Utilizing EEG to detect covert command-following in vegetative traumatic brain injury patients: A review

Julia Leonard

1.7 million people in the US suffer from traumatic brain injury (TBI) each year, typically resulting from car accidents, contact sports, military operations, and falls [1]. Currently, healthcare personnel rely on the Glasgow Coma Scale (GCS) and other behavioral assessments for TBI diagnosis, which are rather subjective and poor diagnostic tools [1]. Other commonplace methods include medical resonance imaging (MRI) and computed tomography (CT) scans, which lack portability and are a financial burden on patients and hospitals. Because of this, both MRI and CT lack easy repeatability. Current techniques result in 36% of TBI patients receiving a misdiagnosis, and proper diagnosis is only seen after 5 assessments over 2 weeks [2]. Diagnosis is important for outcome, as patients that show covert command-following have a better chance of survival [3]. This review will highlight current new methods for diagnosing TBI patients with little or no physical movement and response to environment. Studies utilizing methods such as electroencephalography (EEG) and P300 display how patients in varying disorders of consciousness have covert responses to commands, although behavioral assessments would diagnose them as nonresponsive. 17-20% of vegetative patients completing lacking in physical movements show brain activity response to imagery tasks [4,5]. EEG and P300 prove to be a promising tool moving forward for TBI diagnoses, as it is more portable and a fraction of the cost of MRIs, allowing for multiple assessments over time. Limitations include high heterogeneity in EEG data, which can lead to false positives and negatives, as well as P300 methods need greater control before they can be fully adopted [5,6]. Ultimately, EEG techniques show clinical applicability for TBI diagnosis, especially as the methods continue to improve.

Introduction

1.7 million people in the US suffer from traumatic brain injury (TBI) each year, typically resulting from car accidents, contact sports, military operations, and falls [1]. Severe traumatic injury varies in disorders of consciousness (DOC), which includes brain death, coma, persistent vegetative state (VS), minimally conscious state (MCS), and locked-in syndrome [7]. 14,000 – 35,000 children and adults suffer from VS after severe TBI (sTBI), characterized by a vegetative state of at least one month [8]. For these patients, outcome looks grim, and life is largely determined by clinicians and family [8]. On the other hand, MCS patients show some extent of rehabilitation, as they can inconsistently respond to stimuli, such as eye opening, which results in more funding and better care [7].

Current diagnosis of sTBI largely depends on behavioral assessments, like the Glasgow Coma Scale (GCS) and Coma Recovery Scale – Revised (CRS-R), which are criticized as being a subjective diagnostic tool [1,9]. Clinicians also utilize MRI and CT scans to assess the extent of damage to the brain.

These machines are expensive and lack portability and repeatability. Wannez et al. reported that 36% of TBI patients that lack initial responses receive a misdiagnosis, with accurate diagnosis only seen after 5 assessments over 2 weeks [2]. The lack of repeatability results in underestimation of a person's consciousness and is a main cause of 40% of VS patients being misdiagnosed as VS rather than MCS [2,10]. New methods are needed to assess the extent of brain damage in VS patients, especially when misdiagnosis can result in a choice to end care. 17-20% of VS patients that show no physical movement do have brain activity to external stimuli, such as imagery tasks, giving hope for some recovery [4,5].

This review highlights three studies using electroencephalography (EEG), which measures neuronal activity in a user, to better understand and diagnosis DOC individuals. EEG is promising because it allows for repeatability, portability, and minimal movement of the patient. It also has less noise and easier data analysis compared to other methods [7]. In this setting, EEG is used to measure the P300 and background activity after active stimuli to assess the extent of brain damage in otherwise nonresponsive patients. P300 is a measure of event-related potential (ERP) and cognitive function. The P300 is correlated with a spike in neuronal activity at 300ms that occurs in response to a stimulus [11]. It is important to stress the difference of using passive and active EEG paradigm assessments for DOC patients. Passive stimuli include one's language, familiar faces, and emotional stimuli, which are primed objects and result in cognitive functions that are active without consciousness, as there are semantic and linguistic processed preserved in VS patients [7,12]. Active paradigm assessment is typically more accurate since it involves an auditory or imagery task like counting that requires more complex cortical networks to fire. Currently, Subject's Own Name (SON) and Other First Names (OFN) paradigms, both of which involve counting the number of times a name is heard, are being explored because the response requires a higher level processing, including stimulus recognition, recollection, and retrieval [10, 13]. Therefore, greater DOC severity should result in decreased response to these paradigms. However, active assessment is draining on the user, which can reduce accuracy since P300 is known to fluctuate in different arousal states [6,11]. EMG artifacts can also reduce the accuracy of ERP readings, as well as motion [7]. The studies described in this review will highlight the potential and pitfalls of using bedside EEG and auditory stimuli for DOC diagnosis.

Methods and Results

Three different studies' methods and results are described below to emphasize the different approaches and the lack of standardization for this emerging field. All studies give evidence of being able to distinguish MCS and/or VS from healthy controls or each other using auditory paradigm assessments. However, their overall success varies, perhaps due to the chosen paradigms and analysis techniques.

Study 1: Cavinato et al. 2011 [10]

17 DOC patients (11 VS and 6 MCS) and 10 healthy controls were assessed. DOC patients were divided into either MCS or VS based on Disability Rating Scale (DRS) behavioral assessments. ERP was measured using 4 electrodes placed above the midline of the scalp following a 10-20 system. Extra electrodes were placed on the sides of the head to measure electroocular activity. Three auditory assessments were performed: Sine Tone (ST) paradigm, SON paradigm, and OFN paradigm. ST served as the control passive paradigm, while SON and OFN were active. Names of family members and close friends were excluded from SON and OFN assessments to prevent P300 misreading. No drugs were given during the recordings that would alter wakefulness. Each assessment had 2 sequences of 100 stimuli. EEG amplitudes were measured at 100Hz and filtered with a 0.15-70Hz bandpass filter [10].

All healthy controls and MCS patients had ERP potentials for each paradigm condition. MCS patients did have greater ERP latencies to SON and OFN paradigms compared to the control ST, but this could not be deemed significant. 6 out of 11 VS individuals could not establish a reliable ERP reading. For the readings that were able to be analyzed, VS patients had much lower N1 electrode amplitudes, which correlates with the arousal circuits, during ST compared to the MCS and healthy groups [10].

Study 2: Kempny et al. 2018 [13]

16 patients with DOC lasting for at least 4 weeks and 11 healthy individuals were recruited. Of the DOC group, 5 were diagnosed as VS and 11 diagnosed as MCS using the Sensory Modality Assessment and Rehabilitation Technique (SMART) behavioral assessment tool. Three conditions were assessed: 1) SON paradigm 2) OFN paradigm 3) time-reversed OFN paradigm. Time-reversed OFN was used as an auditory control instead of ST to have an acoustically similar control. Electrodes were placed in the 10-20 layout, with an extra 10-10 electrode placement. SON paradigm assessment was conducted over 44 trials, and OFN and time-reversed OFN totaled 143 trials. Each trial lasted 35.5 sec, with 15 stimuli per trial. The EEG data was filtered at .053-40Hz with a sampling rate of 512 Hz [13].

In general, there was a greater response to the OFN paradigm than SON for the control population, as OFN is a more salient stimulus. However, the MCS and VS groups showed no significance between SON and OFN. 25% of subjects did have individually significant responses to SON and OFN compared to time-reversed OFN [13].

Study 3: Estraneo et al. 2016 [14]

77 TBI, vascular brain injury, or anoxic patients diagnosed with either VS or MCS at the time of hospital admission were recruited for the study. MCS patients were further divided into the MCS+ and MCS- subgroups, MCS+ showing a higher degree of consciousness. Patients with changing DOC diagnoses within a week of the study were excluded. CRS-R was used before and after trials for DOC assessment. 19 electrodes were placed on the scalp and recorded EEG activity for at least 35 minutes. Recordings were done in the morning, and the patients were off sedative medication for at least 15h prior to the studies to ensure wakefulness. Five passive paradigms were tested: 1) eye opening and forced eye closing 2) tactile stimuli 3) noxious stimuli 4) acoustic stimuli (hand clapping) 5) intermittent photic stimulation. EEG recording for each condition was done 3 times over 2 days, with the best recording used for analysis. A bandpass filter of 1-70Hz was used during analysis. The recordings were categorized into alpha, delta, and theta waves. Overall, EEG background activity was categorized as either normal, mildly abnormal, moderately abnormal, diffuse slowing, or low voltage [14].

All patients but one had abnormal EEG background activity compared to healthy individuals, with VS patients having greater abnormalities than MCS+/-. Patients with normal or mildly abnormal EEG rhythms tested higher on the CRS-R scale than moderately abnormal or diffuse slowing. MCS- and VS patients had high sensitivity of low voltage readings, but this was not deemed specific. EEG patterns did differ significantly between MCS+ and VS, and MCS- and VS, but not between MCS+ and MCS-. 20 out of 37 VS patients had no or low voltage reactivity, compared to only 1 of 10 MCS patients, showing MCS patients were more reactive than VS [14].

Discussion

DOC severity is correlated with low EEG amplitudes and disorganization of neuronal activity, which is why current EEG assessments focus on ERP potentials and brain wave analysis. Paradigms are critical to the methods, as assessments must cause a salient response, typically involving activation of subcortical structures related to high-level processing [13]. In all studies reviewed, auditory stimuli showed promise for distinguishing MCS and VS individuals. Study 3 did not display differences in DOC patients in response to tactile or painful stimuli since the corresponding cortical networks do not require high-level processing [14]. MCS patients had greater responses to more complex paradigms, suggesting there are more preserved neuronal circuits compared to VS that can be identified via EEG. When combining results from ERP potentials and background activity, MCS patients have greater ERP amplitudes, greater latency in ERP relating to stimuli response, and more normal alpha rhythms. Interestingly, the only MCS patient in Study 3 that had normal background activity actually emerged from MCS+ one month later, giving feasibility to Estraneo et al.'s methods for diagnosing MCS and VS.

Limitations to all studies include not being able to conclude significance for some or all conditions. This may be due to low sample sizes or the differences in methods. Currently, there is no standard for analyzing EEG data, causing large variability between studies. For example, each group used different controls: Cavinato et al. used a sine tone to simulate general phonetics, Kempny et al. used reverse OFN to control for a language component, and Estraneo et al. used only data comparison to healthy EEG activity. Each test also had differences in electrodes placed, length of assessment, and data analysis. Because of the differences in methods, it is difficult for researchers to compare and decide on the best paradigm assessment, which may slow down advances in the field. It may be beneficial to analyze both ERP potential with alpha rhythms during SON and OFN paradigms to get the most robust diagnosis. Even then, these methods still potentially fall short of differentiating MCS+ from MCS-, and instead should focus on MCS from VS, as VS individuals have the most to lose from a misdiagnosis. It is important to note that EEG can still result in false diagnoses if not repeated over multiple assessments due to varying states of wakefulness in DOC patients [11]. The guideline of conducting 5 assessments over 2 weeks should still apply [2]. As clinical methods become more uniform and reproducible between patients, EEG will be a favorable diagnostic tool to distinguish MCS and VS due to its advantages of portability, easier data analysis, and less expensive equipment compared to MRI and CT scans.

Conclusion

EEG shows promise of better distinguishing between MCS and VS individuals than current behavioral tests, which often result in misdiagnosis. It also offers the benefit of having high portability, lower costs than imaging machines, and easier data analysis. Active paradigms of response to one's own name may be sufficient to determine the extent of brain damage in TBI patients, which is exciting as it involves relatively simple tasks like counting that can give a clinician more information than current behavioral assessments. It is critical for methods to improve and standardize so that EEG will be implemented more in clinical settings for DOC diagnoses.

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