

ORIGINAL ARTICLE

Cognitive Motor Dissociation in Disorders of Consciousness

Y.G. Bodien, J. Allanson, P. Cardone, A. Bonhomme, J. Carmona, C. Chatelle, S. Chennu, M. Conte, S. Dehaene, P. Finoia, G. Heinonen, J.E. Hersh, E. Kamau, P.K. Lawrence, V.C. Lupson, A. Meydan, B. Rohaut, W.R. Sanders, J.D. Sitt, A. Soddu, M. Valente, A. Velazquez, H.U. Voss, A. Vrosgou, J. Claassen, B.L. Edlow, J.J. Fins, O. Gosseries, S. Laureys, D. Menon, L. Naccache, A.M. Owen, J. Pickard, E.A. Stamatakis, A. Thibaut, J.D. Victor, J.T. Giacino, E. Bagiella, and N.D. Schiff

ABSTRACT

BACKGROUND

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Schiff can be contacted at nds2001@med.cornell.edu or at the Feil Family Brain and Mind Research Institute, 1300 York Ave., New York, NY 10065.

Patients with brain injury who are unresponsive to commands may perform cognitive tasks that are detected on functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). This phenomenon, known as cognitive motor dissociation, has not been systematically studied in a large cohort of persons with disorders of consciousness.

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METHODS

In this prospective cohort study conducted at six international centers, we collected clinical, behavioral, and task-based fMRI and EEG data from a convenience sample of 353 adults with disorders of consciousness. We assessed the response to commands on task-based fMRI or EEG in participants without an observable response to verbal commands (i.e., those with a behavioral diagnosis of coma, vegetative state, or minimally conscious state—minus) and in participants with an observable response to verbal commands. The presence or absence of an observable response to commands was assessed with the use of the Coma Recovery Scale—Revised (CRS-R).

RESULTS

Data from fMRI only or EEG only were available for 65% of the participants, and data from both fMRI and EEG were available for 35%. The median age of the participants was 37.9 years, the median time between brain injury and assessment with the CRS-R was 7.9 months (25% of the participants were assessed with the CRS-R within 28 days after injury), and brain trauma was an etiologic factor in 50%. We detected cognitive motor dissociation in 60 of the 241 participants (25%) without an observable response to commands, of whom 11 had been assessed with the use of fMRI only, 13 with the use of EEG only, and 36 with the use of both techniques. Cognitive motor dissociation was associated with younger age, longer time since injury, and brain trauma as an etiologic factor. In contrast, responses on task-based fMRI or EEG occurred in 43 of 112 participants (38%) with an observable response to verbal commands.

CONCLUSIONS

Approximately one in four participants without an observable response to commands performed a cognitive task on fMRI or EEG as compared with one in three participants with an observable response to commands. (Funded by the James S. McDonnell Foundation and others.)

COGNITIVE MOTOR DISSOCIATION¹ IS AN established phenomenon²⁻⁴ in which persons with severe brain injury who are behaviorally unresponsive to commands show brain activation on functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) when presented with cognitive tasks, such as motor imagery commands. The failure to identify cognitive motor dissociation in patients with disorders of consciousness could affect decisions related to the withdrawal of life-sustaining treatment, goals of care, and clinical management. Evidence of cognitive motor dissociation may prompt more thorough investigation of subtle behaviors that are under volitional control,⁵ uncovering potential avenues for communicating with the patient and respecting their autonomy.

In previous studies, cognitive motor dissociation was observed in 10 to 20% of persons with a disorder of consciousness^{3,6-9}; similar findings were observed in persons with acute brain injury^{10,11} or chronic brain injury,¹² as well as across etiologic factors.⁹ Detection of cognitive motor dissociation has been associated with more rapid recovery and better outcomes at 1 year after injury.^{11,13} To be detected on fMRI or EEG, responses to commands must be sustained and reflect not only language comprehension but also recruitment of more cognitive resources (e.g., short-term memory, attention, and persistence) than may be required for responding to a single command at the bedside (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Identifying that a patient who otherwise appears to be unconscious has the capacity for cognitive processing may mitigate emotional harm when the patient's clinical team and family recognize that the patient is aware and treats the patient as such. The harm in assuming that an unresponsive patient is also unaware has been described previously.¹⁴ International clinical guidelines vary with regard to recommendations about the use of fMRI and EEG for detecting cognitive motor dissociation, with some guidelines supporting their use^{15,16} and at least one guideline proposing the need for further study before these techniques are routinely used in clinical practice.¹⁷

Most previous studies of cognitive motor dissociation were conducted at single sites with relatively small cohorts.^{3,6,7,9-11,18,19} Our consortium

assessed cognitive motor dissociation in a multinational cohort of participants with disorders of consciousness who were assessed at specialized centers that have the capability of studying this condition.

METHODS

SITES AND PARTICIPANTS

Six multinational sites contributed behavioral and task-based fMRI data, EEG data, or both to a centrally curated Research Electronic Data Capture (REDCap)²⁰ database from 2006 to 2023. Study participants were adults (≥ 18 years of age) with a disorder of consciousness who were recruited from intensive care units, hospital wards, rehabilitation facilities, nursing homes, and the community. Exclusion criteria at all sites were previous neurologic or psychiatric disease and contraindication for MRI, EEG, or both (e.g., for fMRI, the inability to lay flat or the presence of ferrous metal implants), depending on the techniques used at the site. Additional information about the inclusion and exclusion criteria at each site is provided in Tables S2 and S3. The study was approved by ethics review boards at each site, and procedures for obtaining surrogate consent for participation in the study adhered to local regulations. Participants may have been included in previous studies that assessed specific methodologic approaches or different research questions (Fig. S1).

The first and last authors wrote the first draft of the manuscript, and all the authors reviewed the manuscript before submission. All the authors vouch for the accuracy and completeness of the data. None of the vendors or manufacturers of the fMRI and EEG devices used in the current study provided funding for this study or had any role in the conduct of this study or reporting of the findings.

PROCEDURES

Trained study staff conducted behavioral assessments with the use of the Coma Recovery Scale-Revised (CRS-R), a standardized scale with high interrater reliability and test-retest reliability that has been validated in multiple languages (Table S4)²¹⁻²⁴; scores range from 0 to 23, and higher scores typically indicate better neurobehavioral function. The CRS-R is the tool preferred in international guidelines for the assessment of

levels of consciousness and was the means by which we assigned a diagnosis of a disorder of consciousness to the participants.¹⁵⁻¹⁷ The examiners who administered the CRS-R were unaware of the findings on fMRI and EEG.

Investigators at each of the six sites have experience designing fMRI and EEG studies that include participants with disorders of consciousness, and they adhered to all local, previously published, and validated procedures for acquiring, analyzing, and interpreting fMRI and EEG findings. The procedures for processing and interpreting these findings were automated to minimize bias associated with the subjective discrimination of positive findings from negative findings. The fMRI analysis used established statistical cutoffs and cluster-based correction for multiple comparisons to reduce the potential effect of spurious activations in the prespecified brain regions of interest. EEG analysis used either a comparison of the power spectral density at each channel (corrected for multiple comparisons) or a machine-learning algorithm. Trained study staff who were unaware of the findings from the behavioral assessment removed artifacts from the EEG data. Before evaluating participants with disorders of consciousness, investigators tested the methods for acquiring and analyzing fMRI data^{3,8,10} and EEG data^{10,11,25,26} in healthy participants to ensure that responses on imaging were detectable in persons with intact cognitive processing. These studies included 5 to 16 healthy participants, of whom 70 to 100% had responses to commands on task-based fMRI or EEG.

We included participants who had at least one score on the CRS-R and had undergone assessments of responses to commands (e.g., “imagine playing tennis,” “imagine opening and closing your hand,” and “open and close your hand”) on task-based fMRI, task-based EEG, or both within 7 days before or after the CRS-R assessment. If participants were assessed across multiple days with either fMRI or EEG, our analyses included only the best response on the first day. We also documented the number of participants for whom it was not possible to analyze or interpret data from any fMRI or EEG sessions (e.g., because of the presence of a motion artifact). Study staff from each site entered data into a central REDCap database housed at the Icahn School of Medicine

at Mount Sinai, the data coordinating center. REDCap variables included demographic and clinical characteristics; scores on the CRS-R subscales (auditory, visual, motor, oromotor–verbal, communication, and arousal); total score on the CRS-R; number of attempted task-based fMRI sessions, EEG sessions, or both; number of task-based fMRI sessions, EEG sessions, or both in which a response was detected; and number of task-based fMRI sessions, EEG sessions, or both in which a response was not detected.

ASSESSMENTS

We divided participants into two groups according to whether responses to verbal commands or intelligible speech were observed during the assessment with the CRS-R. Cognitive motor dissociation was operationally defined as a lack of responses to commands and a lack of intelligible speech as assessed with the CRS-R (i.e., a score of <3 on the auditory subscale, <5 on the visual subscale, <3 on the oromotor–verbal subscale, and <1 on the communication subscale) in the context of a response to a task-based fMRI paradigm, a task-based EEG paradigm, or both (a paradigm is a standardized experimental design that evokes consistent brain responses when completed by healthy persons).¹ According to this definition, only participants with a CRS-R assessment that led to a diagnosis of coma, vegetative state (also referred to as unresponsive wakefulness syndrome), or minimally conscious state–minus (the presence of signs of conscious awareness, such as visual pursuit, without responses to commands or intelligible verbal output)²⁷ could be considered to have cognitive motor dissociation. We combined the diagnostic categories of coma and vegetative state because both indicate an unconscious state. We also evaluated responses on task-based fMRI and EEG in participants with an observable response to commands (i.e., participants with a behavioral diagnosis of minimally conscious state–plus [the presence of signs of conscious awareness that include responses to commands or intelligible verbal output] and those who had emerged from the minimally conscious state [the return of the ability to use common objects in a functional manner or correctly respond to basic yes-or-no questions about situational orientation]).

The preservation or recovery of multiple complex cognitive functions that are required to perform the tasks assessed with fMRI and EEG over minutes of sustained engagement minimizes the risk of spurious responses on fMRI²⁸ and EEG.^{29,30} This methodologic approach results in a high percentage of false-negative results (i.e., no response on fMRI or EEG in participants with an observable response to commands and in healthy persons).^{3,10,31,32} Given this context, we interpreted responses on fMRI and EEG in participants without an observable response to commands (i.e., participants with a behavioral diagnosis of coma, vegetative state, or minimally conscious state–minus) to be specific for cognitive motor dissociation but at a potential cost of reduced sensitivity.

STATISTICAL ANALYSIS

We report descriptive characteristics of the participants and the percentage of all the participants with cognitive motor dissociation. We describe differences in the percentage of participants with cognitive motor dissociation according to age, time since injury, diagnosis on the basis of the CRS-R assessment, etiologic factor, and study site. We calculated kappa coefficients to assess the agreement among the behavioral diagnosis, task-based fMRI findings, and task-based EEG findings. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used in place of hypothesis testing.

RESULTS

PARTICIPANTS

The central database included data for 478 participants, of whom 125 (61 participants with no score on the CRS-R available; 43 with no task-based fMRI or EEG data available; 16 with uninterpretable fMRI data, EEG data, or both; and 5 with a score on the CRS-R that was obtained more than 7 days before or after fMRI or EEG) were excluded from the current study (Fig. 1). Characteristics of the 353 participants included in the study are provided in Table 1 and Figure S2.

A total of 215 participants (61%) underwent at least one fMRI assessment, and 260 participants (74%) underwent at least one EEG assessment. Both fMRI and EEG were performed in

122 participants (35%), and fMRI only or EEG only were performed in 231 (65%). The CRS-R assessment occurred within a median of 1 day (interquartile range, 0 to 2) of fMRI and 0 days (interquartile range, 0 to 1) before or after EEG. The CRS-R assessment was performed within 1 day before or after fMRI or EEG in approximately 70% of the participants (Fig. S3). A summary of the demographic representativeness of our sample is provided in Table S5.

FINDINGS IN PARTICIPANTS WITHOUT AN OBSERVABLE RESPONSE TO COMMANDS

Of the 241 participants with a diagnosis of coma or vegetative state (i.e., participants who were unconscious) or minimally conscious state–minus on the basis of the score on the CRS-R, 60 (25%) had a response to commands on task-based fMRI, task-based EEG, or both. The distribution of participants with cognitive motor dissociation according to the score on the CRS-R is shown in Figures S4, S5, and S6. Scores on the CRS-R according to responses on fMRI and EEG are shown in Table S6. The median age was lower among participants with cognitive motor dissociation than among those without cognitive motor dissociation (30.5 years [interquartile range, 22.6 to 43.0] vs. 45.3 years [interquartile range, 26.7 to 59.3]), and a higher percentage of participants with cognitive motor dissociation than without cognitive motor dissociation had brain trauma as an etiologic factor (65% vs. 38%) and a diagnosis of minimally conscious state–minus according to the score on the CRS-R (53% vs. 38%). The CRS-R assessment occurred later after brain injury in participants with cognitive motor dissociation than in those without cognitive motor dissociation (10.7 months [interquartile range, 3.7 to 24.3] vs. 4.3 months [interquartile range, 0.1 to 14.4]) (Table 2). Among participants with cognitive motor dissociation, 18% were assessed with fMRI only, 22% with EEG only, and 60% with both fMRI and EEG. The percentage of participants with cognitive motor dissociation varied across study sites (Table S7). Table S8 shows the percentage of participants with a diagnosis of coma or vegetative state or of minimally conscious state–minus, as assessed with the CRS-R, who had a response or did not have a response on fMRI, EEG, or both.

FINDINGS IN PARTICIPANTS WITH AN OBSERVABLE RESPONSE TO COMMANDS

Of the 112 participants with a diagnosis of minimally conscious state—plus or who had emerged from the minimally conscious state as assessed with the CRS-R, 43 (38%) had a response to commands on task-based fMRI, task-based EEG, or

both (Table 3). Among these participants, 23% were assessed with fMRI only, 19% with EEG only, and 58% with both fMRI and EEG. Responses to commands on fMRI and EEG were absent in more than 60% of the participants who had an observable response to commands during assessment with the CRS-R at the bed-

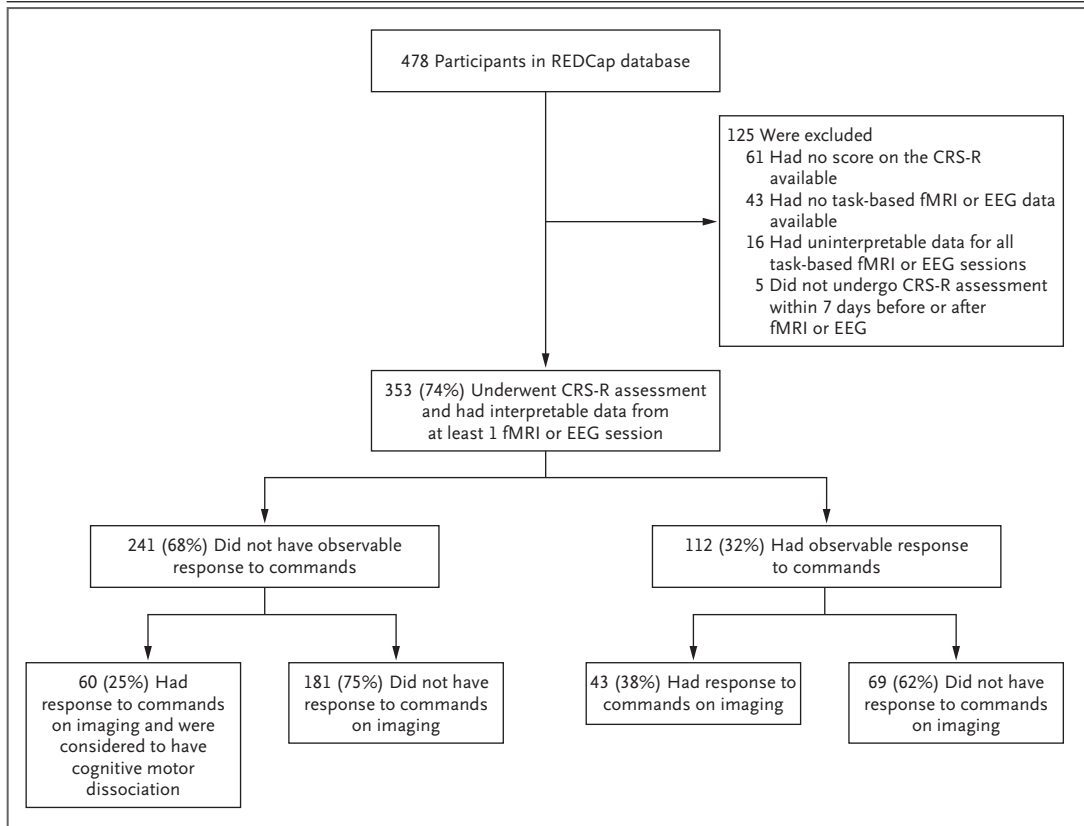


Figure 1. Study Population.

Of 478 participants in the Research Electronic Data Capture (REDCap) database, 353 were assessed with the use of the Coma Recovery Scale–Revised (CRS-R) and at least one command-following paradigm on functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) within 7 days. We defined cognitive motor dissociation operationally on the basis of the CRS-R assessment as a lack of responses to commands and a lack of intelligible speech in the context of a response to a task-based fMRI paradigm, a task-based EEG paradigm, or both. Cognitive motor dissociation occurred in 25% of the participants with no observable response to commands (participants with a behavioral diagnosis of coma or vegetative state [unconscious] or minimally conscious state–minus [the presence of signs of conscious awareness without responses to commands or intelligible verbal output]). Among the participants with an observable response to commands (participants with a behavioral diagnosis of minimally conscious state–plus [defined as the presence of signs of conscious awareness that include responses to commands or intelligible verbal output] and those who had emerged from the minimally conscious state [defined as the return of the ability to use common objects in a functional manner or correctly respond to basic yes-or-no questions about situational orientation]), 62% did not have a response on task-based fMRI, EEG, or both. Participants who had a response to commands on imaging were those with a response to commands on fMRI, EEG, or both, regardless of whether they underwent one or both imaging studies. Participants who did not have a response to commands on imaging were those who underwent fMRI only, EEG only, or both and had no response to commands on imaging.

side. Table S9 shows the percentage of participants with a diagnosis of minimally conscious state–plus or who had emerged from the minimally conscious state, as assessed with the CRS-R, who had a response or did not have a response to commands on fMRI, EEG, or both.

AGREEMENT BETWEEN ASSESSMENT TECHNIQUES

The level of agreement between evidence of a response on the basis of the CRS-R, fMRI, and EEG assessments, as indicated by kappa coefficients, was low. Kappa coefficients ranged from 0.09 to 0.15 for agreement between evidence of a response according to CRS-R findings and evidence according to fMRI or EEG findings and from 0.02 to 0.04 for agreement between evidence on the basis of fMRI findings and EEG findings (Tables S10 and S11).

DISCUSSION

In this multinational study involving a convenience sample with disorders of consciousness, we detected cognitive motor dissociation on task-based fMRI or EEG in approximately 25% of the participants. This percentage is higher than previous estimates.^{3,6,9-11} Although standardized behavioral evaluation remains the reference standard for detecting a response to commands at the bedside, the use of task-based fMRI and EEG can improve detection, and the use of both imaging techniques appears to be a more sensitive approach than the use of one of the techniques alone.

The percentage of participants with cognitive motor dissociation is 5 to 10 percentage points higher in our study than in previous studies.^{3,6,9-11} This finding may be due to our multimodal approach, which classified the participants who underwent assessment with both techniques on the basis of responses on either fMRI or EEG. The percentage of participants with cognitive motor dissociation may have been even higher if all the participants had been assessed with both imaging techniques. Previous studies have shown that cognitive motor dissociation was most common among participants with traumatic brain injury,^{3,6,9,11} those with chronic disorders of consciousness,⁹ and those with a behavioral diagnosis of minimally con-

Table 1. Demographic and Clinical Characteristics of the Participants.*

Variable	All Participants (N=353)
Median age at injury (IQR) — yr	37.9 (23.8–55.8)
Sex — no. (%)	
Male	226 (64)
Female	125 (35)
Missing	2 (1)
Median time between injury and CRS-R assessment (IQR) — mo†	7.9 (1.0–22.1)
Underwent CRS-R assessment <28 days after injury — no. (%)	90 (25)
Etiologic factor — no. (%)	
Brain trauma	176 (50)
Cardiac arrest or hypoxia	57 (16)
SAH, IVH, ICH, or stroke	65 (18)
Other	55 (16)
Diagnosis — no. (%)‡	
Coma or vegetative state	140 (40)
Minimally conscious state–minus	101 (29)
Minimally conscious state–plus	77 (22)
Emerged from the minimally conscious state	35 (10)

* Percentages may not total 100 because of rounding. ICH denotes intracerebral hemorrhage, IQR interquartile range, IVH intraventricular hemorrhage, and SAH subarachnoid hemorrhage.

† The Coma Recovery Scale–Revised (CRS-R) is a tool preferred in international guidelines for the assessment of levels of consciousness.

‡ The diagnosis was made on the basis of the score on the CRS-R. A diagnosis of coma or vegetative state indicated an unconscious state. Minimally conscious state–minus is defined as the presence of signs of conscious awareness without responses to commands or intelligible verbal output. Minimally conscious state–plus is defined as the presence of signs of conscious awareness that include responses to commands or intelligible verbal output. Emerged from the minimally conscious state is defined as the return of the ability to use common objects in a functional manner or correctly respond to basic yes-or-no questions about situational orientation.

scious state–minus,¹¹ findings that were indicated in our study. However, cognitive motor dissociation was also detected in participants with nontraumatic causes of brain injury (e.g., stroke and cardiac arrest), those with acute disorders of consciousness, and those who were behaviorally unconscious, as indicated by a diagnosis of coma or vegetative state.

The prevalence of cognitive motor dissociation may have been underestimated in previous studies and the current study for multiple reasons. First, the paradigms used in studies of

Table 2. Demographic and Clinical Characteristics of the Participants without an Observable Response to Commands.*

Characteristic	No Observable Response to Commands (N=241)	Response to Commands on Imaging† (N=60)	No Response to Commands on Imaging‡ (N=181)
Diagnosis — no. (%)§			
Coma or vegetative state	140 (58)	28 (47)	112 (62)
Minimally conscious state—minus	101 (42)	32 (53)	69 (38)
Imaging technique — no. (%)			
fMRI only	61 (25)	11 (18)	50 (28)
EEG only	101 (42)	13 (22)	88 (49)
fMRI and EEG	79 (33)	36 (60)	43 (24)
Median age at the time of injury (IQR) — yr	40.2 (25.2–57.2)	30.5 (22.6–43.0)	45.3 (26.7–59.3)
Sex — no. (%)			
Male	146 (61)	39 (65)	107 (59)
Female	93 (39)	21 (35)	72 (40)
Missing	2 (1)	0	2 (1)
Median time between injury and CRS-R assessment (IQR) — mo	6.3 (0.6–16.9)	10.7 (3.7–24.3)	4.3 (0.6–14.2)
Underwent CRS-R assessment <28 days after injury — no. (%)	72 (30)	12 (20)	60 (33)
Underwent CRS-R assessment ≥28 days after injury — no. (%)	169 (70)	48 (80)	121 (67)
Etiologic factor — no. (%)			
Brain trauma	108 (45)	39 (65)	69 (38)
Cardiac arrest or hypoxia	45 (19)	4 (7)	41 (23)
SAH, IVH, ICH, or stroke	48 (20)	9 (15)	39 (22)
Other	40 (17)	8 (13)	32 (18)

* Percentages may not total 100 because of rounding.

† Data are for participants with a response to commands on functional magnetic resonance imaging (fMRI), electroencephalography (EEG), or both, regardless of whether they underwent one or both imaging studies. These participants were considered to have cognitive motor dissociation.

‡ Data are for participants who underwent fMRI only, EEG only, or both and had no response to commands on imaging.

§ The diagnosis was made on the basis of the score on the CRS-R.

task-based fMRI and EEG may require more cognitive resources (e.g., short-term memory, selective attention, and mental persistence) than in typical command-following trials performed at the bedside. Although this hypothesis has not been proven,³³ it is supported by our finding that responses on fMRI and EEG were detected in only 38% of the participants with an observable response to commands at the bedside. Second, the fMRI and EEG analytic techniques used at the study sites were intentionally designed to minimize the potential for a false-positive result, which may increase the likelihood of a false-negative finding. Third, most studies assess participants with the use of either fMRI or

EEG. We found that participants who were assessed with both imaging techniques were more likely to have cognitive motor dissociation than those who were assessed with one technique. Fourth, behavioral fluctuation is common among patients across all disorders of consciousness, which may contribute to the lack of a response on fMRI or EEG or to disparate findings between these two techniques.^{34–36}

Several limitations should be considered when interpreting the results of this study. Participants were recruited with the use of a variety of methods, including consecutive enrollment of critically ill patients in the intensive care unit and enrollment of persons with chronic illness

Table 3. Demographic and Clinical Characteristics of the Participants with an Observable Response to Commands.

Characteristic	Observable Response to Commands (N=112)	Response to Commands on Imaging* (N=43)	No Response to Commands on Imaging† (N=69)
Diagnosis — no. (%)‡			
Minimally conscious state—plus	77 (69)	26 (60)	51 (74)
Emerged from the minimally conscious state	35 (31)	17 (40)	18 (26)
Imaging technique — no. (%)			
fMRI only	32 (29)	10 (23)	22 (32)
EEG only	37 (33)	8 (19)	29 (42)
fMRI and EEG	43 (38)	25 (58)	18 (26)
Median age at the time of injury (IQR) — yr	33.8 (22.1–54.5)	29.4 (21.9–46.6)	38.6 (22.3–55.3)
Sex — no. (%)			
Male	80 (71)	30 (70)	50 (72)
Female	32 (29)	13 (30)	19 (28)
Median time between injury and CRS-R assessment (IQR) — mo	12.9 (3.5–48.8)	12.6 (5.5–57.4)	12.9 (3.1–43.8)
Underwent CRS-R assessment <28 days after injury — no. (%)	18 (16)	10 (23)	8 (12)
Underwent CRS-R assessment ≥28 days after injury — no. (%)	94 (84)	33 (77)	61 (88)
Etiologic factor — no. (%)			
Brain trauma	68 (61)	30 (70)	38 (55)
Cardiac arrest or hypoxia	12 (11)	1 (2)	11 (16)
SAH, IVH, ICH, or stroke	17 (15)	9 (21)	8 (12)
Other	15 (13)	3 (7)	12 (17)

* Data are for participants with a response to commands on fMRI, EEG, or both, regardless of whether they underwent one or both imaging studies.

† Data are for participants who underwent fMRI only, EEG only, or both and had no response to commands on imaging.

‡ The diagnosis was made on the basis of the score on the CRS-R.

or injury who were in the postacute phase of brain injury. All the participants with chronic brain injury had survived their initial illness or injury and had access to a research facility with advanced fMRI and EEG capabilities. This survival bias may reflect greater cognitive reserve and resilience over time among the participants. As such, the results of our study may not be generalizable to the overall population of patients with cognitive motor dissociation. In the absence of standardized approaches to the evaluation of cognitive motor dissociation, participating sites used heterogeneous strategies to acquire, analyze, and interpret data, which led to differences in the number, type, and ordering of the cognitive tasks assessed on fMRI and EEG. These differences, along with variations in recruitment strategies and participant characteris-

tics, may have contributed to the unequal percentage of participants with cognitive motor dissociation observed at each site (range, 2 to 45%). Our findings may therefore not be generalizable across all centers.

Large-scale validation studies are needed to improve data acquisition and analysis for clinical translation. The statistical analyses that were conducted as part of this study were univariate and descriptive. Thus, we were unable to evaluate the independent contribution of any one variable in predicting cognitive motor dissociation.

The agreement between cases of cognitive motor dissociation detected by fMRI as compared with EEG was low, which may have been due to fluctuations in conscious awareness in the participants or to differences in the underlying paradigm assessed by each technique. Although the

participants underwent assessments with the CRS-R, fMRI, and EEG a variable number of times, for consistency we analyzed the best score on the CRS-R and the best response on each imaging technique, and we are unable to determine the number of assessments that were excluded. Serial assessment with the CRS-R, fMRI, and EEG may lead to improved detection of cognitive motor dissociation but requires the ready availability of these imaging techniques. Finally, access to both the specially trained personnel and techniques that are needed to assess persons for cognitive motor dissociation is currently available in only a few academic medical centers worldwide, which limits the feasibility of performing these assessments in general practice.

The results of our study, which used neuroimaging and electrophysiological techniques, indicate that cognitive motor dissociation is more common than previously realized. Although task-based fMRI and EEG are not yet widely available for the clinical assessment of disorders of consciousness, the knowledge that cognitive motor dissociation is not rare should prompt further study to explore whether its detection can lead to improved outcomes. In addition, the standardization, validation, and simplification of task-based fMRI and EEG methods that are used to detect cognitive motor dissociation are needed to prompt widespread clinical integration of these techniques and investigation of the bioethical implications of the findings.³⁷

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APPENDIX

The authors’ full names and academic degrees are as follows: Yelena G. Bodien, Ph.D., Judith Allanson, F.R.C.P., Ph.D., Paolo Cardone, M.S., Arthur Bonhomme, M.D., Jerina Carmona, M.P.H., Camille Chatelle, Ph.D., Srivas Chennu, Ph.D., Mary Conte, Ph.D., Stanislas Dehaene, Ph.D., Paola Finioia, Ph.D., Gregory Heinson, B.S., Jennifer E. Hersh, M.B.E., Evelyn Kamau, M.Sc., Phoebe K. Lawrence, B.S., Victoria C. Lupson, B.Sc., Anogue Meydan, B.S., Benjamin Rohaut, M.D., Ph.D., William R. Sanders, B.S., Jacobo D. Sitt, M.D., Ph.D., Andrea Soddu, Ph.D., Mélanie Valente, B.S., Angela Velazquez, M.D., Henning U. Voss, Ph.D., Athina Vrosgou, M.Sc., Jan Claassen, M.D., Brian L. Edlow, M.D., Joseph J. Fins, M.D., Olivia Gosseries, Ph.D., Steven Laureys, M.D., Ph.D., David Menon, M.D., Lionel Naccache, M.D., Ph.D., Adrian M. Owen, Ph.D., John Pickard, M.Chir., Emmanuel A. Stamatakis, Ph.D., Aurore Thibaut, Ph.D., Jonathan D. Victor, M.D., Ph.D., Joseph T. Giacino, Ph.D., Emilia Bagiella, Ph.D., and Nicholas D. Schiff, M.D.

The authors' affiliations are as follows: the Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital (Y.G.B., J.T.G.), and the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital (B.L.E.), Charlestown, and the Center for Neurotechnology and Neurorecovery, Massachusetts General Hospital (Y.G.B., C.C., P.K.L., A.M., W.R.S., B.L.E.), the Department of Physical Medicine and Rehabilitation, Harvard Medical School (Y.G.B., J.T.G.), and the Department of Neurology, Massachusetts General Hospital and Harvard Medical School (Y.G.B., C.C., B.L.E.), Boston — all in Massachusetts; the Department of Neurosciences, Addenbrookes Hospital (J.A.), and the Department of Clinical Neurosciences (J.A., S.C., E.K., V.C.L., J.P., E.A.S.), the Division of Neurosurgery, School of Clinical Medicine (S.C., P.F., E.K., J.P.), the Wolfson Brain Imaging Centre (V.C.L., D.M., J.P.), and the Division of Anaesthesia, Department of Medicine (D.M., E.A.S.), University of Cambridge, Cambridge, and the School of Computing, University of Kent, Canterbury (S.C.) — all in the United Kingdom; the Coma Science Group, GIGA Consciousness, University of Liege (P.C., A.B., C.C., O.G., S.L., A.T.), and Centre du Cerveau, University Hospital of Liege (P.C., A.B., C.C., O.G., A.T.), Liege, and the European Research Council Executive Agency, Brussels (C.C.) — all in Belgium; the Department of Neurology, Columbia University Irving Medical Center, New York–Presbyterian Hospital (J. Carmona, G.H., A. Velazquez, A. Vrosgou, J. Claassen), the Feil Family Brain and Mind Research Institute (M.C., J.E.H., J.D.V., N.D.S.), the Division of Medical Ethics (J.E.H., J.J.F.), and the Departments of Neurology (J.D.V., N.D.S.) and Radiology (H.U.V.), Weill Cornell Medicine, Rockefeller University Hospital (J.J.F., J.D.V., N.D.S.), and the Department of Population Health Science and Policy, Center for Biostatistics, Icahn School of Medicine at Mount Sinai (E.B.) — all in New York; Collège de France, Université Paris Sciences et Lettres (S.D.), Sorbonne Université, Paris Brain Institute–Institut du Cerveau et de la Moelle Épinière, INSERM, Centre National de la Recherche Scientifique (B.R., J.D.S., M.V., L.N.), and Assistance Publique–Hôpitaux de Paris, Hôpital Pitié–Salpêtrière, Département Médico-Universitaire Neurosciences (B.R., M.V., L.N.) — all in Paris; the Departments of Physics and Astronomy (A.S.), Physiology and Pharmacology (A.M.O.), and Psychology (A.M.O.), and the Western Institute for Neuroscience (A.S., A.M.O.), University of Western Ontario, London, ON, and the CERVO Brain Research Centre, Quebec, QC (S.L.) — all in Canada; Yale Law School, New Haven, CT (J.J.F.); and the Consciousness Science Institute, Hangzhou Normal University, Hangzhou, China (S.L.).

REFERENCES

- Schiff ND. Cognitive motor dissociation following severe brain injuries. *JAMA Neurol* 2015;72:1413-5.
- Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. *Science* 2006;313:1402.
- Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med* 2010;362:579-89.
- Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. *Nat Rev Neurol* 2021;17:135-56.
- Whyte J, DiPasquale MC, Vaccaro M. Assessment of command-following in minimally conscious brain injured patients. *Arch Phys Med Rehabil* 1999;80:653-60.
- Kondziella D, Friberg CK, Frokjaer VG, Fabricius M, Møller K. Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016;87:485-92.
- Curley WH, Forgacs PB, Voss HU, Conte MM, Schiff ND. Characterization of EEG signals revealing covert cognition in the injured brain. *Brain* 2018;141:1404-21.
- Bardin JC, Fins JJ, Katz DI, et al. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. *Brain* 2011;134:769-82.
- Schnakers C, Hirsch M, Noé E, et al. Covert cognition in disorders of consciousness: a meta-analysis. *Brain Sci* 2020;10:10.
- Edlow BL, Chatelle C, Spencer CA, et al. Early detection of consciousness in patients with acute severe traumatic brain injury. *Brain* 2017;140:2399-414.
- Claassen J, Doyle K, Matory A, et al. Detection of brain activation in unresponsive patients with acute brain injury. *N Engl J Med* 2019;380:2497-505.
- Stender J, Gosseries O, Bruno M-A, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. *Lancet* 2014;384:514-22.
- Eggebike J, Shen Q, Doyle K, et al. Cognitive-motor dissociation and time to functional recovery in patients with acute brain injury in the USA: a prospective observational cohort study. *Lancet Neurol* 2022;21:704-13.
- La Puma J, Schiedermaier DL, Gulyas AE, Siegler M. Talking to comatose patients. *Arch Neurol* 1988;45:20-2.
- Kondziella D, Bender A, Diserens K, et al. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol* 2020;27:741-56.
- Giacino JT, Katz DI, Schiff ND, et al. Practice guideline update recommendations summary: disorders of consciousness: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Neurology* 2018;91:450-60.
- Royal College of Physicians. Prolonged disorders of consciousness following sudden onset brain injury: National clinical guidelines. London: RCP, 2020.
- Naci L, Sinai L, Owen AM. Detecting and interpreting conscious experiences in behaviorally non-responsive patients. *Neuroimage* 2017;145:Pt B:304-13.
- Sitt JD, King JR, El Karoui I, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. *Brain* 2014;137:2258-70.
- Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004;85:2020-9.
- Bodien YG, Chatelle C, Taubert A, Uchani S, Giacino JT, Ehrlich-Jones L. Updated measurement characteristics and clinical utility of the Coma Recovery Scale-Revised among individuals with acquired brain injury. *Arch Phys Med Rehabil* 2021;102:169-71.
- Schnakers C, Majerus S, Giacino J, et al. A French validation study of the Coma Recovery Scale-Revised (CRS-R). *Brain Inj* 2008;22:786-92.
- Tamashiro M, Rivas ME, Ron M, Salierno F, Dalera M, Olmos L. A Spanish validation of the Coma Recovery Scale-Revised (CRS-R). *Brain Inj* 2014;28:1744-7.
- Goldfine AM, Victor JD, Conte MM, Bardin JC, Schiff ND. Determination of awareness in patients with severe brain injury using EEG power spectral analysis. *Clin Neurophysiol* 2011;122:2157-68.
- Cruse D, Chennu S, Chatelle C, et al. Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 2011;378:2088-94.
- Thibaut A, Bodien YG, Laureys S, Giacino JT. Minimally conscious state "plus": diagnostic criteria and relation to functional recovery. *J Neurol* 2020;267:1245-54.

28. Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci U S A* 2016;113:7900-5.
29. Goldfine AM, Bardin JC, Noirhomme Q, Fins JJ, Schiff ND, Victor JD. Reanalysis of "Bedside detection of awareness in the vegetative state: a cohort study." *Lancet* 2013;381:289-91.
30. Noirhomme Q, Brecheisen R, Lesenfants D, Antonopoulos G, Laureys S. "Look at my classifier's result": disentangling unresponsive from (minimally) conscious patients. *Neuroimage* 2017;145:Pt B:288-303.
31. Boly M, Coleman MR, Davis MH, et al. When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage* 2007;36:979-92.
32. Peterson A, Cruse D, Naci L, Weijer C, Owen AM. Risk, diagnostic error, and the clinical science of consciousness. *Neuroimage Clin* 2015;7:588-97.
33. Glover S, Baran M. The motor-cognitive model of motor imagery: evidence from timing errors in simulated reaching and grasping. *J Exp Psychol Hum Percept Perform* 2017;43:1359-75.
34. Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S, Coma Science Group collaborators. The repetition of behavioral assessments in diagnosis of disorders of consciousness. *Ann Neurol* 2017;81:883-9.
35. Papadimitriou C, Weaver JA, Guernon A, Walsh E, Mallinson T, Pape TLB. "Fluctuation is the norm": rehabilitation practitioner perspectives on ambiguity and uncertainty in their work with persons in disordered states of consciousness after traumatic brain injury. *PLoS One* 2022;17(4):e0267194.
36. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002;58:349-53.
37. Fins JJ. *Rights come to mind: brain injury, ethics, and the struggle for consciousness*. New York: Cambridge University Press, 2015.

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