Bedside detection of awareness in the vegetative state – a cohort study

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Abstract

Background

Patients who are diagnosed as vegetative have periods of wakefulness, but appear to be entirely unaware of themselves or their environment. However, recent studies using functional magnetic resonance imaging (fMRI) have shown that a significant minority of these patients are consciously aware; indeed, in some patients, communication with the outside world can be achieved with fMRI, even in cases where no possibility for behavioural (physical) interaction exists. Issues of expense and accessibility, however, preclude the use of fMRI assessment in the majority of vegetative patients.

Methods

A novel electroencephalography (EEG) paradigm involving motor imagery was developed to detect command following – a universally accepted clinical indicator of awareness – in the absence of any overt behaviour, in a group of 16 patients who met the internationally agreed criteria for a diagnosis of vegetative state.

Findings

19% of the patients were repeatedly and reliably able to generate appropriate EEG responses to two distinct commands, despite being behaviourally entirely unresponsive. There was no significant relationship between aspects of the patients' clinical histories (age, time since injury, etiology, behavioural score) and their ability to follow commands with this task. When separated according to etiology, 2/5 (20%) of the traumatic and 1/11 (9%) of the non-traumatic patients were able to successfully complete this task.

Interpretation

Despite rigourous clinical assessment, a significant proportion of vegetative state patients are misdiagnosed. The EEG method described here is relatively cheap, portable, widely available and objective, allowing the widespread use of this bedside technique for the re-diagnosis of patients who behaviourally appear to be entirely vegetative, but who may, in fact, harbour residual cognitive function and even conscious awareness.

Funding

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Introduction

It is now well accepted that the vegetative state (VS) is frequently misdiagnosed when behavioural criteria are used[1-3]. Thus, up to 43% of patients who have been diagnosed as VS are reclassified as (at the least) minimally conscious when assessed by experienced teams[1-3]. But is it possible that a further subset of conscious patients exists, but that they evade detection even after extensive clinical investigation in specialised centres? Indeed, recent functional neuroimaging studies have called into question several of the core principles that underpin the diagnosis of the VS; in particular, the extent to which we can truly consider that a patient is unaware of themselves and their environment simply because they exhibit no overt behavioural responses to any form of external stimulation.

For example, using functional magnetic resonance imaging (fMRI), Owen et al.[4] demonstrated that a patient who appeared to be entirely vegetative was, in fact, aware and able to modulate her blood oxygen-level dependent (BOLD) response to perform a variety of mental imagery tasks. Using the same technique, Monti and Vanhaudenhuyse et al.[5] showed that this patient was not unique; indeed 17% (4/24) of a group of patients diagnosed as VS were shown to be consciously aware and were able to perform these tasks reliably in the fMRI scanner. Moreover, one of these patients was able to answer “yes” and ”no” questions by modulating his fMRI response, despite being unable to initiate any form of functional communication at the bedside. These studies confirm, beyond any doubt, that there exists a population of patients who meet all of the behavioural criteria for the VS, but nevertheless retain a level of covert awareness that cannot be detected, even after thorough expert behavioural assessment.

In spite of these advances, performing fMRI in this patient group remains enormously challenging; in addition to considerations of cost and scanner availability, the physical stress incurred by patients as they are transferred to a suitably equipped fMRI facility is significant. Movement artefacts often occur in imaging datasets from patients who are unable to remain still, while metal implants, including plates and pins which are common in many traumatically injured populations, may rule out fMRI altogether.

Electroencephalography (EEG) measures the activity of groups of cortical neurons from scalp electrodes and is far less expensive than MRI, both in terms of initial cost and maintenance. EEG recordings are unaffected by any resident metallic implants and, perhaps most importantly, can be used at the bedside[6]. In the EEG record, imagined movements (motor imagery) are evident in the form of reductions of power – or event-related desynchronisations (ERD) – of the mu (~7-13Hz) and/or beta (~13-30Hz) bands over the topographically appropriate regions of the motor cortex – for example, over the lateral premotor cortex for hand movements and over more medial premotor cortex for toe movements[7]. In some individuals, these ERDs may also be accompanied by event-related synchronisations (ERS; relative increases in power) over motor areas contralateral to, or surrounding, the ERD[8, 9]. Using classification techniques it is now possible, on the basis of these EEG responses alone, to determine the form of motor imagery being performed by a conscious individual with a high degree of accuracy[10]. Here, we investigated whether the same general principles could be adapted to reliably detect covert conscious awareness in a convenience sample of sixteen patients who were assumed to be entirely vegetative on the basis of repeated and thorough clinical evaluation by specialist teams.

Methods

Patients

Sixteen VS patients were assessed at two European centres – Addenbrooke's Hospital, Cambridge, UK, and University Hospital of Liège, Belgium. Demographic and diagnostic information are presented in Table 1. Five of the patients had sustained a traumatic brain injury (TBI), while the remaining eleven had sustained a non-traumatic brain injury (non-TBI). There were no significant differences between the two groups in terms of length of time since injury (Mann-Whitney $U(16) = 14$, $p=.126$), or Coma-Recovery Scale-Revised (CRS-R) score (see Behavioural Assessment for a description of this assessment; Mann-Whitney $U(16) = 38$, $p=.202$). Patients who had sustained non-TBIs were significantly older than those who had sustained TBIs (medians 44-years and 29-years respectively, Mann-Whitney $U(16) = 6$, $p=.015$).

Informed assent was acquired from all patients' families and medical teams. For patients tested in Cambridge, ethical approval was provided by the National Research Ethics Service (National Health Service, UK). Ethical approval for those tested in Liège, was provided by the ethics committee of the University Hospital and Faculty of Medicine of the University of Liège.

Healthy Control Participants

Twelve participants, median age 25 years (range 21-31 years), were recruited from the School of Social Sciences, University of Western Ontario (London, ON, Canada). All participants were English speakers and reported no neurological conditions. Informed consent was obtained from all participants prior to the experiment. Ethical approval was provided by the Psychology Research Ethics Board (Department of Psychology, University of Western Ontario, London, ON, Canada).

Behavioural Assessment

All patients were admitted for 4-5 days as part of a separate protocol and were assessed with the CRS-R[11] on each day. The CRS-R was developed in order to differentiate between VS and minimally-conscious patients and includes six subscales addressing auditory, visual, motor, oromotor, communication and arousal functions. The highest CRS-R score and diagnosis from this 4-5 day assessment is included in Table 1. At no point during the 4-5 days of CRS-R assessments did any patient demonstrate behaviour inconsistent with a diagnosis of VS.

Motor Imagery Task Procedure

The EEG task was separated into two blocks – right-hand imagery and toe imagery. All patients completed at least 4-blocks of each type of movement (range 4-8), dependent on the patient's level of agitation at the time of assessment. All healthy controls completed 6-blocks. Block order was pseudo-randomised so that no more than 2-blocks of the same imagery type were completed consecutively. Each block began with the auditory presentation of the task instructions for that block. For the right-hand and toe blocks respectively, the instructions were:

"Every time you hear a beep, try to imagine that you are squeezing your right-hand into a fist and then relaxing it // wiggling all of the toes on both your feet, and then relaxing them. Concentrate on the way your muscles would feel if you were really performing this movement. Try to do this as soon as you hear each beep."

The instructions were followed (after 5-seconds), by the binaural presentation of 15 tones (600Hz, 60ms-duration) with an inter-stimulus interval of between 4.5 and 9.5 seconds (randomly selected from a uniform distribution on each trial). Each block concluded with an instruction to relax. All participants were provided with a short break before the onset of the next block.

All healthy participants also completed a control condition identical to the above motor imagery paradigm, with the exception that they were instructed by the experimenter to listen to the instruction and then simply mind-wander during the block – i.e. *not* to follow the commands. The order of task completion was randomised for each healthy participant.

EEG pre-processing

EEG was recorded from either a 129-electrode cap (Cambridge, UK and London, ON) or a 257-electrode cap (Liège; Electrical Geodesics Inc., Oregon) referenced to the vertex. In order to equalise the number of channels across patients, the 129-channels corresponding to those in the 129-electrode cap were subsequently selected from the 257-channel cap. This step ensured that the same number of EEG features were used for classification of motor imagery, and that accuracies were comparable across centres. Data were filtered offline between 1-40Hz, segmented into epochs of 5.5-seconds (including 1.5-seconds prior to each tone), and baseline corrected within 500ms prior to the tone. Bad channels were identified by inspection (channel variance > ~250) and replaced with interpolations of their neighbours (InvDist, EEGLAB[12]). All channels, including the online reference, were re-referenced offline to the average of their four geodesically nearest neighbours using a laplacian operator. This method of local average referencing has been shown to produce focal patterns of ERD and ERS[13]. Trials containing large movement artefacts were excluded. A median of 114 trials contributed to each patient's single-trial analysis (range 60-202). The 25 electrodes located over the motor area (covering the area centrally from C3 to C4; see Panel 1 for their locations) were selected from the original 129-electrodes to contribute to the single-trial classification, since this is the area of the scalp over which motor-imagery related activity is known to be localised. The median number of channels from these 25 that were interpolated prior to the analyses was 2 (range 0-8). The median number of trials contributing to the healthy controls' analyses was 171 (range 154-180), with a median of 1 (range 0-6) interpolated channel.

Classification Analyses

For each participant, a linear support vector machine (SVM)[14] classifier was trained with the filtered and artefact-rejected data to classify single trials into one of two classes (right-hand or toe motor imagery). EEG data from the 25 electrodes selected across the motor cortex in every trial were downsampled to 100Hz. Log power values within the mu (7-13Hz), low beta (13-19Hz), middle beta (19-25Hz), and high beta (25-30Hz) frequency ranges were calculated at each time-point. All the band-power values within the 'action period' between 0.5s to 3.5s after the tone in each trial were then concatenated by channel and used to construct a single feature vector for each trial. This allows the classifier to be trained on discriminative spatiotemporal patterns in the EEG across the two types of motor imagery. Block-wise cross-validation was employed to determine the classifier's generalisation error across the entire dataset. Specifically, the classifier was repeatedly trained and tested, by leaving out two blocks at a time (one right-hand, and one toe block), training on the remaining blocks and testing the generated SVM therefrom with the excluded blocks. During each repetition, features in the training and test set were z-score normalised with the mean and standard deviation of the training set. This block-wise cross-validation procedure, along with the pseudo-randomised block order, ensures that task-irrelevant intra- and inter-block correlations in the EEG cannot significantly account for the classification results.

To estimate overall accuracy for a patient or control, all the binary single-trial classification outcomes from the block-wise cross-validation procedure above were concatenated and modeled as a binomial process (using MATLAB's binofit function). This procedure assumed that the individual classification outcomes were binomially distributed, and calculated the maximum likelihood estimate of the overall correct classification probablity. These maximum likelihood estimates were then converted to % accuracy scores. Finally, a test of whether the 99% and 99.9% confidence intervals for the estimates included chance (50%) was used to ascribe a significance level to each score.

In order to confirm that significant classifiability could not come about as a result of global, non-task-relevant changes in background EEG which co-varied with the pseudo-randomized block order, the same analyses as above were applied to band-power features from a 'baseline period' 500ms wide, starting 500ms before each tone. The classification accuracy in the action period after each tone (as described above) was judged to be significantly greater than the classification accuracy in this baseline period if it fell outside of the binomial confidence intervals (99% and 99.9%) for the baseline accuracy. These comparisons not only ensured that classification accuracy was significant following each tone, but also that it was non-significant before the tone, and then increased significantly following it. That is, the classification accuracy in the action period was generated by consistently timed motor imagery initiated after each tone.

All calculations were performed in MATLAB, using a combination of custom scripts, EEGLAB[12] functions, and the g.BSanalyze software provided by g.tec medical engineering GmbH. Statistical analyses on the relationship between aspects of patients' clinical history and their ability to follow-command with this EEG task (linear and logistic regressions) were performed with SPSS.

Role of the funding source

The funding sources had no involvement in study design, collection, analysis, or interpretation. The corresponding author had full access to all data in the study and had final responsibility to submit for publication.

Results

Three of the 16 VS patients (19%) were able to follow the given commands to a degree that was significantly detectable (all $p<.01$) with this EEG technique (individual classification accuracies are listed in Table 1). The classification accuracies for these 3 patients ranged from 61-78% (mean 70%). None of these three patients returned significantly classifiable EEG during the baseline period (500ms prior to each tone; mean: 56%, all $p>.05$). For all three patients, the classification accuracy in the time-window after each tone was significantly greater than that achieved in the baseline period (all $p<.01$).

When separated according to etiology, two of the five TBI VS patients (40%, all $p<.001$) and 1 of the eleven non-TBI patients (9%, $p<.01$) returned positive EEG outcomes. There were no significant differences in classification accuracies between these two sub-groups (means 48% and 52% respectively; Mann-Whitney $U(16) = 27$, $p=.955$), nor in the proportions of patients significantly following commands (Fisher's exact test, $p=.214$).

Nine of the twelve healthy control participants (75%) produced EEG data that could be classified significantly above chance (all $p<.01$). The accuracies for these nine participants ranged from 60-91% (mean 68%), with the three non-significant controls producing EEG that could only be classified between 44-53%. When completing the control condition – listening to the same imagery task but not following the commands – no healthy control participant returned EEG responses that could be significant classified according to the commands (mean: 51%, range: 45-58%, all $p>.05$).

A stepwise multiple linear regression analysis including the factors i) age at time of injury (months), ii) time since injury (months), iii) CRS-R score, and iv) etiology (traumatic/non-traumatic) failed to significantly predict classification accuracy. A binary logistic regression analysis with the same factors also failed to predict positive EEG outcome (significant classification or otherwise). These results indicate that it is not possible to predict a patient's ability to follow commands in this EEG task on the basis of any of these aspects of their clinical history.

Discussion

Standard clinical assessments of command-following, which are based on behavioural observation, are fundamentally subjective. The results of recent fMRI studies have suggested that up to 17% (4/23) of patients considered to be in the VS following behavioural assessment are, in fact, capable of following commands when those commands do not require an overt motoric behaviour, but rather, a change in blood oxygenation level dependent (BOLD) reponse[4, 5]. Here we have demonstrated that covert awareness in the VS can be identified with a similar level of accuracy by means of a considerably cheaper and more portable bedside method. Indeed, using this technique, 19% (3/16) of the patients who appeared to be entirely vegetative on the basis of repeated specialist behavioural assessment were shown to be aware and capable of significantly and consistently modulating their EEG responses to command.

In order to fully appreciate the true weight of these results, it is first necessary to consider the multiple criteria that must be met before a significant positive EEG result can be returned for any given patient. First, it is necessary for each patient to modulate the appropriate frequency bands of the EEG signal that are associated with motor imagery, over the same regions of the head where this activity is known to occur in aware individuals (see Figure 1). Second, in order for each type of imagery to be accurately classified, this modulation must occur in a consistent way across trials of the same imagery type – i.e. with a consistent time-course and frequency content – but must also differ consistently *between* the two types of imagery (right-hand and toe). Finally, the classification of the patient's EEG data must be significant in a binomial test.

Is it possible that appropriate patterns of activity could be elicited in these patients in the absence of awareness? Could they somehow reflect an 'automatic' response to aspects of the task instructions, such as the words 'right-hand' and 'toes', and not a conscious and overt 'action' on the part of the patient? This is extremely unlikely and we know of no data that would support such a conclusion using a task like the one employed here. The task instructions were delivered once at the beginning of each block of 15 cues (short tones) that signalled the time to begin each imagery trial. Any 'automatic' response to the previously presented verbal instruction would then have to abate and recur in synchrony with these cues; cues that carried no information in of themselves about the task to be performed. Indeed, 75% of the healthy control participants returned positive EEG outcomes when completing this motor imagery task. However, when these same individuals were instructed *not* to follow the commands – i.e. not to engage in motor imagery – not one participant returned a positive EEG outcome. Evidently, any automatic brain responses generated by listening to the instructions are not sufficient for significant task performance; rather, an act of consistently-timed, volitional command-following is required. Furthermore, in all three of the patients who returned significant positive EEG outcomes following the commands, EEG activity *before* the commands was non-classifiable, providing further evidence that they were all producing task-appropriate EEG responses in time with the cues – as required by the task instructions.

In this context then, it is clear that successful performance of these EEG tasks represents a significant cognitive feat, not only for those patients who were presumed to be vegetative, but also for healthy control participants. That is to say, to be deemed successful, each respondent must have consistently generated the requested mental states to command for a prolonged period of time within each trial, and must have consistently done so across numerous trials. Indeed, one behaviourally VS patient (Patient 13) was able to produce EEG-responses that were classified with a success rate of 78% ($p<.001$). In other words, consistently appropriate EEG responses were generated across ~100 trials. It is notable that all but one of the twelve control participants produced EEG data that were less accurately classified than this patient.

Conversely, consider what these patients appeared to be capable of when assessed behaviourally; that is, when tested using accepted, standard clinical measures that were administered by experienced, specialist teams. All of the patients were tested with the CRS-R across at least 4 days, and at no point during any of these assessments did any of these patients demonstrate any behavioural sign of awareness (e.g. visual fixation, visual pursuit, localisation to pain). More importantly, none exhibited any evidence of a residual ability to respond to command. It is clear, then, that these patients were not misdiagnosed in the normal sense of the word. Indeed, rigourous assessments by experienced teams showed they were all correctly diagnosed (as vegetative) according to existing behavioural criteria. Clearly however, those criteria did not adequately capture the actual condition of these patients in at least 19% of the cases.

What, then, is the appropriate diagnosis for these patients who can follow command with an EEG response, but not with any overt physical behaviour? Of course, we cannot draw any strong conclusions about their inner worlds based solely on an ability to generate accurate and consistent EEG responses to command. However, performance of this complex task does make multiple demands on many cognitive functions, including sustained attention (over 90-second blocks), response selection (between the two imagery tasks), language comprehension (of the task instructions) and working memory (to remember which task to perform across multiple trials within each block) – all aspects of 'top-down' cognitive control that are usually associated with – indeed, could be said to characterise – normal conscious awareness[15]. A fuller characterisation of the residual cognitive abilities in this patient group, and how they contribute to command-following, is a question for future studies. However, the results of the current study demonstrate that functional neuroimaging – and in this case EEG specifically – is better suited for providing such a characterisation than existing methods of clinical assessment, since none of these patients were able to follow commands behaviourally.

Why is there a range of significant classification accuracies for both patients and healthy controls? There are several possible reasons for this. First, brain-state classification without any prior training on the part of the individual has been shown previously to produce relatively low classification accuracies in healthy participants (e.g. ~75% for right-hand vs. feet imagery[8]) and it follows that the same would be true for any patient group. Second, differences in attention or working memory capabilities are also likely to have played a role in the variance of classification accuracies within the patient group. Indeed, a patient whose diminished working memory leads them to forget the instructions for the current block after, say, 10 tones will only produce EEG 'noise' for the classifier in the remaining 5 tones, leading to reduced classification accuracy.

Why were three healthy controls unable to produce EEG that could be classified significantly above chance? As noted above, naïve participants who receive no feedback or training in imagery tasks are likely to produce relatively lower classification accuracies. Indeed, some healthy individuals remain unable to produce reliable classification, even with feedback training[10] – so called 'brain-computer interface illiterates'. The absence of a positive EEG outcome for three (aware) healthy controls highlights the importance of interpreting only positive results in patients, since it demonstrates unequivocally that a null EEG outcome does not necessarily reflect a lack of awareness. Alongside behavioural assessment and other functional neuroimaging approaches[16], multiple testing sessions with this EEG paradigm across a number of days will provide each patient with greater opportunity to demonstrate their covert awareness, if it exists.

The method described here has the potential to fundamentally change the assessment of this challenging patient group because EEG is highly portable, inexpensive, can be performed at the bedside, is available in most hospitals, and can be used with patients who have metal implants. Moreover, in the most comprehensive fMRI study to date, the data from 17% (9/54) of patients could not be interpreted at all due to excessively noisy data from motion artefacts[5]. In comparison, EEG is less affected by small motion artifacts, resulting in a drop-out rate of zero in the current study.

These results demonstrate that consistent responses to command – a reliable and universally accepted indicator that a patient is not vegetative – need not be expressed behaviourally at all, but rather, can be determined accurately on the basis of EEG responses. The success of this technique also paves the way for the development of so-called brain-computer interfaces[17] – or simple, reliable communication devices – in this patient group. Such devices will provide a form of external control and communication based on mappings of distinct mental states – for example, imagining right-hand movements to communicate "yes", and toe movements to communicate "no". Indeed, the degrees of freedom provided by EEG have the potential to take this beyond binary responses to allow methods of communication that are far more functionally expressive, based on multiple forms of mental state classification[18-20]. The development of techniques for the real-time classification of these forms of mental imagery will open the door for routine two-way communication with some of these patients, allowing them to share information about their inner worlds, experiences and needs.

Conflicts of interest

All authors declare no financial or personal conflicts of interest.

Author Contributions

DC designed the task, collected all healthy control data and all patient data from Cambridge, UK, developed the analyses methods with SC and wrote the manuscript. SC developed the analyses methods and conducted the analyses of all patient data with DC and contributed to the final manuscript. CC conducted the behavioural and EEG assessments of all patients at University Hospital of Liège, Belgium, and contributed to the final manuscript. TAB and DFE provided conceptual input throughout and contributed to the final manuscript. JDP was the clinician responsible for all patients at Addenbrooke's Hospital, Cambridge, UK, and contributed to the final manuscript. SL was the clinician responsible for all patients at University Hospital of Liège, Belgium, and contributed to the final manuscript. AMO provided conceptual advice throughout and wrote the manuscript with DC.

Research in Context

Systematic Review

Owen et al. were the first to identify a patient in the vegetative state who, despite being unable to follow commands with her behaviour, was able to follow commands by means of modulating her fMRI-detected BOLD response. Monti and Vanhaudenhuyse et al. later showed that 17% (4/24) of a group of patients considered to be vegetative were similarly capable of covertly following command with fMRI. Due to the expense and lack of portability of this method, however, fMRI is incapable of providing a truly practical means of assessment for this patient group. Thus far, there have been no reports of covert yet consistent and reliable command-following performed by a patient in the vegetative state *outside* of an fMRI scanner.

Interpretation

The prevalence of covert command-following within our cohort of vegetative patients – 19% (3/16) – is in accord with that already reported with fMRI, and reinforces the evidence that a significant minority of this patient group retain awareness that is not consistent with their externally-observable behaviour. The method reported here is the first evidence that covert command-following may be detected at the bedside of a vegetative patient, by means of the considerably cheaper and more accessible medium of EEG, and therefore has the potential to reach all vegetative patients and fundamentally change their bedside assessment.

Figures

Panel 1. Scalp locations of the 25 electrodes contributing to the classification analyses. The locations of C3, C4, Cz, and FCz are labelled.

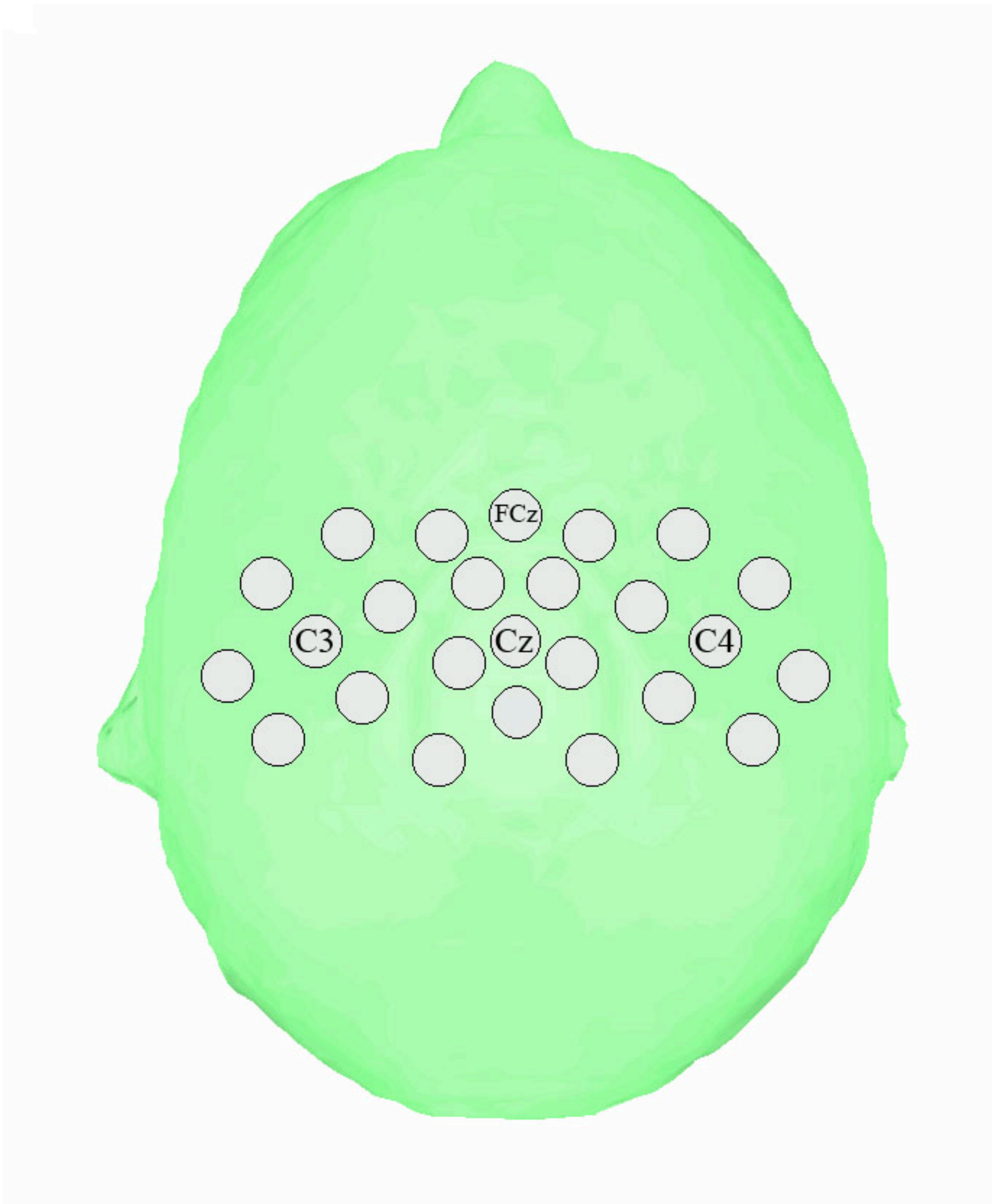

Figure 1.

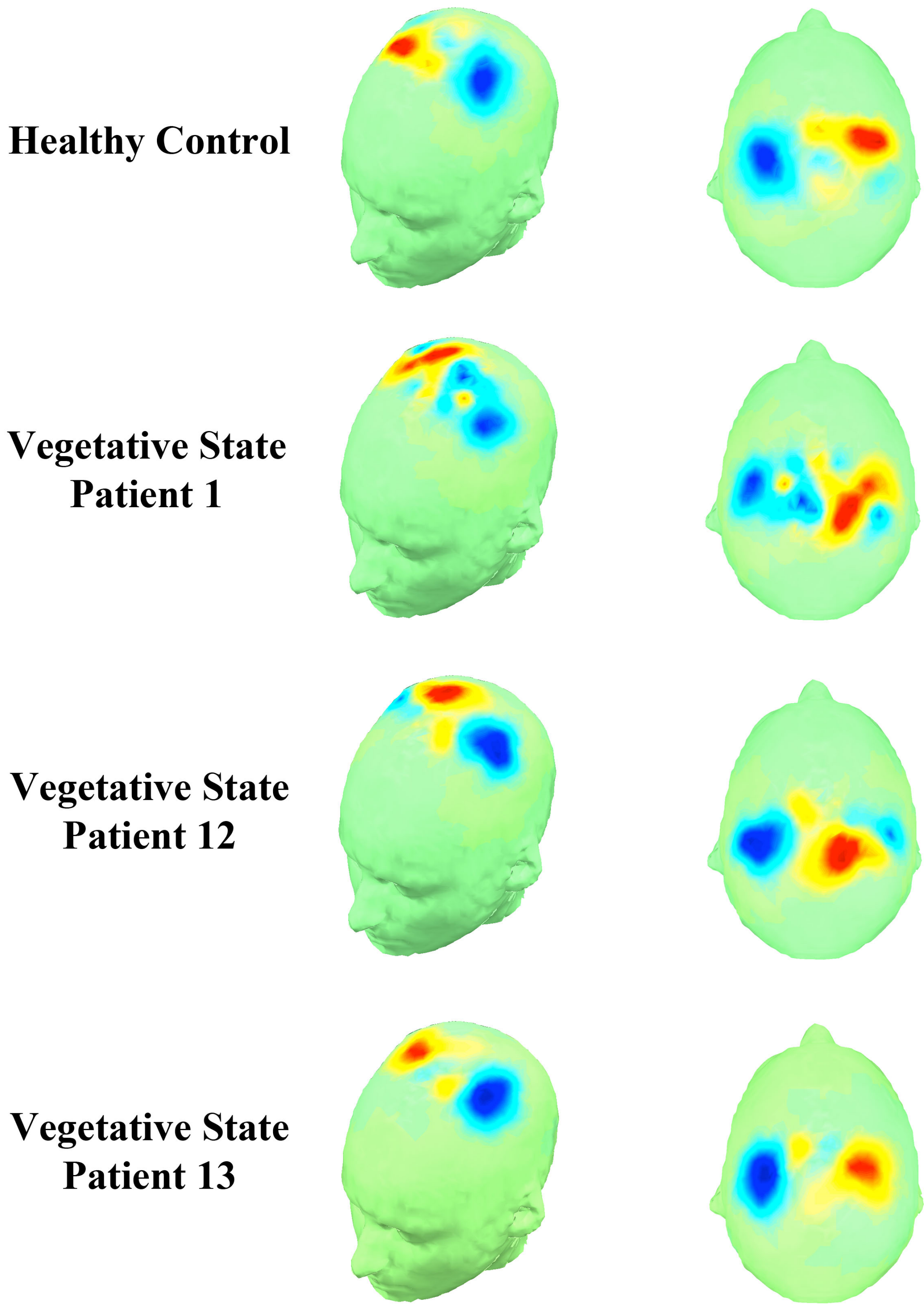
Healthy Control
Vegetative State Patient 1
Vegetative State Patient 12
Vegetative State Patient 13

Figure 1 Legend. When the scalp distributions of data from the classification procedure are plotted, it is evident that the neurophysiological basis of the positive EEG outcome – with clear foci over the hand and toe motor-areas – are formally identical when compared between a healthy control participant and those three vegetative state patients who significantly followed commands with this EEG task. (Maps show the scalp distribution of the single feature – time-point x frequency-band – with the highest absolute coefficient value from one training run of the cross-validation procedure. Red colours indicate coefficient values greater than zero, blue indicate values less than zero).

Table 1. Patient demographics and EEG classification accuracies. ***CRS-R: Coma Recovery Scale – Revised; **: p<.01, ***: p<.001, x: Non-signficant.***

Patient ID	Gender	Age at Assessment (years)	Interval post-ictus (months)	Etiology	CRS-R	Diagnosis	Number of trials contributing to analyses	EEG Classification Accuracy	Significant EEG Command Following?
1	M	35	9	Anoxia	7	VS	202	61.38	**
2	M	63	39	Anoxia	5	VS	113	61.90	x
3	M	55	21	Anoxia	4	VS	160	47.50	x
4	M	35	32	Anoxia	6	VS	69	43.47	x
5	M	30	24	Anoxia	6	VS	102	51.96	x
6	F	41	56	Anoxia	5	VS	132	53.78	x
7	M	63	32	Anoxia	7	VS	76	56.58	x
8	F	44	1	Anoxia	3	VS	86	48.83	x
9	M	48	94	Anoxia	6	VS	116	58.62	x
10	F	36	77	Stroke	3	VS	114	39.47	x
11	M	62	1	Stroke	6	VS	142	48.59	x
12	M	45	23	Trauma	6	VS	146	71.23	***
13	M	29	3	Trauma	6	VS	96	78.13	***
14	M	29	16	Trauma	6	VS	150	40.70	x
15	M	14	18	Trauma	6	VS	60	41.66	x
16	M	21	7	Trauma	7	VS	98	47.95	x

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