The clinical diagnostic utility of electrophysiological techniques in assessment of patients with disorders of consciousness following acquired brain injury – Protocol for a systematic review

Hauger, S.L., Schanke, A-K., Andersson, S., Chatelle, C., Schnakers, C., Løvstad, M.

Author Affiliations:
Department of Research, Sunnaas Rehabilitation Hospital (Hauger, Drs Løvstad and Schanke)
Department of Psychology, University of Oslo (Drs Anderson, Løvstad and Schanke)
Laboratory for NeuroImaging of Coma and Consciousness, Massachusetts General Hospital, Boston and Department of Cognitive Neurosciences, University Hospital of Lausanne, Switzerland (Dr Chatelle)
Department of Neurosurgery, University of California Los Angeles (Dr Schnakers)

Corresponding author:
Solveig Lægreid Hauger
Department of Research, Sunnaas Rehabilitation Hospital, 1450 Nesoddtangen, Norway (solveig.hauger@gmail.com)

1. Introduction
1.1 Background

Modern developments in neuroimaging and electrophysiological methods have over the last couple of decades allowed both structural and functional studies of the living brain. This has enabled monitoring of ongoing mental activities, and exploration of the neural correlates of human behaviors. Hence, much of contemporary evidence and theories of brain processes are informed by novel neuroimaging techniques, offering insight into age-old questions about brain-behavior relationships, and a developing understanding of underlying neural mechanisms. Although previously often regarded as scientifically intractable, consciousness can now be successfully studied with modern neuroscientific techniques, such as positron emission tomography (PET), functional MR imaging (fMRI), MR diffusion tensor imaging (DTI), and electrophysiological techniques.

In parallel with this methodological development, a great interest has found place with respect to patients with disorders of consciousness (DoC) following severe acquired brain injury, i.e. patients in either the vegetative (VS) or the minimally conscious state (MCS). Whereas the VS is characterized by absence of any behavioral signs of awareness, but regained intermittent wakefulness, the MCS, by contrast, is characterized by the presence of inconsistent, but clearly discernible behavioral evidence of awareness of self or the environment (i.e. visual pursuit, localization to pain, or reproducible command-following). Novel neuroimaging and electrophysiological techniques have offered new insight and enhanced theoretical understanding of these patient’s level of consciousness, brain connectivity, metabolic and cognitive functioning. PET-studies have found substantial global decrease in brain metabolism in VS patients, whereas patients in MCS have shown partially preserved bilateral frontoparietal network. Recently, the MCS entity has been suggested divided into MCS+ and MCS-, depending on the complexity of behavioral
responses, where MCS+ is defined by the presence of command-following, intelligible verbalization, or gestural or verbal yes/no responses. In contrast, MCS− is characterized by nonlinguistic signs of conscious awareness, such as visual pursuit and localization of noxious stimuli. Interestingly, higher cerebral metabolism in left-sided cortical areas has been found in MCS+, compared to MCS−.

The main approach to clinical diagnosis of DoC is based upon behavioral assessment strategies. Misdiagnosis rates of DoC have been estimated to be as high as ≈40%.[16-18] The lack of a ‘gold standard’ for detection of conscious awareness in DoC is a prominent confounding factor for accurate diagnostic assessment, and it is recommended to apply standardized neurobehavioral rating scales designed to detect subtle, but clinically significant signs of consciousness.[19,20] Various behavioral scales have been developed, but in a recent evidence-based review, the Coma Recovery Scale-Revised (CRS-R) was the recommended standardized scale, while the Sensory Modality Assessment Technique (SMART), Western Neuro Sensory Stimulation Profile (WNSSP), Sensory Stimulation Assessment Measure (SSAM), Wessex Head Injury Matrix (WHIM), and Disorders of Consciousness Scale (DOCS) were recommended used with moderate reservations.[21]

The development within neuroscience methods has also resulted in optimism regarding the application of these approaches in individual clinical diagnostic and prognostic considerations.[22-24], in part due to several studies indicating that active cognitive processing can be detected with imaging techniques in the absence of behavioral signs of consciousness.[25-30] Instead of applying merely passive experimental paradigms that elicit relatively “automatic” responses from the brain without the need of willful mental action, these studies apply tasks that require active, mental operations, which in contrast to passive paradigms require the subject to exert voluntary mental responses to command.[31,32] Thus, in order to infer consciousness it is necessary to apply tasks that involve active cognitive processing. In sum, these findings suggest that there are patients who retain cognitive capacity for command-following with the aid of functional neuroimaging- and electrophysiological methods, where such voluntary mental actions cannot be detected behaviorally at bedside.

1.2. Clinical diagnostic utility of electrophysiological methodology in DoC patients

Imaging-methods, such as fMRI and positron emission tomography (PET) require high levels of technical skills, they are expensive, and most often not readily accessible in rehabilitation facilities. On the other hand, techniques based on electrophysiology have the benefit of being low-cost, noninvasive, more easily accessible, and can be conducted repeatedly at bedside, and hence, are more clinically accessible. Event related potentials (ERPs) represent time-locked electroencephalographic (EEG) activity elicited by external events, thus providing a neurophysiological correlate of cognitive processing at the millisecond level, from early and largely sensory components to later and cognitively mediated waveforms, such as the P3.[33-35] Task-related systematic changes in oscillatory variation can also be an indice of cognitive effort, and can be analyzed through the analysis of event-related desynchronisation (ERD) in frequency bands.[36,37] Surface electromyogram (EMG) is, on the other hand, recording of electrical activity in muscles, and is a commonly used tool to study physiological principles of muscles related to i.e. movement generation.[38,39]

Two systematic reviews have aimed at providing an estimate of the sensitivity and specificity of both functional imaging and electrophysiological methods in detecting signs of preserved consciousness in DoC patients.[40,41] Bender and colleagues reviewed a variety of novel diagnostic applications of advanced neuroimaging and neurophysiological procedures and
conducted a quantitative meta-analysis of the diagnostic sensitivity and specificity of each of the included neurodiagnostic methods, i.e. fMRI, PET, ERP EEG and eye-tracking. However, due to strict inclusion criteria, only four electrophysiological studies using active task paradigms were included in their review. Moreover, the use of a standardized behavioral assessment tool with acceptable psychometric properties was not included as criteria for reference standard in their review.

On the other hand, Kondziella and colleagues included a large number of both electrophysiological and functional imaging studies in their systematic review. In their meta-analysis they assessed whether the clinical diagnosis of VS versus MCS was accurately reflected by the presence or absence of signs of consciousness as revealed by fMRI and/or EEG-based techniques. A major weakness of their review is however the authors’ interpretation of preserved consciousness based on responses to passive tasks with no requirements of willful modulation of brain activity. Inference of consciousness based on passive experimental task paradigms is evidently insufficient, as passive tasks without demand of volitional mental effort can elicit a P3 response in comatose or VS patients, and in healthy subjects under anaesthesia, and therefore cannot be used to disentangle conscious from unconscious patients. Therefore, a prerequisite is to include “active” experimental paradigms requiring volitional cognitive effort, allowing detection of covert command-following by comparing responses in active versus passive tasks, thus showing command-specific changes. Furthermore, Kondziella and colleagues provide a pooled calculation of group wise odds ratio (OR) for command-following during active paradigms in novel neuroscientific methods in VS and MCS. However, grouped meta-calculations of sensitivity and specificity across different neuroscientific methods and various experimental conditions can only be considered to be very rough estimates. In addition, an accurate meta-calculation of sensitivity and specificity regarding these methods’ diagnostic accuracy is difficult, as there is a lack of a true gold standard method to confirm level of consciousness. Moreover, such meta-calculations take into little account to what degree these methods provide supplementary information of the patient’s ability to follow command compared to behavioral measures. Meta-calculations also lack descriptions of false negative rates; where functional imaging and electrophysiological methods fail to capture signs of command-following in patients who demonstrate discernible behavioral evidence of command-following.

In summary, to date, no comprehensive review has managed to sufficiently estimate the clinical diagnostic utility of electrophysiological techniques. There is a need to review the efficacy of electrophysiological studies using active experimental paradigms in revealing covert command-following at a patient-by-patient level. This is paramount in order to establish the diagnostic value of these methods in clinical practice, where correct assessment of a DoC patient’s level of consciousness is crucial, but challenging.

1.3. Rationale for the review

Modern functional imaging and EEG-based techniques have elicited optimism regarding their potential in improving diagnostic accuracy in DoC. However, the body of existing systematic reviews and overview articles of the methods have various shortcomings in providing a sufficient estimate of the clinical usefulness of implementing these neurophysiological measures in clinical practice. A major limitation of existing reviews is lack of reports regarding responder rates at an individual level, both in healthy subjects and DoC patients, and also an insufficient account of false negatives. Some reviews lack a representative body of studies included, either because of overly strict study inclusion
criteria regarding sensitivity/specificity, while others have not required use of active paradigms \(^{40,41,55}\). Yet other papers only provide a topical overview without explicit systematic literature search strategies \(^{48,50,51,53-55}\). In addition, no existing reviews provide an overview of the rate of excluded subjects across studies due to methodological artifacts, which is quite common in electrophysiological methods in general, and might be expected to be even higher in groups known to have ample muscle artifact, and lack cooperative abilities in the test-situation.

In a clinical context, it is necessary to establish to what extent we can gain additional diagnostic information from electrophysiological assessments, as a supplement to standard behavioral assessment tools at an individual patient level. In order to evaluate the potential of implementing electrophysiological methods in clinical practice, two main issues need to be explored. A primary issue is to establish the experimental robustness of paradigms in healthy volunteers, who are by definition perfectly conscious, and thereby should be able to willfully follow a mental task. Secondly, the rates of responders in DoC patients as well as the rate of false negatives needs to be assessed more precisely, in order to evaluate the clinical utility of neurophysiological techniques. In summary, it is still not well described to what extent active electrophysiological paradigms can complement standardized neurobehavioral assessment. The present systematic review therefore has the potential to provide a novel contribution to the field.

1.4. Objectives
The primary objective for the systematic review was phrased using the PICO-approach (patient problem, intervention, comparison and outcome; \(^ {56}\)): In patients with DoC (P), to what extent can electrophysiological techniques used in combination with active experimental paradigms (I) supplement standard behavioral measures (C) in detecting voluntary cognitive processing (O)?

The secondary objectives of this systematic review are to gain knowledge regarding the following questions:

1. Which active experimental paradigms seem to be the most robust? To address this, we will investigate rates of responders in healthy controls as well as DoC patients in the experimental tasks of included studies.
2. What are the false negative rates (patients with discernable behavioral signs of command-following that cannot be detected with electrophysiological methods) in both healthy controls and DoC patients?

Thus, this study will synthesize relevant current knowledge in order to explore the diagnostic utility of active electrophysiological techniques, and to provide evidence-based recommendations for clinical use based on the strengths of task robustness, quality of studies’ risk of bias and evidence of responder rates and feasibility with regard to subject exclusion rates.

2. Methods
Recommendations for systematic reviews will be followed \(^ {57-59}\). To ensure transparent and complete reporting of the review, the PRISMA guidelines will be followed \(^ {60-62}\).

2.1. Criteria of relevance for studies included
Studies will be selected according to the criteria outlined below:

- Electrophysiological methods used in combination with experimental paradigms encompassing active contrasted to passive task conditions.
• Empirical studies, no case reports.
• Publications in English.
• Use of standardized behavioral assessment scales for diagnosis of consciousness level (CRS-R, WHIM, SSAM, WNSSP, DOCS or SMART).
• Studies published after the publication of consensus-based criteria for diagnosing MCS, i.e. 2002.
• Studies N> 5 subjects.

We will exclude literature reviews and systematic reviews.

2.2. Criteria for patients included
We will include studies investigating patients who meet the diagnostic criteria for VS and MCS after acquired brain injury, where level of consciousness is established with standardized behavioral assessment tool with acceptable psychometric properties, either the CRS-R, WHIM, SSAM, WNSSP, DOCS or SMART scales.

2.3. Data collection and analysis
Studies will be searched for in the following databases:
• Medline
• Embase
• PsycINFO
• Database of Abstracts of reviews of effects (Cochrane Library).
• Cochrane Central Register of Controlled Trials (Cochrane Library)

This search will be repeated immediately prior to submission to locate any additional recent publications.

2.4. Search terms applied
The specific search strategies will be created in collaboration with a Medical Science Librarian with expertise in systematic review searching. Primary search terms we will use defining DoC are: Consciousness disorder, disorder of consciousness, vegetative state, persistent vegetative state, unresponsive wakefulness syndrome, or minimally conscious state. Each of the primary terms will be paired with secondary terms defining aspects of electrophysiological measurement: electrodagnosis, electrophysiology, neurophysiology, electroencephalography, encephalogram, EEG, myography, or electromyography. These will be paired with third terms related to measure outcome: Event Related Potentials, ERP, evoked potentials, P300, active task/condition/paradigm, residual function, covert attention/awareness/cognition or command-following.

In Medline, systematic search strategies will include primary, secondary and third search terms in both medical subject headings (MeSH) and in title/abstract. Search will be conducted sequentially by employing each primary term with the Boolean operator AND in combination with each secondary and third term. Filter terms (year from 2002-current; English language) will be used to eliminate irrelevant articles. The search terms will be tested to check that they effectively locate the types of articles that are consistent with the inclusion criteria prior to conducting the search in all engines. A draft Medline search strategy is included in Appendix 1. After the Medline strategy is finalized, it will be adapted to the syntax and subject headings of the other databases. As relevant studies are identified, reviewers will check for additional relevant cited and citing articles. If necessary, personal communication with first authors will be conducted to obtain further relevant data that are not included in the primary study, i.e. individual subject data.

2.5. Selection of studies
We will evaluate all studies applying electrophysiological methods, and experimental designs encompassing active compared to passive task conditions in order to investigate residual cognitive capacity in patients with DoC. Only original research articles will be included. Titles will be reviewed first, followed by assessing abstracts where titles indicate relevance (and where necessary assessing the entire paper), using the inclusion and exclusion criteria to exclude those papers that were not relevant to this review. The initial selection will be conducted by one author (SLH), and double-checked by an independent second author (ML). Any disagreements will be resolved by consensus or by discussion with a third reviewer (author SA). Each selected article will be entered into a reference management database (Endnote). After the initial search, all articles identified in subsequent searches will be checked against the articles in the summary table and duplicates will be excluded during the search process. A summary table will be established throughout the searching process and each article that meets the inclusion criteria will be summarized in this table. Data will be extracted by two authors (SLH & ML), and any disagreement will be resolved by consensus or by discussions with an additional author (SA). Abstracted data will include diagnostic information, methodology, study design details, number of included/excluded subjects, rates of individual responders, and false negatives.

2.6. Quality appraisal of retrieved literature
Quality appraisal of the retrieved literature will be conducted using of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). This is a tool for assessment of the risk of bias of included studies in systematic reviews of diagnostic accuracy. It comprises 4 domains; patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concerns regarding applicability. A judgment of the possible risk of bias on each of the domains will be made from the extracted information, rated as ‘high risk’ or ‘low risk’. If there is insufficient detail reported in the study we will judge the risk of bias as ‘unclear’ and the original study investigators will be contacted for more information. As recommended, the QUADAS-2 signaling questions will be tailored to fit the objectives of this specific review. The authors SLH and ML will independently conduct the quality appraisal of each included primary study, and any disagreement will be resolved by consensus, or a third author will make the final conclusion (SA). We will compute graphic representations of potential bias within included studies. All authors will read, provide feedback and approve the final protocol.

3. Outcome
The primary outcome of the review will be addressing the status of clinical diagnostic utility of electrophysiological studies with active task paradigms in DoC. The review will specifically explore to what degree these methods seem to provide clinically significant supplementary information of the patient’s capacity for volitional cognition compared to behavioral rating scales. To address task robustness we will evaluate the rate of responders in active tasks, both in healthy control subjects and DoC patients. Regarding utility in detecting residual covert cognitive processing at an individual level in patients with DoC, we will address both rates of individual responders as well as rates of false negatives, meaning failure of electrophysiological techniques to detect command following in DoC patients with unequivocal behavioral signs of command following.

3.1. Synthesizing results
A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies. The
narrative synthesis will explore the relationship and findings both within and between the included studies. We expect that the studies included in the review will be characterized by heterogeneity in study design along with variability in the robustness of active tasks used. Hence, we anticipate that meta-calculation of sensitivities and specificities across varying methods and experimental conditions may be ineffectual. Sensitivity is here understood as the ability to detect electrophysiological signs of consciousness in patients with discernible behavioral signs of consciousness. Moreover, we are interested in probing the sensitivity of electrophysiological techniques to detect command-following in DOC patients with robust behavioral signs of command following (MCS+). As noted, the rate of false negatives are also of clinical interest, that is cases of clear behavioral signs of consciousness that are not verified electrophysiologically. Specificity will also be explored, and is understood as the ability of electrophysiological techniques to confirm VS, by the lack of both electrophysiological and behavioral signs of consciousness. We are also interested in investigating the specificity of electrophysiological techniques to accurately identify patients who show low-level signs of consciousness (e.g. visual pursuit), but not behavioral command-following (MCS-), and whom fail to demonstrate neurophysiological signs of command-following. However, as there is no established veridical benchmark of level of consciousness, a precise estimate of sensitivity and specificity across studies may therefore be regarded as challenging to establish. Thus, the diagnostic accuracy in electrophysiological techniques ability to disentangle VS from MCS, and even more specifically MCS+ from MCS-/VS, is to be questioned.

4. Funding
This systematic review is supported by the Norwegian Extra Foundation for Health and Rehabilitation through EXTRA funds (Grant 2012/2/0084). The funding partner has no involvement in the methodological aspects of the project, such as the design of the project’s protocol, or the collection, analyses and interpretation of the data.

References