sample. No significant differences were

TABLE 1 | Demographic, clinical, and neurophysiological features of the sample (VS/UWS vs. MCS).

		VS/UWS	MCS	Significance (p)
Number		82	64	
Sex (number; F/M)		26/56	28/36	1.00
Age (years; mean ± SD)		51.2 ± 13.3	49.1 ± 15.2	1.00
Age at the brain injury (years; mean ± SD)		48.3 ± 13.9	45.1 ± 16.0	1.00
Disease duration (months; median [IQR])		25.0 (29.5)	32.7 (47.2)	1.00
Etiology (number)	ABI	42	11	**
	TBI	22	20	
	OTHER	18	33	
CRS-r (median [IQR])		6 (1.0)	10 (4.3)	****
CRS-r_Auditory		1 (0.0)	2 (2.0)	**
CRS-r_Visual		1 (1.0)	3 (0.25)	**
CRS-r_Motor		2 (0.0)	2 (1.0)	**
CRS-r_Verbal		1 (0.0)	1 (1.0)	*
CRS-r_Communication		0 (0.0)	0 (1.0)	**
CRS-r_Arousal		2 (1.0)	2 (0.0)	**
Presence of cortical response(s) in EPs and ERPs (number; yes/no)	AUD	37/45	46/18	0.024
	SOM	46/36	54/10	0.176
	VIS	20/62	42/22	*
	COG	14/68	41/23	***

Abbreviations: ABI = anoxic brain injury; AUD = cortical responses to auditory EPs; COG = cortical responses to ERPs; CRS-r = Coma Recovery Scale-revised; EPs = evoked potentials; ERPs = event-related potentials; IQR = inter-quartile range; MCS = minimally conscious state; SD = standard deviation; SOM = cortical responses to somatosensory EPs; TBI = traumatic brain injury; VIS = cortical responses to visual EPs; VS/UWS = vegetative state/unresponsive wakefulness syndrome.
*$p<0.01$.
**$p<0.001$.
***$p<0.0001$.
****$p<0.00001$.

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present when considering sex, age, age at the brain injury, and disease duration between the VS/UWS and the MCS groups of patients. On the contrary, the two groups of patients showed a marked difference in the etiologies distribution. Patients with ABI were prevalent in the VS/UWS group. In contrast, patients with etiologies different from ABI and TBI (i.e., OTHER) were prevalent in the MCS group. Specifically, 44 patients (30 MCS) had hemorrhagic etiologies, three patients (2 MCS) experienced ischemic stroke, and 4 patients (1 MCS) had mixed etiologies.

3.2 | Neurophysiological Features

The lower part of Table 1 and Figure 1 shows neurophysiological results.

In the whole sample ($N = 146$), auditory, somatosensory, and visual cortical responses to a-SVP, SEPs, f-VEPs, and ERPs were present (i.e., AUD, SOM, VIS, COG = 1) in 83 (56.8%), 100 (68.5%), 62 (42.4%), and 55 (37.7%) patients, respectively.

No significant differences were found in SOM, while AUD, VIS, and COG differed between VS/UWS and MCS groups, with the presence of cortical response(s) in EPs and ERPs being more prevalent in the MCS group of patients.

3.3 | Unsupervised Clustering—The Choice of the Number of Clusters

Figure 2 graphically displays the results of the analyses performed to individuate the optimal number of clusters and to assess the adequacy of the clustering algorithms employed. All the used approaches obtained a PAC consistently lower than 25%, meaning that for 75% of the observation, the assigned cluster was consistent across the five bootstrapping resamples, except for KM; analogously, KM reached the lowest silhouette's coefficient across all the considered number of clusters K.

We individuated the flexion in the WSS curves at $K = 3$; again, $K = 3$ was considered well-suited for satisfying the values of both PAC and silhouette scores. Hence, we performed the unsupervised cluster analysis, dividing the sample into three clusters ($K = 3$).

The significance analysis conducted on the performed clustering returned a p-value of $p < 0.00001$.

3.4 | Unsupervised Clustering—Clusters Characterization

Figure 3 shows the processes used for the unsupervised clustering and the different percentages of VS/UWS and MCS patients in the three groups. COG and VIS were the most important variables used by the algorithm to include patients in one of the groups. Cluster #1 included patients characterized by the absence of cortical responses to f-VEPs and ERPs (COG = 0, VIS = 0); Cluster #3 was mainly composed of patients showing a response to ERPs (COG = 1), while Cluster #2 included patients without cortical response to ERPs, but with a conserved cortical response to f-VEPs (COG = 0, VIS = 1). AUD and SOM contributed only marginally to the identification of the clusters. Figure 3A highlights the gradual transitions between clusters.

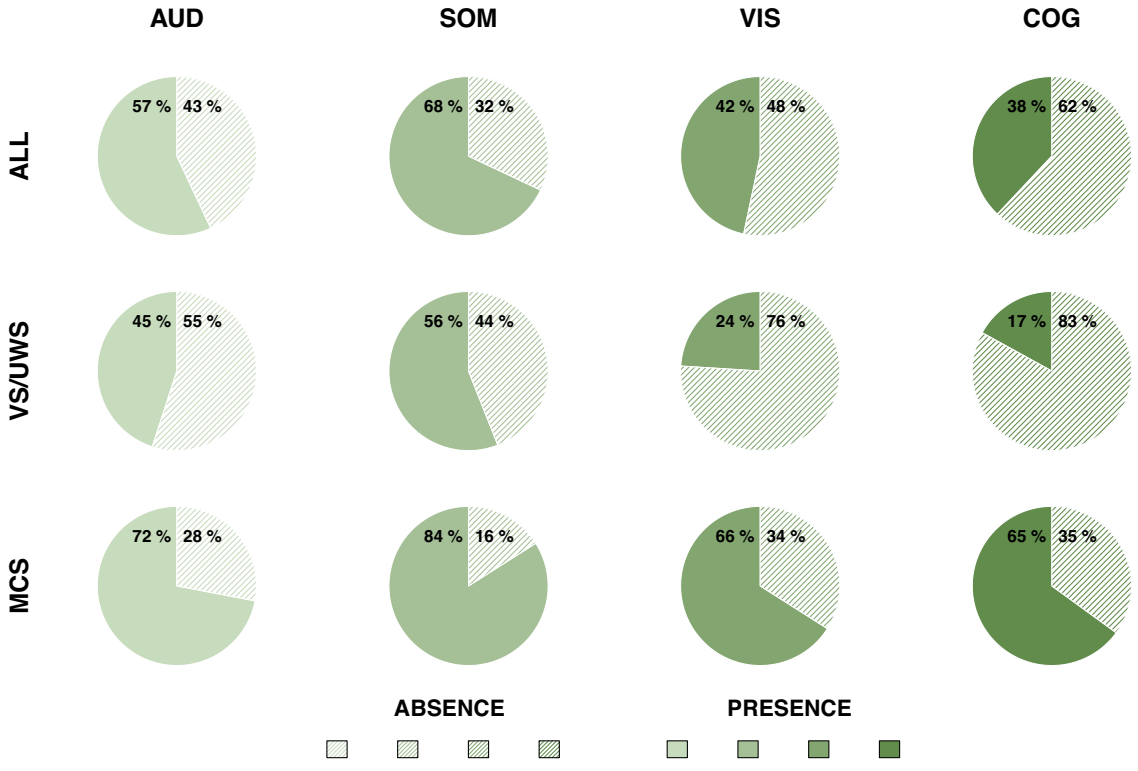

FIGURE 1 | The presence or absence of cortical responses to acoustic (AUD), somatosensory (SOM), and visual (VIS) evoked potentials and event-related potentials (COG) is displayed for the entire sample, VS/UWS and MCS patients.

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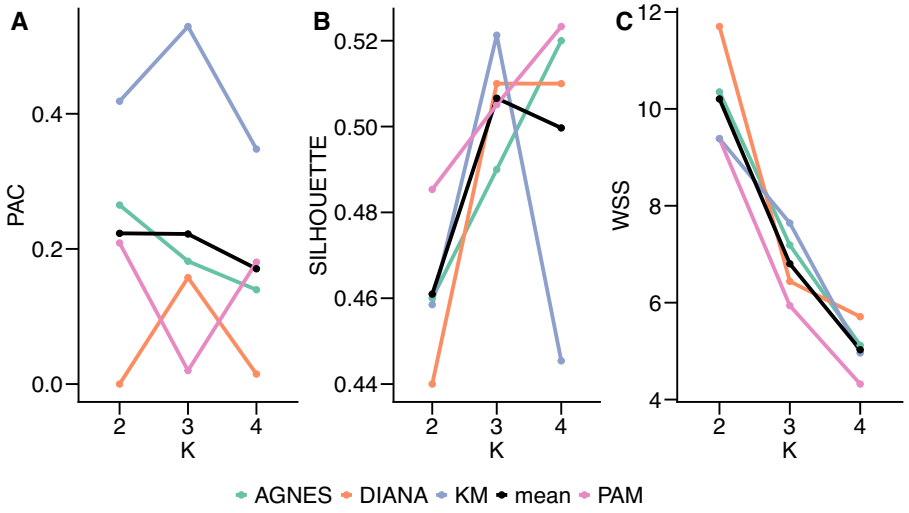

FIGURE 2 | The results of the analyses aimed at choosing the clustering algorithm and number. The panels show (A) the PAC score, (B) the Silhouette coefficient, and (C) the WSS from left to right (the black lines represent the mean performance).

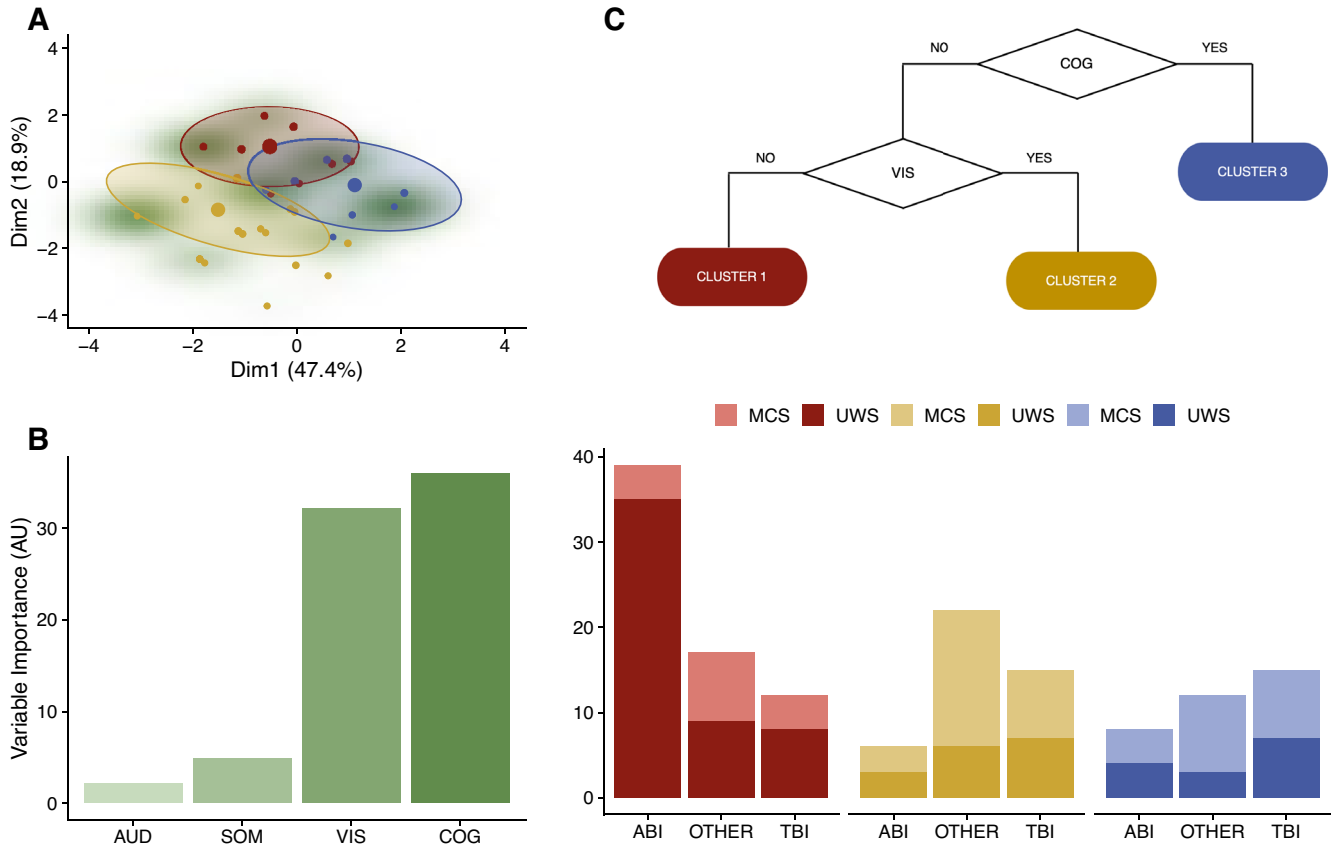

FIGURE 3 | Density of the three clusters individuated (A); variable importance quantified via an arbitrary metric based on the Gini's index and the clusters' numerousness, when splitting the dataset (B); decision diagram depicting the rules allowing to split the datasets into clusters (C, upper panel) and the distribution of diagnoses and etiologies across them (C, lower panel).

Table 2 provides details on the distribution of patients with different diagnoses and etiologies across the individuated clusters. The three clusters showed no significant differences in sex, age, age at the time of brain injury, and disease duration. At the same time, they highly significantly differed for both etiology (ABI vs. TBI vs. OTHER; $p < 0.0001$) and diagnosis (VS/UWS vs. MCS; $p < 0.001$). In #1, ABI (57.4%) and VS/UWS (76.5%) patients were predominant; conversely, MCS was prevalent in #2 (62.8%) and #3 (60.0%), as well as OTHER etiology for #2 (22/35, 51.2%), while ABI etiology was marginally represented in #3 (22.9%) and, especially, in #2 (14.0%) with respect to #1. Given the different prevalence of VS/UWS and MCS in the clusters, patients included in #1 showed CRS-r scores significantly lower than those included in #2 and #3.

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TABLE 2 | Demographic and clinical features of the clusters individuated from the unsupervised clustering.

		Cluster 1	Cluster 2	Cluster 3	Significance (p)
Number		68 (46.6%)	43 (29.4%)	35 (24.0%)	
Sex (number; F/M)		20/48	22/21	10/25	0.79
Age (years; mean ± SD)		49.0 ± 13.8	51.5 ± 14.7	51.4 ± 14.2	1.00
Age at the brain injury (years; mean ± SD)		45.7 ± 14.5	48.1 ± 16.2	47.9 ± 14.2	1.00
Disease duration (months; median [IQR])		26 (39.7)	26 (29.5)	34 (35.0)	1.00
Etiology (number)	ABI	39 (57.4%)	6 (14.0%)	8 (22.9%)	**
	TBI	12 (17.6%)	15 (34.8%)	15 (42.9%)	
	OTHER	17 (25.0%)	22 (51.2%)	12 (34.2%)	
CRS-r (median [IQR])		7 (2.0)	9 (4.0)	9 (4.5)	*
Presence of cortical response(s) in EPs and ERPs (number; yes/no)	AUD	26/42	28/15	29/6	**
	SOM	31/37	37/6	32/3	****
	VIS	1/67	38/5	23/12	****
	COG	2/66	0/43	35/0	****
Diagnosis (number)	VS/UWS	52 (76.5%)	16 (37.2%)	14 (40.0%)	**
	MCS	16 (23.5%)	27 (62.8%)	21 (60.0%)	

Abbreviations: ABI = anoxic brain injury; AUD = cortical responses to auditory EPs; COG = cortical responses to ERPs; CRS-r = Coma Recovery Scale-revised; EPs = evoked potentials; ERPs = event-related potentials; IQR = inter-quartile range; MCS = minimally conscious state; SD = standard deviation; SOM = cortical responses to somatosensory EPs; TBI = traumatic brain injury; VIS = cortical responses to visual EPs; VS/UWS = vegetative state/unresponsive wakefulness syndrome.
*$p < 0.01$.
**$p < 0.001$.
****$p < 0.00001$.

The difference in the presence of patients with cortical responses to EPs and ERPs reflected in part the different relevance of the variables used by the algorithm for the identifications of clusters and the different prevalence of MCS or VS/UWS in the three clusters; thus patients included in #2 and #3 showed a significantly higher fraction of patients with cortical responses to a-SVP and SEPs (AUD = 1 and SOM = 1) than those included in #1; again, patients included in #3 showed a significantly higher fraction of patients with cortical responses to ERPs (COG = 1) than those included in #1 and #2. Finally, patients included in #2 showed a significantly higher fraction of patients with cortical responses to f-VEPs (VIS = 1) than those included in #3 and #1, with patients included in #3 showing a significantly higher fraction of patients with cortical responses to f-VEPs (VIS = 1) than those included in #1.

4 | Discussion

We aimed at identifying recurring patterns within data derived from multimodal EPs-ERPs in a sample of chronic DOC patients. EPs and ERPs measured at different latencies indicate various stages of neural processing. In combination, they provide a more comprehensive understanding of sensory pathways' integrity and higher cortical processes' functioning. This integrative approach improves our ability to distinguish among patients who exhibit only reflexive responses from those who retain some level of consciousness.

We found significant differences in the presence of cortical responses between VS/UWS and MCS patients. VIS and COG were significantly more present in the MCS group, while we found only a trend for SOM and AUD. These results align with previous studies showing that cortical responses are significantly more related to MCS than VS/UWS [11–13]. However, whether the presence of detectable cortical responses to EPs and ERPs is a marker of consciousness in brain-injured patients is still a matter of debate. Indeed, the presence/absence of cortical responses to EPs is not directly related to the presence/absence of consciousness, since EPs do not explore the ability/possibility of the brain to integrate the collected information. In several neurological diseases, EPs can be abnormal or even non-existent while the patient is conscious [43, 44]. Conversely, in intraoperative neuromonitoring, EPs are usually recorded while the patient is sedated and unresponsive [45]. However, the persistence of visual, auditory, and somatosensory cortical responses detected using EPs may indicate at least partial integrity of the pathways from the periphery to the cortex [12].

Similarly, ERPs in DOCs offer valuable insights into the neural mechanisms underlying consciousness, because they often reveal abnormalities in the brain's response to stimuli, indicating a breakdown in the integrative process and compromised capability in combining and processing information, typical of patients clinically diagnosed with VS/UWS. Therefore, the persistence of cortical responses to EPs and ERPs in brain-injured patients is probabilistically, even if indirectly, related to a high level of

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cognitive functioning and conditions in which consciousness could be present, even though only partially. Counterintuitively, we detected ERP responses in 17% of VS/UWS patients, demonstrating that some behaviorally unresponsive patients can present "high-order" processes when assessed with instrumental tools. Besides, the recent international guidelines on DOCs diagnosis [4, 5] highlighted the importance of radiological and neurophysiological techniques, despite the actual differential diagnosis between MCS and VS/UWS still heavily relying on the CRS-r that critically depends on manifested behaviors not fully representing the entirety of consciousness. In other words, there would still be patients with partial preservation of consciousness who might be behaviorally misclassified as VS/UWS. In this context, detectable responses to ERPs suggest that some level of high-order integrative processes (MMN and P300) and attention (P300) are still functioning, even in the absence of behavioral responses [18, 19]. Our results aligned with previous studies, highlighting that the MMN and P300 can also be found in VS/UWS patients above chance [12, 46, 47], thus encouraging the assessment of late-latency cortical responses in every DOC patient.

The absence of SEPs early component in 16% of MCS patients may appear counterintuitive as well. However, these results align with previous research [10–13] suggesting that the absence of N20 does not exclude the presence of minimal consciousness, especially in chronic cases in whom cortical reorganization or localized lesions may determine the absence of SEPs early components. These findings highlight the importance of interpreting SEPs (particularly early components like N20) within a comprehensive assessment in chronic DOCs, as their prognostic and diagnostic value varies significantly depending on the context (acute vs. chronic).

Concerning the individuated patterns, three distinct clusters emerged. The most important variables distinguishing them were COG and VIS, as reflected also by the extracted rules. The patients with cortical responses to ERPs were included in #3; by contrast, the remaining ones were included in #2 or #1 if visual cortical responses were present or absent, respectively. The three clusters significantly differed for both etiologies and diagnosis distribution. In cluster #1, the patients were predominantly diagnosed with VS/UWS, resulting from ABI, coherently with previous studies [11–13] linking the persistence of cortical responses to a greater probability of maintaining consciousness. More interestingly, #2 and #3 are similar in terms of diagnoses, CRS-r scores, and etiologies distribution, with a slight prevalence of OTHER in #2. Hence, these similarities may suggest that f-VEPs yield similar diagnostic power to ERPs in individuating MCS patients in chronic DOCs.

We hypothesize two reasons why the preservation of f-VEPs is correlated with the MCS diagnosis in DOCs: (i) the proximity of f-VEP generators to brain areas necessary for the maintenance of consciousness, (ii) f-VEPs being not merely perceptual responses but determined by a vast and interconnected relay system. Importantly, these two possibilities are not mutually exclusive.

As for hypothesis (i), visual areas are anatomically close to the precuneus that is associated with several functions, including episodic memory recall [48], motor imagery [49], and integration of sensory information [50]. It also contributes to several facets of consciousness within the Default Mode Network (DMN) [51]: self-awareness, self-referential thinking, and personal identity (for a review, see [52]). Not by chance, functional connectivity of the precuneus has been considered a marker differentiating levels of consciousness among DOC patients [53]. Moreover, the precuneus is closely functionally interconnected with occipital lobes [52], contributing to generate the cortical response to f-VEPs. Additionally, both structures are supplied by the posterior cerebral artery. Hence, f-VEPs preservation may reflect a higher probability of precuneus integrity.

Considering hypothesis (ii), previous works point out that selective attention can amplify f-VEPs [54] when associated with specific stimuli. Furthermore, different cortical rhythms coexist for visual processing in occipital areas, where "perceptual" alpha rhythm may co-occur with at least a theta rhythm performing attentional sampling [55]. This evidence supports the hypothesis that visual perception and, consequently, f-VEPs are influenced by high order processes. Hence, the preservation of f-VEPs probably indicates an at least partial preservation of selective attention, beyond the integrity of brain structures necessary to the visual processes. Partial preservation of selective attention in principle entails conscious stimuli/information processing [56]. Also, neuroimaging studies underlined the importance of the visual system in the preservation of consciousness: in a work analyzing ABI patients, magnetic resonance imaging (MRI) abnormalities were prevalent in posterior cerebral regions and better predictors of residual functioning than whole-brain injury measures [57]. Analogously, when evaluating low-order networks in chronic DOCs, the visual network had higher diagnostic accuracy in individuating MCS patients than auditory and sensorimotor ones [58]. Moreover, its integrity resulted as relevant as DMN for diagnosis [59].

A growing body of data pointed out that "low-level" visual behaviors and responses correlated with at least partial preservation of consciousness. Indeed, four successive Rasch analyses [27, 60–62] showed that in the CRS-r, the preservation of visual fixation is one of the most consistent items to identify MCS. Therefore, although several of the CRS-r cognitively mediated items are visually presented, the importance of detecting indirect measures of posterior neurofunctional circuits preservation is in line with different theories [63, 64] supporting the pivotal role of a posterior "hot zone" for consciousness more than fronto-parietal network integration which, instead, could reflect attentional processing [57]. Moreover, a previous study [65] focusing on patients recovering from VS/UWS observed a progression of visual processing associated with higher levels of consciousness. This supports our hypothesis and suggests that VEPs parameters could reflect underlying neurocognitive recovery processes. Conversely, a study [66] showed that some VS/UWS patients exhibiting visual fixation did not differ from non-fixating VS/UWS patients in cerebral metabolism or cortico-cortical connectivity. Thus, visual fixation may result from subcortical or brainstem-mediated reflexes rather than higher-order cortical processing. Similarly, other authors [67] emphasized that visual fixation in some VS/UWS patients might be sustained by residual (but insufficient) visuo-motor network activity and may not reflect conscious perception, unless accompanied by other evidence of functional fronto-parietal network engagement (e.g.,

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P300, gamma power modulation). In other words, while some studies support visual fixation is related to MCS, this behavior alone is not a certain indicator of consciousness. Further studies exploring the complexity of visual functioning in DOC patients are needed to better clarify this point.

Some limitations must be accounted for. First, we did not consider the impact of medications on patients' responses, as this was beyond the scope of our work. In most studies involving DOC patients, participants assume multiple medications based on their clinical needs. Our work aims at reflecting real clinical situations rather than specifically selected populations. Importantly, none of the patients involved in our study took short-acting benzodiazepines, neuroleptics, or zolpidem within 4 h prior to the clinical evaluation/neurophysiological testing. Therefore, the influence of these medications in our sample was likely minimal. Second, ERPs encompassed MMN and P300. This choice is debatable, since MMN is an automatic, preattentive response typically elicited by an infrequent change in a sequence of auditory stimuli and is considered a marker of basic auditory discrimination and sensory memory. It does not require voluntary attention or behavioral response, and it is often preserved even in patients with limited awareness. Conversely, the P300 is attention-dependent and typically reflects conscious detection of salient or deviant stimuli. It is more strongly associated with voluntary processing, working memory updating, and, in some paradigms, intentional engagement. Despite their differences, here, MMN and P300 were used to explore residual auditory high-order processing, due to variations in the availability of specific paradigms and the clinical heterogeneity across DOC patients. Moreover, many patients (even MCS) could have aphasia or comprehension deficits; hence, it is not always possible communicating with them to obtain an attentional engagement for eliciting the P300. Finally, despite multimodal evaluation being encouraged by international guidelines on DOCs, we only considered neurophysiological examinations due to their feasibility and low associated costs. Nevertheless, our results should be considered along with the results of additional examinations performed with different instrumental tools by future studies.

5 | Conclusion

EPs and ERPs are essential for managing chronic DOCs [1–6]. They provide an objective way to assess the integrity and functionality of neural pathways in patients with impaired consciousness. It can be challenging to differentiate between VS/UWS and MCS, and EPs can offer valuable neurophysiological data to complement clinical observations and neuroimaging techniques. EPs and ERPs can detect residual cognitive processing and responsiveness in patients, even when there are no overt behavioral signs, making them increasingly valuable for refining diagnoses, predicting outcomes, and orienting rehabilitative treatment for chronic DOC patients. However, it is not clear yet if there are differences in diagnostic accuracy between the different types of potentials that can be administered, even though ERPs are traditionally considered the most accurate for detecting consciousness in comatose and chronic DOC patients. All the latest studies and observations converge in emphasizing the importance of the integrity of the visual system for preserving consciousness in DOC patients. In this framework, our results suggest that f-VEPs are as effective as ERPs in identifying the presence of consciousness in a large sample of chronic DOC patients, even with a practical and easy-to-perform analysis of the simple presence/absence of the cortical response to flash. With this analysis, we pave the way for an extensive application of f-VEPs in the challenging clinical context and give the rationale for implementing f-VEPs in an integrated diagnostic work-up for chronic DOC patients.

Author Contributions

Conceptualization: D.R.S. (lead), F.G.M. and L.C. (support); methodology: L.C. (lead), F.G.M. and D.R.S. (support); software: L.C. (lead), A.N. and C.R. (support); formal analysis: L.C.; resources: B.C., C.I., E.S., F.B., J.N., L.G., M.C., D.S., and V.P. (equal); data curation: F.G.M., C.I., F.B., and M.C. (equal); writing – original draft preparation: D.R.S.; writing – review and editing: F.G.M. (lead); C.I., E.S., F.B., L.C., M.C., D.S., V.P., J.N., L.G., C.R., A.N., M.L., and D.R.S. (support); visualization: A.N., C.R., D.R.S., L.C. (equal); supervision: M.L., D.R.S.; project administration: F.G.M. (lead), D.R.S. and M.L. (support); funding acquisition: D.S. (lead), D.R.S. and M.L. (support).

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Ethics Statement

The study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Institutional Ethics Committee of Fondazione IRCCS Istituto Neurologico Carlo Besta of Milan, Italy (approval number 51 of 2 May, 2018).

Consent

Informed consent was obtained from the legal representatives of patients involved in the study. Written informed consent has been obtained from patients' legal representatives to publish this paper.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data will be available on request.

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