Clinical Implementation of Functional MRI and EEG to Detect Cognitive Motor Dissociation: Lessons Learned in an Acute Care Hospital

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Abbreviations: BOLD *blood-oxygen-level dependent;* CMD *cognitive motor dissociation*; CRS-R *Coma Recovery Scale-Revised*; DoC *disorders of consciousness;* EEG *electroencephalography*; fMRI *functional magnetic resonance imaging;* FDA *Food and Drug Administration;* FSL *FMRIB's Software Library;* MGH ECP *Massachusetts General Hospital Emerging Consciousness Program*

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Abstract

Cognitive motor dissociation (CMD) occurs when patients with disorders of consciousness (DoC) resulting from severe brain injury demonstrate the ability to follow commands on task-based functional MRI (fMRI) or EEG assessment despite demonstrating no behavioral evidence of language function on bedside assessment. Recognizing the diagnostic and prognostic value of identifying patients with CMD, evidence-based guidelines published in the United States and Europe now recommend that these assessments are conducted as part of clinical care in patients for whom the behavioral assessment is ambiguous. We describe our experience evaluating patients with DoC for CMD using task-based fMRI and EEG. Although our center, and others, have used these tests in a research capacity for more than a decade, implementing them for clinical use posed multiple challenges and opportunities for innovation. We now have an institutionally supported, standardized, and effective approach for conducting clinical assessments of CMD and present lessons learned in this process so that other centers can more easily implement these evaluations. Among the key lessons are the need to consider ethical implications of clinical assessment for CMD; garner support of peers and departmental leadership; establish local standardized protocols for patient selection, data acquisition, analysis, and interpretation; and develop systems of effective communication of test results to families and clinical teams. As consensus or independent validation of optimal methods to assess CMD have not yet been established, the approach described is intended to be flexible, allowing for iterative improvements as more evidence becomes available.

Introduction

For patients with severe brain injury, failing to detect signs of consciousness could lead to inaccurate diagnosis, prognosis, and treatment, including premature withdrawal of life sustaining therapy or limited access to rehabilitative care. Assessment of consciousness relies primarily on the behavioral examination, which is typically conducted using non-standardized testing procedures and results in approximately 40% of patients who retain consciousness being misdiagnosed as unconscious.[1] Standardized behavioral measures such as the Coma Recovery Scale-Revised (CRS-R)[2, 3] decrease misdiagnosis rates but remain susceptible to confounding factors that may mask consciousness.[4]

Over the past two decades, advanced diagnostic tools (e.g., task-based functional magnetic resonance imaging [fMRI] and electroencephalography [EEG]) aimed at detecting consciousness have consistently demonstrated that 15-20% of patients who are behaviorally unresponsive respond to commands (e.g., “imagine playing tennis”) covertly.[5-8] This phenomenon, known as cognitive motor dissociation (CMD),[9] has been observed in patients with disorders of consciousness (DoC) across etiologies and recovery trajectories.[10, 11] Though task-based fMRI and EEG both have methodological limitations, [12, 13] when combined with behavioral assessments, these approaches are poised to decrease DoC misdiagnosis and improve prognostic precision.

Prior to 2018, task-based fMRI and EEG assessment of consciousness were conceptualized as research tools used only at institutions with access to specialized infrastructure and personnel trained to acquire, analyze and interpret the data.[5-8, 10, 14-16]

However, guidelines co-sponsored by the American Academy of Neurology (AAN), American Congress of Rehabilitation Medicine (ACRM), National Institute on Disability, Independent Living and Disability Research (NIDILRR)[2] now recommend that that these techniques *may* be considered when patients present with ambiguous behavioral findings. The European Academy of Neurology (EAN)[17] guidelines more generally recommend that task-based fMRI and EEG paradigms are considered as part of multimodal assessment in patients without command following at the bedside. Notably, the United Kingdom Guidelines do not recommend clinical use of these techniques for diagnosis[18] though debate about these recommendations persists[19, 20] (see Supplementary Table 1). Clinical use of these tools is further recommended by organizations such as the Neurocritical Care Society's Curing Coma Campaign[21] and the International Federation of Clinical Neurophysiology.[22] Thus, task-based fMRI and EEG are now placed squarely in the realm of clinical assessment of DoC, accelerating the need to address challenges associated with their implementation.

In response to receiving an increasing volume of requests from local clinicians to perform clinical evaluation of CMD, we established the Massachusetts General Hospital Emerging Consciousness Program (MGH ECP) in January 2020. The goal of this program is to provide guideline-informed care to patients with DoC, and to support their families with state-of-the-art diagnostic and prognostic information. In our efforts to integrate CMD detection into clinical assessment of patients with DoC, we learned valuable lessons that we present here for the clinical community.

Lesson 1: Ethical Considerations Warrant Explicit Deliberation when Conducting Task-based fMRI and EEG to Detect Consciousness after Severe Brain Injury

Essential ethical considerations emanate from decisions to conduct advanced fMRI and EEG assessments to detect and predict recovery of consciousness following severe brain injury.[23-25] These considerations proceed from the fundamental principles of biomedical ethics, including respect for patient autonomy, beneficence, non-maleficence, and justice. Accordingly, the provision of advanced assessments to behaviorally unresponsive patients following brain injury may be consistent with the framework that clarifying a patient's level of consciousness is intertwined with fundamental human and civil rights.[26] When and how these assessments ought to be used; how to responsibly communicate results; approaches to equity and disparities in access; and how to capture the benefits of these technologies while safeguarding against unintended harms are issues requiring proactive ethical consideration.[27, 28]

Task-based fMRI and EEG, and the expertise needed to process and interpret results in the context of DoC, are readily available in a select few medical centers around the world, leaving most patients who could potentially benefit from these assessments without access.[29] This predicament may generate moral distress for clinicians who are aware of the potential utility of these assessments and of their endorsement by professional society guidelines yet remain fundamentally unable to offer them. Furthermore, inequitable access to these tools underscores systemic disparities that require pragmatic solutions to democratize the availability of advanced consciousness assessments.[27] When advanced assessments for behaviorally unresponsive patients are unavailable, clinicians

and surrogates remain uninformed about the potential for CMD, magnifying the likelihood of misdiagnosis and goal-discordant decision making. On the other hand, the effect on surrogates of increased uncertainty, which may result when behavioral, fMRI, and EEG diagnoses are discordant, is not known, requiring sensitive and prospectively considered approaches to data sharing and communication.

Lesson 2: Establish Institutional Consensus for Implementing Guideline Recommendations for Use of Task-Based fMRI and EEG in DoC Clinical Management

Published guidelines supporting use of advanced fMRI and EEG for clinical assessment of CMD do not provide direction for the use of these techniques. We developed a proposal to apply the guidelines locally and sought the support of the leadership and core clinical teams within the Departments of Neurology and Radiology. The hospital's administrative leadership was then engaged to facilitate implementation. The implementation phase included hosting information sessions for clinical teams to provide education about these techniques, their application to specific clinical cases, and operational procedures for ordering the tests. In planning, a common concern among some of our colleagues was the lack of independent validation of these assessments and the nuance required to interpret findings. These concerns prompted us to adopt commercially available data acquisition and analysis platforms when possible, and to develop standardized guidance for interpreting results and communicating findings to families (Lessons 3, 7 and 8).

Lesson 3: Review and Understand the Regulatory Considerations Related to Transitioning from Research to Clinical Implementation of Task-Based fMRI and EEG

Task-based fMRI and EEG have been used to detect CMD in the context of research for nearly two decades. U.S. Food and Drug Administration (FDA)-approved software is available for analysis of fMRI data related to presurgical planning, but the blood-oxygen-level dependent (BOLD) fMRI sequence parameters and analytic processes may not be optimized to detect CMD. Nevertheless, because our local institutional policy does not permit clinical use of radiologic tools developed for research applications, we converted our fMRI paradigms into a format that is compatible with BrainLab Elements BOLD MRI mapping (iPlan Cranial 3.0.6.14, AG Munich Germany), a commercially available fMRI package used at MGH. Our initial evaluation of the presence of CMD is based on the output of this software. We also conduct a quality assurance analysis with FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl (FSL, see Lesson 6)[6] to quantitatively evaluate whether BOLD responses are localized to the expected brain regions. Both the use of BrainLab (or other commercial fMRI systems) for detection of CMD as well as the application of quantitative tools in FSL await independent clinical validation.

While several readily deployable and fully standardized packages exist for fMRI analysis (e.g., Prism Clinical Imaging, NordicNeuroLab, Icometrix, and Omniscient), similar FDA-approved EEG approaches are not available. We acquire EEG data with FDA-approved clinical devices but continue to use previously published investigational EEG acquisition and analytic pipelines[6, 8, 30] for data analysis of clinical data (see Lesson 5). As with fMRI,

independent clinical validation and standardization of the EEG analytic tools to detect CMD is needed.

Lesson 4: Develop Standard Operating Procedures for Patient Selection

Assessment of consciousness via task-based fMRI and EEG may not be suitable for all patients with DoC. The AAN-ACRM-NIDILRR guidelines stipulate that patients with an "ambiguous diagnosis" after serial standardized behavioral assessments may be considered for further advanced diagnostics, while the EAN guidelines recommend advanced diagnostics for patients who do not follow commands on behavioral assessment. Neither guideline operationalizes these criteria. Recently published decision trees provide guidance on when task-based fMRI[31] and EEG[22] are indicated. In both cases, repeated, standardized assessment with a behavioral tool such as the CRS-R[3] is recommended prior to pursuing task-based fMRI or EEG. In the absence of a definition of "ambiguous diagnosis", any patient with a behavioral diagnosis of coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS) or low-level minimally conscious state (MCS-) may be a candidate for task-based fMRI and EEG. This is particularly salient in the acute care setting, where multiple known and unknown confounding factors may mask consciousness and where CMD has been detected even in patients with a behavioral diagnosis of coma.[8]

Timing of fMRI and EEG assessments should be carefully considered in the context of the clinically actionable outcomes that may result. For example, when comprehensive information is gathered prior to a family meeting about goals of care, a CMD assessment

may inform the potential for recovery and alter clinical counseling.[32] Furthermore, patients with CMD may be provided access to rehabilitative services that would otherwise be denied, and thus assessments may be appropriate prior to planning for discharge. Safety considerations that may prevent or delay acquisition of task-based fMRI or EEG data are outlined in Supplementary Materials, Supplementary Table 2.

Lesson 5 – Optimize Standardized Data Acquisition for the Clinical Setting

One of the greatest barriers to translation of task-based fMRI and EEG is their reliance on technologies that have not been standardized, clinically validated, or commercially produced. Adapting research fMRI and EEG data acquisition protocols to the clinical setting requires simplification and harmonization.

Overarching Data Acquisition Recommendations

Aside from the technological aspects of acquiring and analyzing data, we take simple, pragmatic steps to ensure high-quality data acquisition. For fMRI, we test sequences in healthy individuals who can confirm that stimuli are clearly audible above scanner noise. We conduct a sound-check prior to each patient scan and on multiple occasions identified technical issues (e.g., sound turned down, earphone clogged) that would have confounded our results. When positioning each patient in the MRI the scanner, we use padding to optimize immobilization and comfort as motion in the scanner can cause irreversible artifact. EEG studies are conducted with minimal distraction (e.g., television and radio turned off; no conversations or other interactions when possible) and interruptions for nursing care are coordinated, when possible, to occur during breaks. To

increase the likelihood of observing a volitional response, we limit sedating medications and maximize arousal with the Arousal Facilitation Protocol.[3, 33]

Task-based fMRI and EEG Data Acquisition

There is no consensus about which paradigms should be used for task-based fMRI and EEG assessment of consciousness. We selected the motor imagery command "imagine opening and closing your hand" because hand movement is often used in behavioral bedside clinical assessments and was previously shown to detect CMD in the intensive care unit.[6] We use an "OFF"/"ON" block design that is approximately 5 minutes in duration for fMRI and approximately 12 minutes for EEG. Supplementary Figure 1 and Supplementary Tables 3 and 4 provide the design and parameters of the task-based fMRI and EEG acquisitions and necessary equipment.

Lesson 6 – Optimize Data Analysis Pipelines for Rapid Results Reporting

There are no published guidelines for the optimal approach to analyzing fMRI and EEG data acquired to detect CMD. Multiple analytic strategies exist (e.g., region of interest[5, 6] versus multi-variate pattern analysis[34] for fMRI, and support vector machine learning[6, 8, 30] versus spectral analysis[7, 15, 16] for EEG). Even studies using similar strategies rarely harmonize acquisition and analytic parameters. Details of our fMRI and EEG data processing approach are provided in the Supplementary Materials.

Task-based fMRI Data Processing

Our primary analytic approach is the standard pipeline available in a commercially available fMRI software (i.e., BrainLab). Clinical images (structural and functional) are imported from the PACS imaging server into BrainLab. Basic imaging acquisition parameters (e.g., TR, stimulus block duration, etc.) are entered into the graphic-user-interface and submitted for processing. The output of a BrainLab analysis is a structural underlay in the patient's native space with a functional overlay showing areas where the BOLD signal is greater during the task (ON) as compared to the rest (OFF) blocks. The statistical thresholding can be manipulated interactively. The images are read via visual inspection which, as expected, can lead to substantial variability in the interpretation.

As a quality assurance step, in addition to the BrainLab analysis, we conduct a parallel, quantitative analysis with FSL following previously published procedures[6]. Unlike BrainLab, data in FSL can be spatially normalized into a standard space so that suprathreshold activations within pre-specified brain regions previously shown to be involved in a task can be examined. We combine bilateral supplementary motor areas (SMA) from the Harvard-Oxford Cortical Structural Atlas and premotor cortices (PMC) from the Juelich Histological Atlas to form a single region of interest. CMD is confirmed when at least one suprathreshold cluster of voxels is present within the SMA or PMC (Figure 1).

Task-based EEG Data Processing

We analyze data using EEGlab[35] and customized MATLAB code (MathWorks, Natick, MA). As in prior work[6], we use a support vector machine with a linear kernel to classify

the data matrices as corresponding to either task (ON) blocks or rest (OFF) blocks. This approach provides multiple pieces of complementary information: 1) a p-value that indicates the probability with that the classifier distinguished task from rest conditions by chance; 2) an accuracy value that indicates the classifier's performance; 3) power spectral density averaged across epochs for the ON and OFF conditions of each channel; and 4) a topological map of the contribution of each channel to classifying the conditions (Figure 2). EEG data are especially vulnerable to variations in the analytic pipeline; small changes may lead to large variations in the results. We validate our analytic pipeline in healthy control subjects and re-validate the pipeline whenever modifications are made. An independent EEG expert on our team (SC) reviewed the code for errors.

Using Research Software for Clinical Applications

We considered the multiple implications of using research software for clinical assessment of CMD. Research software is not FDA-approved and is not validated for clinical use. Results could vary based on the version of software that is used, small changes to analytic pipelines, or manual aspects of data processing such as determining whether fMRI spatial normalization has failed or if an EEG channel is corrupted by artifact. Where possible, we leverage commercial clinical tools such as BrainLab for fMRI. However, commercial tools that can quantify responses to generate a binary determination about CMD do not exist for EEG. In both cases, quantitative analysis, which we believe is critical to ensuring standardized data interpretation, is only available with research-grade software. Thus, our fMRI analysis includes complementary qualitative and quantitative analytic approaches (BrainLab and FSL) while our EEG analysis includes

only a quantitative analytic approach (support vector machine). We debated the merits of using research tools in a clinical setting and ultimately determined that these tools provide clinicians and patients' families with potentially critical information about CMD.

Lesson 7: Interpreting fMRI and EEG Results

In the absence of published guidelines for interpreting CMD results, a subgroup of authors designed a local CMD data interpretation algorithm that was quantitative, rigorous, and transparent (Figures 3 and 4). For fMRI, we aimed to achieve a balance between adhering to common neuroradiologic clinical practices (i.e., visual inspection of images - which can lead to variability in determining CMD) and leveraging a robust research literature which predominantly establishes the presence or absence of CMD by identifying suprathreshold voxels in a specific ROI. For EEG, a clinical, visual inspection approach for detecting CMD does not exist, so we rely on quantitative methods (i.e., determining the statistical significance and accuracy of a classifier that discriminates the command-following condition from a period of rest).

Our interpretation results in a determination of "probable", "possible", or "indeterminate" CMD (Figures 3 and 4). "Probable" CMD detected by task-based fMRI requires that at least one cluster of voxels in the expected ROI exceeds the most conservative (i.e., largest) statistical threshold. "Probable" CMD detected by task-based EEG requires the classifier to be statistically significant and have an accuracy of ≥ 0.6. "Possible CMD" is used when a positive result is observed, but only at a lower level of statistical stringency than what is needed for a determination of "probable" CMD. When CMD is not observed,

the result is “indeterminate” because there are many factors unrelated to consciousness that could produce a negative CMD result (Table 1). The thresholds are intended to promote internal consistency in data interpretation and serve as guides rather than prescribed cut-points. Visual inspection of the data may result in deviation from the interpretation algorithm (see Supplementary Materials). A board-certified neuroradiologist (fMRI) or electrophysiologist (EEG), make the final determination regarding the presence of CMD, often in consultation with clinicians from the MGH ECP.

The Challenge of Interpreting Negative fMRI and EEG Results

One of the paramount challenges in analyzing and interpreting stimulus-based fMRI and EEG data is the high rate of negative findings, which have been reported across studies in patients who follow-commands at the bedside[6, 14] and even in healthy control subjects.[6, 15, 36, 37] Task-based fMRI and EEG may fail to detect evidence of command-following for a variety of reasons outlined in Supplementary Table 5. It is critical that fMRI and EEG are used not in isolation, but in conjunction with serial, standardized behavioral assessment. Our approach to detecting CMD is unlikely to result in a false positive because of the rigorous statistical thresholding used in data analysis, but as a result, the potential risk of false negative results increases. Therefore, a positive result is considered meaningful while a negative result is considered “indeterminate”.

Lesson 8: Communicating Results to Families and Clinical Teams

Communicating task-based fMRI and EEG findings to patients and clinical teams requires maintaining a balance between providing the results, explaining the nuanced

interpretation of the findings, and describing the strengths and limitations of each methodology. To maximize clinical impact, our analyses are conducted within hours of fMRI or EEG, ensuring results are shared in a timely manner. Until recently, scientific evidence supported assessment of CMD primarily for diagnostic purposes. However, CMD may also be associated with a greater likelihood of recovering at least partial independence by as early as 3-months post injury and a faster time to achieving that level of function.[8, 30] Thus, we communicate the diagnostic and prognostic relevance of CMD (Table 1) while providing context around the lack of formal independent clinical validation of these approaches.

In studies by our group[6] and others,[38] families have expressed strong preferences for knowing the results of fMRI and EEG assessments, even if the results are inconclusive. Thus, with Institutional Review Board approval, we have been sharing the outcome of CMD assessments conducted in the research setting for more than 11 years. Details of our approach to communicating CMD results have been previously published.[39] Key elements include an overview of the assessments that were performed, description of the limitations of task-based fMRI and EEG, and use of visual aids to convey the results. The neuroradiology and electrophysiology teams write individual reports describing the findings that are uploaded into the patient's medical record. The clinical team incorporates findings into their overall clinical impression prior to conducting a family meeting.

Lesson 9: Integrating the Clinical Team Through Education and Training

We have found that clinicians caring for patients with DoC are engaged and interested in using task-based fMRI and EEG to better understand level of consciousness and are

appreciative of an overview of these techniques and the evidence that support their use. We provide frequent education in formal (e.g., via seminars) and informal (e.g., at the bedside or the scanner) settings on the advantages and limitations of using these approaches for detecting consciousness after a severe brain injury.

Training Required for Acquisition of Task-based fMRI and EEG Data

As with standard MRI, nursing staff, and often respiratory therapists, are required to prepare the patient for travel to the scanner and for monitoring vital signs during the scan. MRI technicians are trained to use MRI-compatible headphones and to simultaneously start the fMRI scans and the fMRI audio files. EEG technicians prepare the same standard 19-electrode montage used in routine acquisitions. An auxiliary EEG channel (e.g., DC-10) and audio-check are required. Common issues that technicians encounter and can easily troubleshoot are poorly connected cables, low volume on the amplifier or laptop/tablet, and incorrect montage selection. For both fMRI and EEG, the nurse documents arousal level and applies the Arousal Facilitation Protocol,[3, 33] as needed. Sedating medications and confounding factors (e.g., head movement and fluctuations in wakefulness) are also recorded.

Lesson 10 – Understanding Payment and Reimbursement

Insurance companies in the U.S. are not accustomed to reimbursing hospitals for task-based fMRI and EEG for patients with DoC. However, multiple Current Procedural Terminology (CPT®) codes may be applied for the technical and professional fees associated with task-based fMRI and EEG data acquisition and interpretation.[40] We

confirmed with our medical billing department that our institution has billed and received reimbursement for these services where appropriate.

Discussion

We describe clinical implementation of task-based fMRI and EEG for detection of CMD at an academic medical center. These procedures are carried out as part of the MGH ECP mission to deliver guideline-informed care for patients with DoC. Clinical guidelines recommending the use of advanced fMRI and EEG approaches for detecting consciousness in some patients were released more than five years ago.[2] Nevertheless, implementation of these guidelines has been slow due to limited clinical validation and commercially available products to streamline standardized data acquisition and analysis. The lessons we learned in establishing a clinical protocol for detection of CMD may be translatable to other healthcare systems, but we also recognize that expanding access to these assessments will require concerted regulatory and implementation efforts.

Figure Legends:

Figure 1. **fMRI Results of a Motor Imagery Task in a Healthy Individual and Patient with a Behavioral Diagnosis of Vegetative State**. A healthy individual (left panel) and a patient with a diagnosis of vegetative state on the Coma Recovery Scale-Revised (right panel) completed an fMRI motor imagery task consisting of the command to "imagine opening and closing your right hand". fMRI data analyzed using a commercial platform (A,C) and research tools (B,D) show activations (red clusters which are areas that exceed the statistical threshold of T=3.1 [A,C] and Z=3.1 [B,D]) within supplementary and premotor areas. When data are analyzed using research tools, a region of interest mask composed of the supplementary motor area and premotor cortex (blue area in B,D) can be used to quantitatively confirm the location of the areas of activation.

Figure 2. **EEG Results of a Motor Imagery Task in a Healthy Individual and Patient with a Behavioral Diagnosis of Vegetative State**. A healthy individual (left panel) and a patient with a diagnosis of vegetative state on the Coma Recovery Scale-Revised (right panel) completed an EEG motor imagery task consisting of the command to "imagine opening and closing your right hand". In both cases, the classifier discriminated between the "ON" condition (i.e., imagine) and "OFF" condition (i.e., stop imagining). Cognitive motor dissociation for the patient is "possible" rather than "probable" because the accuracy is not ≥ 60% (see Figure 4). In the topographic plots, hot colors (e.g., saturated red) are associated with electrodes that discriminate between the "ON" and "OFF" conditions.

Figure 3. **Task-based fMRI Data Interpretation Algorithm**. Data are visually inspected for evidence of artifact (e.g., from motion, metallic implants). Data are then analyzed using a commercially available fMRI software and visualized with a statistical threshold (T=3.1, p~0.001). If suprathreshold activations are observed, Research FSL software (e.g., FSL) is used as a quality assurance check to evaluate whether activations are within the expected regions associated with the task (e.g., supplementary motor area and premotor cortex). If activations are not observed using commercial software or are not within the prespecified region of interest, the statistical threshold is decreased to T=2.35 (p~0.01). The final interpretation of probable (green box) or possible (beige box) cognitive motor dissociation (CMD) is related to the threshold at which activations are observed as well as their location. No activations in supplementary motor area (SMA) and premotor cortex (PMC) are interpreted as an "indeterminate" result (red box). The number in the brackets of each colored box is linked to an interpretation of the result provided in Table 1. Note: The T- and Z-statistics have slightly different meanings (e.g., only the Z-statistic is corrected at the cluster level) but the thresholds are the same to maximize consistency.

Figure 4. **Task-based EEG Data Interpretation Algorithm**. Data are visually inspected for evidence of artifact (e.g., from motion). Data are then analyzed using an EEG support vector machine classifier. If the classifier significantly differentiates the Task "ON" ("imagine") from the Task "OFF" ("stop imagining") conditions (i.e., $p<0.05$), the accuracy is evaluated to establish whether cognitive motor dissociation (CMD) is probable (green box) or possible (beige box). If the classifier does not differentiate the two conditions

($p \geq 0.05$), the result is indeterminate (red box). The number in the brackets of each colored box is linked to an interpretation of the result provided in Table 1.

Table 1: Sharing fMRI and EEG Results with Families and Clinicians		
Scenario	**fMRI or EEG CMD Result**	**Interpretation**
1	Data quality unacceptable or irreparable analytic errors	Factors such as excessive motion, signal drop-out from a ventricular peritoneal shunt (fMRI), or poor spatial registration (fMRI) prevent data analysis and interpretation.
2	Indeterminate	Negative results should not be interpreted as an "inability to follow commands" because many factors can contribute to a negative response (e.g., fluctuating arousal, normal variability in brain responses, motion artifact, sedation, task complexity, etc).
3	Possible	Despite the absence of evidence for language function on behavioral exam, the patient may be able to understand language and follow commands.
4	Probable	Despite the absence of evidence for language function on behavioral exam, the patient probably understands language and follows commands; in patients with acute disorders of consciousness, CMD may be associated with a greater likelihood of achieving at least partial independence.

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Figure 1

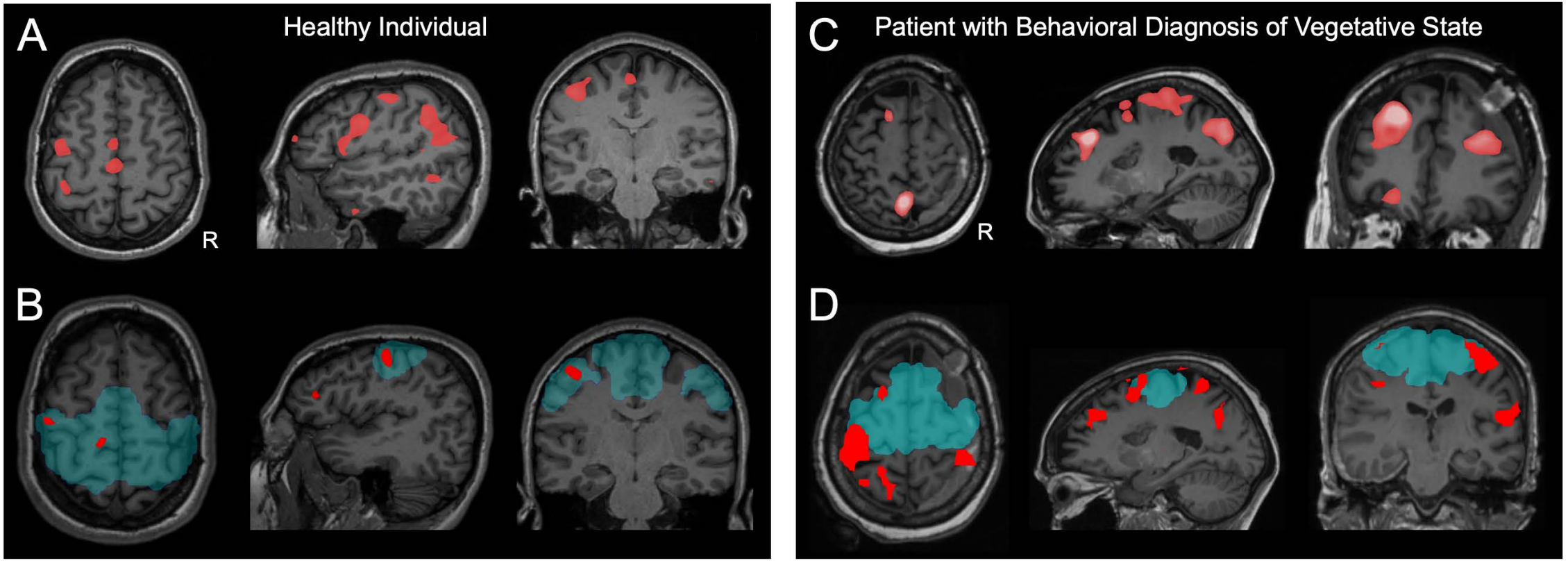

A
Healthy Individual
R
B
C
Patient with Behavioral Diagnosis of Vegetative State
R
D

Figure 2

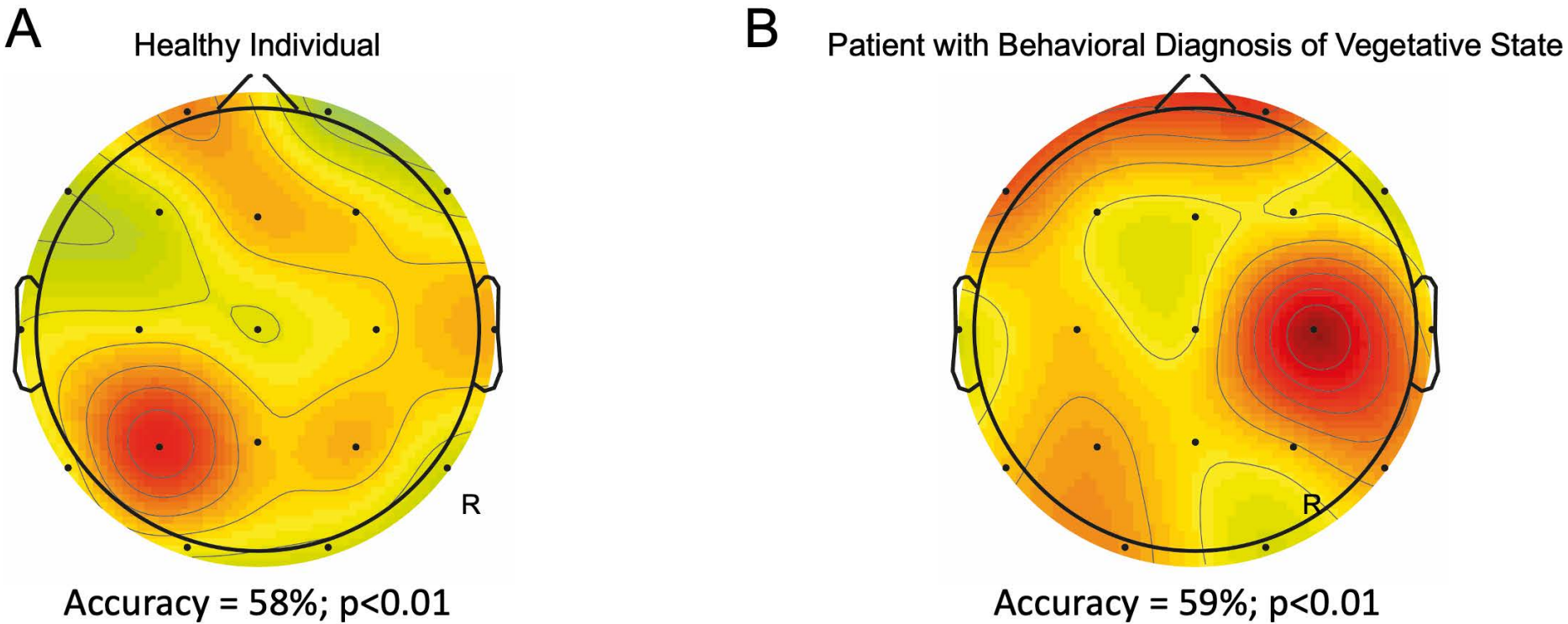

A
Healthy Individual
R
Accuracy = 58%; p<0.01
B
Patient with Behavioral Diagnosis of Vegetative State
R
Accuracy = 59%; p<0.01

Figure 3

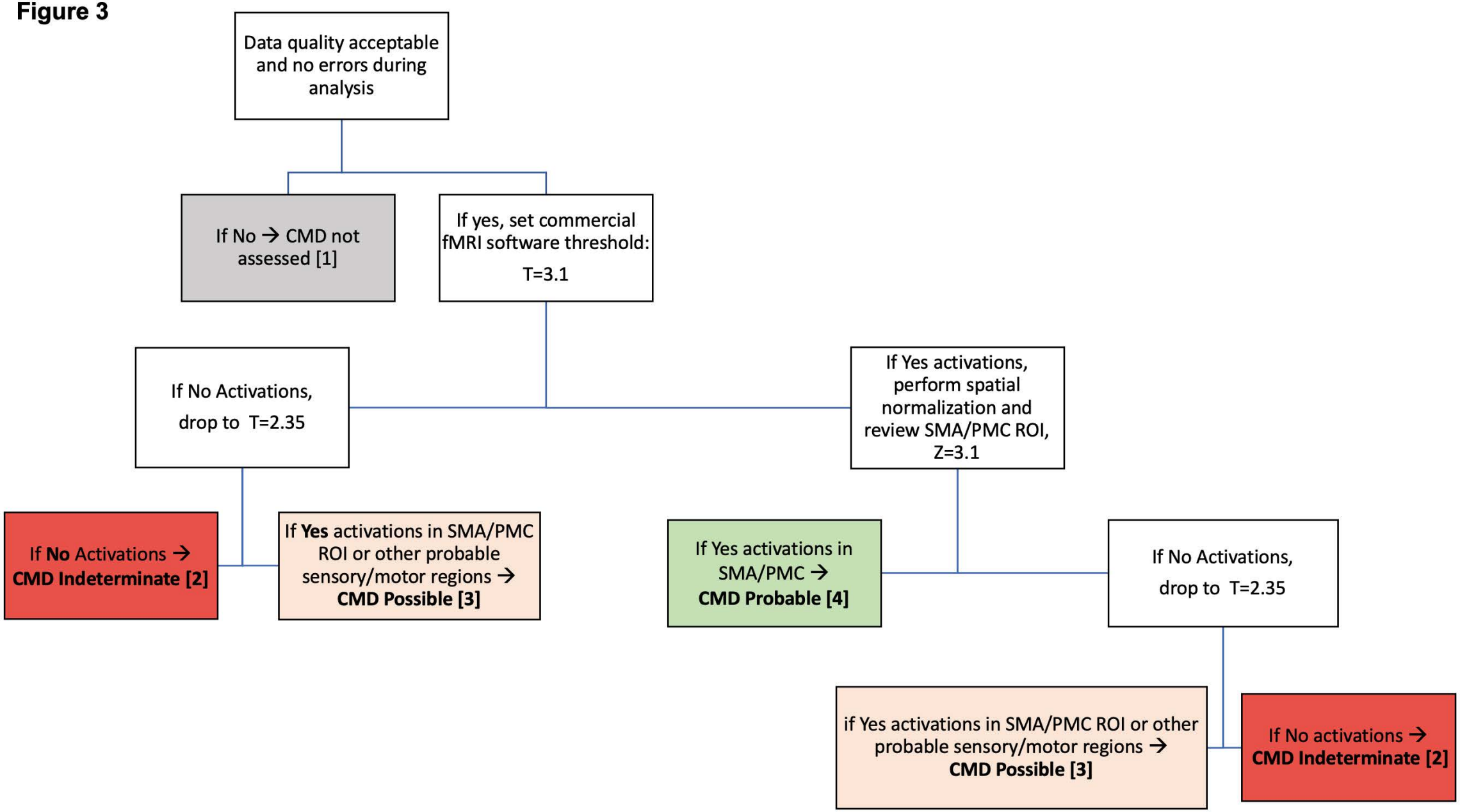
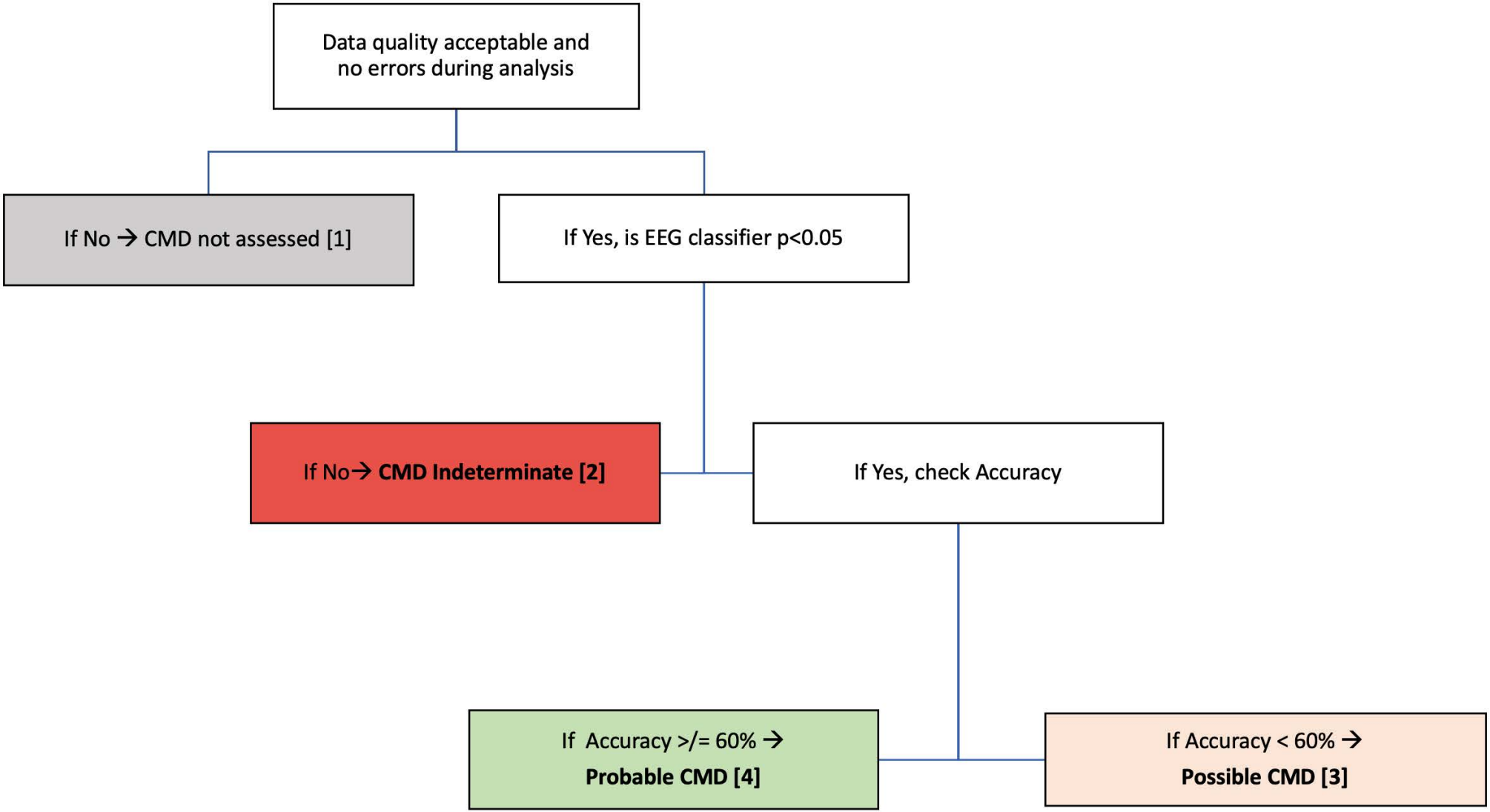

Data quality acceptable and no errors during analysis
If No → CMD not assessed [1]
If yes, set commercial fMRI software threshold: T=3.1
If No Activations, drop to T=2.35
If Yes activations, perform spatial normalization and review SMA/PMC ROI, Z=3.1
If **No** Activations → **CMD Indeterminate [2]**
If **Yes** activations in SMA/PMC ROI or other probable sensory/motor regions → **CMD Possible [3]**
If Yes activations in SMA/PMC → **CMD Probable [4]**
If No Activations, drop to T=2.35
if Yes activations in SMA/PMC ROI or other probable sensory/motor regions → **CMD Possible [3]**
If No activations → **CMD Indeterminate [2]**

Figure 4


Data quality acceptable and no errors during analysis
If No → CMD not assessed [1]
If Yes, is EEG classifier p<0.05
If No→ CMD Indeterminate [2]
If Yes, check Accuracy
If Accuracy >/= 60% → Probable CMD [4]
If Accuracy < 60% → Possible CMD [3]

Clinical Implementation of Functional MRI and EEG to Detect Cognitive Motor Dissociation: Lessons Learned in an Acute Care Hospital

Supplementary Materials

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Supplementary Text

Lesson 4: Develop Standard Operating Procedures for Patient Selection

The risks of task-based functional MRI (fMRI) are generally the same as for standard MRI, with contraindications including intracranial pressure monitor, ferrous implants, and other metallic fragments. We have also encountered temporal lobe fractures that prevent the use of headphones, in which case a speaker system may be used to deliver auditory stimuli. While some ventriculoperitoneal (VP) shunts may be safe in MRI scanners, the echo planar imaging sequences required to obtain blood-oxygen level dependent (BOLD) fMRI data are particularly sensitive to the artifact produced by the shunt, and data may be uninterpretable. The patient must be medically stable to travel, whether this requires transport from the ICU room to the scanner or from an outside facility to a facility that has fMRI and EEG capabilities. For patients with acute brain injuries and a concern for increased intracranial pressure or frequent suctioning requirements, we typically perform a "flat trial" in the ICU to determine if the patient can safely tolerate lying supine for an MRI scan. EEG poses fewer safety risks, though scalp burns and extensive scalp wounds may prevent electrode application. For both fMRI and EEG, involuntary movements such as bronchospasm or bruxism may lead to motion or muscle artifacts, respectively, rendering the data uninterpretable. Our task-based fMRI and EEG paradigms also rely on an intact auditory processing system, which may be affected by the injury.

Lesson 5: Optimize Standardized Data Acquisition for the Clinical Setting

Selection of the Task

There is no standard task that is used to detect CMD, although motor imagery has been used most often. There is some indication that an instruction to "open and close your hand" rather than "imagine opening and closing your hand" may yield meaningfully different cortical activity,[1] but the standard to-date for fMRI research has been to instruct imagined command-following, in part because of the potential for motion artifact resulting from attempts to move the hand in the MRI scanner. For consistency, we chose to use the imagined command for EEG as well, although motion artifact is less of a concern for EEG.

Task-based EEG Data Acquisition

Data are acquired on a Nexus Xltec system at a sampling rate of at least 256 Hz; data acquired at sampling rates higher than 256 Hz are down-sampled to 256 Hz during the pre-processing analysis. We use a standard 19-electrode banana montage (XLTEK EEG system, Natus Medical Inc.) that is applied by the EEG technician. An mp4 video file that is pre-loaded onto a device (laptop, tablet, or smartphone with a VLC media player that has chapter marker capabilities) provides guidence to the EEG technologist for setting up the equipment (Supplementary Table 4) and troubleshooting a variety of issues. The device is connected via an auxiliary channel to the EEG system (e.g., DC-10 channel) which allows for visualization and alignment of the task instructions to the EEG data. An ARTcessories HeadAmp box amplifier connected to headphones standardizes the volume of the instructions provided to the patient. The EEG acquisition is immediately preceded by the Arousal Facilitation Protocol,[2, 3] a standardized procedure developed as part of the Coma Recovery Scale-Revised (CRS-R)[3] that is designed to promote wakefulness and optimize responsivness.

It is important that 30 uninterrupted minutes are available for EEG data acquisition as distractions (e.g., family members in room, television or radio) and clinical interventions may confound the EEG recording. When interruptions are unavoidable, it is recommended to coordinate them to occur between task periods. A sign on the patient's door and education of the clinical team facilitates acquisition of high-quality EEG data.

The start and end of the paradigm must be annotated on the EEG tracing to subsequently select and export only the EEG recording related to the paradigm. To analyze the data, the Natus EEG clinical

system allows acquired data to be converted from the proprietary *.stc* format to the European Data Format (EDF, and EDF+) and a .txt file that contains the annotations recorded.

Lesson 6: Optimize Data Analysis Pipelines for Rapid Results Reporting

Task-based fMRI Processing

In addition to using the BrainLab Elements BOLD MRI mapping (iPlan Cranial 3.0.6.14, AG Munich Germany) software to determine CMD, we conduct a complimentary FMRIB's Software Library (FSL) quantitative analysis. fMRI data are transferred from the clinical scanner to an on-site server designed specifically for storing and processing advanced MRI data. Our fMRI analysis pipeline is carried out in FMRI Expert Analysis Tool (FEAT) version 6.06 in FSL 5.0.7 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, FSL). All data processing is conducted within the BIDS[4] framework to ensure standardization of data storage and analysis.

Briefly, pre-processing steps include: 1) data conversion from DICOM to nifti file format; 2) reorientation of nifti files into FSL space; 3) stripping the skull away; 4) slice-time correction, and 4) generating a motion outlier file. First-level analysis transforms the data into a standard template space (MNI152) and convolves each fMRI run with a canonical hemodynamic response function contrasting the periods following the instruction to open and close the hand with the periods following instruction to stop opening and closing the hand. We combine an individual voxel Z-threshold of ≥ 3.1 with a cluster threshold of $p \leq 0.05$ to generate statistically conservative BOLD response maps. In a final step, we use Featquery to identify whether any suprathreshold voxel clusters are within a pre-specified region of interest (ROI) that combines bilateral supplementary motor areas (SMA) from the Harvard-Oxford Cortical Structural Atlas and premotor cortices (PMC) from the Juelich Histological Atlas[5] into a single region.

EEG Processing

We analyze data using EEGlab (Delorme and Makeig, 2004) and customized MATLAB code (MathWorks, Natick, MA). Starting from raw (EDF) the data of the 3 recording blocks are concatenated and stored in an EEGlab structure format (.fdt and .set files). All recordings are high-pass filtered (third-order Butterworth, zero-phase shift digital filter, 1Hz) prior to a visual channel and epoch inspection. Epochs of 1 second are re-referenced to the average before eye-movement and muscle activity are removed using independent component analysis (ICA). Then, data are low-pass filtered at 30Hz (third-order Butterworth, zero-phase shift digital filter), if needed down-sampled at 256Hz, and re-referenced using the Hjorth Laplacian transform to optimize spatial localization and avoid contaminating activity at the reference.[6]

Power spectral density is calculated for each epoch and channel using the Chronux toolbox (1 taper, frequency resolution of 1Hz). Absolute power estimates are averaged within four frequency bands [delta (1–3 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz)], resulting in a matrix used for classifier analysis.

As in prior work,[7] we use a support vector machine with a linear kernel[8] to classify the data matrices as corresponding to either stimulation blocks (ON) or rest blocks (OFF). A 20-fold cross-validation procedure is repeated 10 times to ensure a stable classifier accuracy estimate. For each of the 10 iterations of the cross-validation, we randomly generate 20 partitions of each subject's data matrix and use 19 folds for training and the 20th fold for evaluation. We repeat this process 20 times for each partition. The average accuracy across these 10 iterations of the cross-validation is used for further analysis. To test for significance, we perform a permutation test[9] based on 500 permutations[10] where the data labels are exchanged (ON versus OFF) and the shuffled labels train and evaluate a classifier following the same procedure we used on the original data. The p-value is the sum of all accuracies

from the permuted data that are equal to or higher than the accuracies from the original (i.e. non-permuted) data, divided by the number of permutations.[11]

While the abovementioned preprocessing steps are commonly used to remove typical EEG artifacts (i.e., eye movements, eye blink, and muscular activity), the feature extraction is based on power spectra because imagined movements produce an increase (event-related synchronization, or ERS) and/or decrease (event-related desynchronization, ERD) in spectral power of the μ (about 7–13 Hz) or β (about 13–30 Hz) frequency bands over central electrodes.[12] This support vector machine approach yields optimal classification results in healthy participants when compared with other tools[13] and provides a p-value and accuracy that are easily interpretable.

Lesson 7: Interpreting Task-based fMRI and EEG Results

Interpreting Task-based fMRI Results

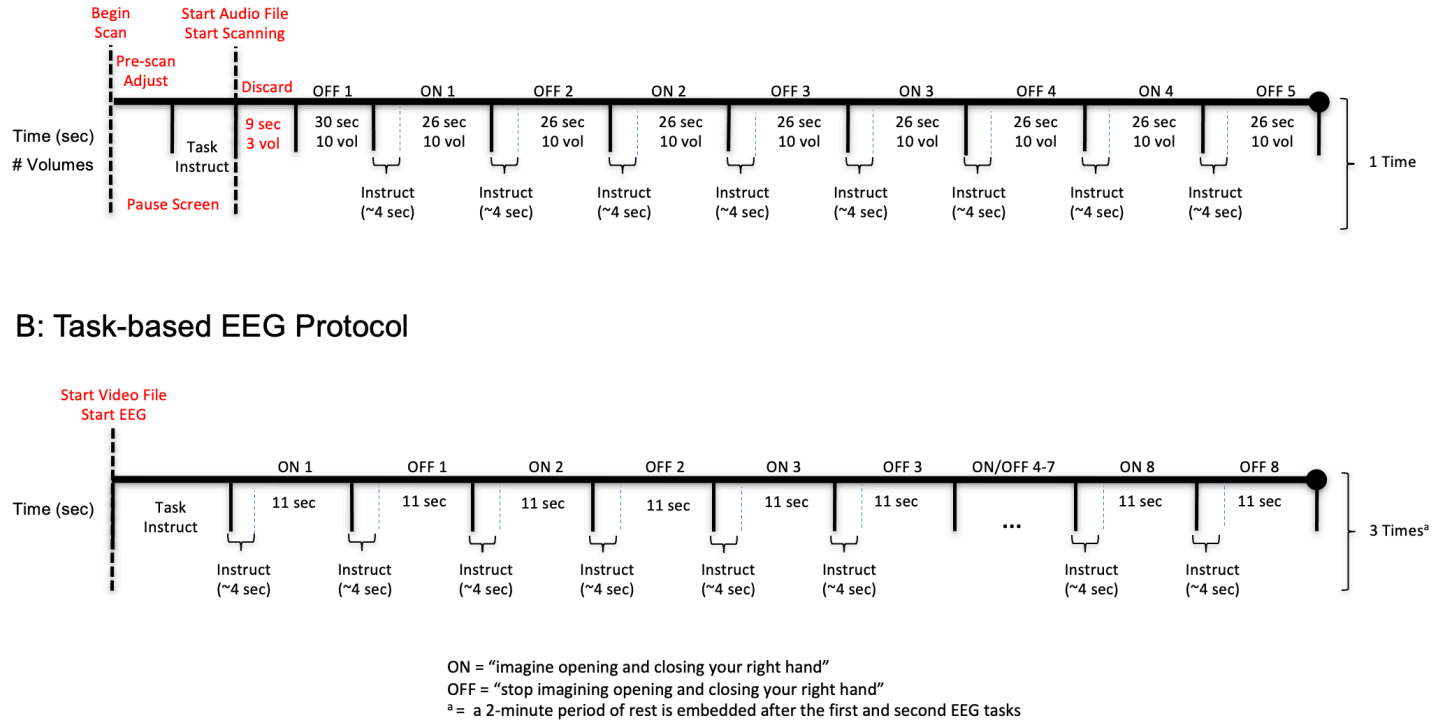
Aside from a clear, specific suprathreshold activation within the SMA-PMC ROI, multiple patterns of activation suggesting the potential for CMD may be observed. For example, a cluster of activation just outside the ROI would not lead to a determination of "probable" CMD, but may lead to a determination of "possible" CMD based on the data interpretation algorithm in Figure 3. Such an observation may be attributed to: 1) normal individual variability in responses to the motor imagery task; 2) functional reorganization of cortical regions underlying command-following due to injury to the primary regions; 3) misalignment between the structural MRI, fMRI and ROI (i.e., the area of activation is in the expected region, but there was an error in spatial registration of the ROI to the MRI data during pre-processing; or 4) the motor imagery task elicits cognitive processes unrelated to covert command-following (e.g., networks involved in attention and memory). We have also observed suprathreshold clusters both within the SMA-PMC ROI and non-specifically across the entire brain which may reflect the involvement of multiple cognitive processes in the motor imagery paradigm or false positive activations.

Interpreting Task-based EEG Results

The support vector machine permutation test generates a p-value that represents the probability with which the classifier differentiated the EEG response to the command condition from the EEG response to the rest condition by chance. A p-value <0.05 suggests less than a 5% chance that the two conditions were differentiated by chance, and therefore provides evidence of covert command-following, which is used to establish the CMD diagnosis. However, it is important to consider the p-value in the context of the accuracy, which is a metric also provided by the EEG analysis. Accuracy must exceed 50% for the classifier to statistically differentiate the conditions. However, in some cases, a significant p-value is associated with an accuracy that is only slightly greater than 50%, suggesting that the cerebral activity provided to the support vector machine can differentiate between command and rest in only slightly more than half of the instances.

High classification accuracies require either near perfect performance or long periods of data acquisition, which is infeasible in the acute care setting. Therefore, a visual examination of the topographic map and power spectral density is recommended to better interpret the p-value and accuracy results, especially when accuracy is low (i.e., 51-60%). Confidence in the finding is increased if the topographic map reveals that the electrodes with the most significant contribution to the classifier are located over central areas, although considerable spatial variation in EEG power modulation has been found in patients with DoC.[14] If a modulation of the spectral curves is observed in the beta range (>20 Hz) over occipital and/or frontotemporal electrodes, the presence of confounding muscular activity should be carefully ruled out.[15]

Supplementary Figure 1



Supplementary Figure 1. Protocol Design for Task-based fMRI and EEG. The task-based fMRI paradigm (A) consists of 9 30-second "ON"/"OFF" conditions. During the "off" condition the patient hears only the noise inherent to the MRI scanner. During the "ON" condition, the patient hears a short instruction (Instruct) to "imagine opening and closing your right hand" for 4 seconds and, 26 seconds later, a short instruction to "stop imagining". After the scan begins and pre-scan adjustments are made, the scanner protocol pauses, and the detailed task instructions are played. When the scan starts again, it is synchronized with the start of an audio file that is pre-recorded with the paradigm. First there is 39 seconds of silence (scanner noise). Data from the first 9 seconds of this period are discarded in the data analysis and data from the subsequent 30 seconds constitute the first "OFF" block. Then the instruction to "imagine opening and closing your right hand" is heard, and the paradigm continues with 30-second blocks. The entire task is 4 minutes and 39 seconds long (not counting the initial detailed instruction that precedes the start of the scanning). The task based EEG paradigm (B) consists of 16 "ON"/"OFF" conditions. During the "OFF" condition there is silence. During the "ON" condition, the patient hears an instruction to "imagine opening and closing your right hand" and, 11 seconds later, an instruction to "stop imagining". After the EEG audio file is started, the detailed task instructions are heard followed by the first "ON" condition. The paradigm is 4 minutes long (not counting the initial detailed instruction) and is repeated an additional two times for a total duration of 12 minutes.

Supplementary Table 1: Comparing Clinical Guidelines on the Use of Task-based fMRI and EEG for Detecting Consciousness			
Guideline/Document	**Recommendation- direct quote**	**Additional Rationale- direct quote**	**Considerations**
AAN/ACRM/NIDILIRR: Summary of Evidence-based Guideline for Clinicians	2e. In situations where there is continued ambiguity regarding evidence of conscious awareness despite serial neurobehavioral assessments, or where confounders to a valid clinical diagnostic assessment are identified, clinicians may use multimodal evaluations incorporating specialized functional imaging or electrophysiologic studies to assess for evidence of awareness not identified on neurobehavioral assessment that might prompt consideration of an alternate diagnosis. – Level C	There is currently insufficient evidence to support or refute the routine clinical use of functional neuroimaging (functional MRI [fMRI] or PET) or routine EEG or evoked response potential studies as clinically useful adjuncts to behavioral evaluations to detect conscious awareness in patients diagnosed with VS/UWS.	• Recommendation is for chronic DoC (i.e., ≥ 28 days) • Recommendation is for diagnosis only • Serial neurobehavioral assessments should precede fMRI or EEG assessment of consciousness • "Ambiguity" in consciousness assessment is not defined • Level C evidence: recommendation has "low confidence" (level U is the only category that is lower and is associated with "very low confidence"). This indicates that the recommendation *may* be followed.
EAN	fMRI PICTO 5. It is suggested that active fMRI paradigms should be considered as part of multimodal assessment in patients without command following at the bedside (moderate evidence, weak recommendation). EEG PICOT 4. It is suggested that quantitative analysis of high-density EEG be considered for the differentiation between VS/UWS and MCS as part of multimodal assessment (moderate evidence, weak recommendation).	Active fMRI paradigms allow identification of a specific and important group of patients who can follow commands despite appearing completely unresponsive at the bedside (i.e. CMD). Beware that sedation and cognitive impairment such as language disorders might confound results, and – importantly – absence of command following is not proof of absence of consciousness. It follows that active fMRI paradigms have a high specificity but very low sensitivity for the detection of covert consciousness. Active paradigms with high-density EEG (and low-density EEG) allow a specific and important group of patients to be identified who can follow commands despite appearing completely unresponsive at the bedside (i.e. CMD). High-density EEG paradigms appear to have a high specificity but very low sensitivity for the detection of covert consciousness.	• Guidelines span acute and chronic DoC • Recommendations are for diagnosis only and not for prognosis • Recommendations are "weak"

UK RCP	Assessment, Diagnosis, and Monitoring: …electrophysiological tests and more sophisticated imaging techniques (such as fMRI, PET scans etc) do not form part of routine clinical evaluation for patients with PDOC	While it is acknowledged that there is a small cohort of patients who present behaviourally as being in VS but demonstrate covert responses within an fMRI scanner, the prognostic significance of these findings is as yet unclear. This raises the ethical dilemma of whether or not and how to disclose this information to clinicians and patients' families. Currently, therefore, these more hi-tech investigations do not form part of the standard assessment battery, nor do they represent a 'practicable step' required by s.1(3) MCA to support a person's capacity to make relevant decisions. They should be only applied in the context of a registered research program	• Criticisms and support for this guideline, which recommends the use of task-based fMRI and EEG only for research-based assessments of CMD, have been published[16, 17]
Abbreviations: AAN *American Academy of Neurology*, ACRM *American Congress of Rehabilitation Medicine*, EAN *European Academy of Neurology*, EEG *electroencephalography;* fMRI *functional magnetic resonance imaging*; MCA *Mental Capacity Act;* NIDILIRR *National Institute on Disability, Independent Living and Rehabilitation Research*, PDOC *prolonged disorders of consciousness,* UK RCP *United Kingdom Royal College of Physicians*			

Supplementary Table 2: Contraindications and Safety Considerations			
MRI	Contraindication	Implanted ferrous metal	May shift causing internal injury or heat up, causing thermal injury
		External fixator	May be attracted to the magnetic field and pulled into scanner bore
	Safety Concern	Traveling from ICU to Scanner	• Travel ventilator may not provide sufficient oxygenation/ventilation • Disconnecting and reconnecting lines, tubes, and drains
		Lying flat	• Intracranial hypertension • Reduced monitoring inside scanner • Aspiration
	Data Quality Concern	VP shunt	Causes artifact
		Cranioplasty material	Causes artifact
		Restlessness	Causes artifact
		Sedation	Confounds arousal and awareness
EEG	Contraindication	Scalp burns	Infection risk and pain
		Lacerations	Infection risk and pain
	Safety Concern	Skin irritation	Typically resolves quickly
	Data Quality Concern	Diaphoresis	Causes poor signal or artifact
		Restlessness	Causes artifact
		Sedation	Confounds arousal and awareness
		Hemicraniectomy	Causes breach artifact
		Epileptiform activity	Causes poor signal or artifact
		Eye movement, chewing, other muscle activity	Causes signal artifact

Supplementary Table 3: fMRI Scanning Parameters	
Parameter	**BrainLab**
Duration of Experimental Data	4 min 30 sec
Time Discarded on Scanner	9 sec (3 volumes)*
Initial Volumes for Coregistration	NA
# total experimental volumes	93
# total volumes	90
TR	3000 msec
TE	30 msec
Voxel size	3 x 3 x 3 mm
IPAT	NA
SMS	NA
FOV	192mm*
Matrix	64\0\0\64
Flip Angle	90
Bandwidth	2440
# slices per volume	41
# volumes per block	10
# rest blocks per run	5
# stim blocks per run	4
Block duration	30 sec
Auto Align	On > Head-Brain
Total duration of sequence	4 min 39 sec

Supplementary Table 4: Minimum Equipment Requirements	
Modality	**Equipment**
MRI	3T MRI
	MRI-compatible headphones or earbuds
	Device (e.g., tablet) for playing audio files with instructions and paradigms
	Cable connecting external audio device to the MRI audio system
EEG	EEG system with at least one auxiliary port for a trigger cable that connects to a tablet/laptop
	Tablet/laptop + charger
	Wired earbuds
	3.5mm AUX audio cable splitter to connect the tablet/laptop to 1) the EEG auxiliary port, and 2) the in-ear wired headphones
	AUX audio cable (3.5mm/3.5mm) to connect the tablet/laptop (through the cable splitter) to the EEG auxiliary port

Supplementary Table 5: Factors that may Contribute to a Negative fMRI/EEG Result	
Confounding Factor	**Approaches to mitigation**
Heavy sedation	Document all medications and include in reporting
Motion degradation	Trial MRI and EEG conditions before assessment; for MRI, use padding, sheets and blankets to restrict head movement
Hearing impairment preventing detection of instructions	Brainstem auditory evoked response (BAER) testing
Language impairment preventing comprehension of instructions	Conduct assessments focused on dissociating language impairment from impaired level of consciousness (e.g., test for command-following using gestures and visual cues)
Fluctuations in arousal	Conduct assessments shortly after stimulating medications are administered; consider Arousal Facilitation Protocol prior to beginning the task
Normal variation	Compare data to a large sample of healthy subjects
Paradigm too cognitively demanding	Develop and validate hierarchical paradigms of increasing difficulty that minimize reliance on language function, sustained attention, working memory, etc.

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