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## Detection of Brain Activation in Unresponsive Patients with Acute Brain Injury

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### ABSTRACT

#### BACKGROUND

Brain activation in response to spoken motor commands can be detected by electroencephalography (EEG) in clinically unresponsive patients. The prevalence and prognostic importance of a dissociation between commanded motor behavior and brain activation in the first few days after brain injury are not well understood.

#### METHODS

We studied a prospective, consecutive series of patients in a single intensive care unit who had acute brain injury from a variety of causes and who were unresponsive to spoken commands, including some patients with the ability to localize painful stimuli or to fixate on or track visual stimuli. Machine learning was applied to EEG recordings to detect brain activation in response to commands that patients move their hands. The functional outcome at 12 months was determined with the Glasgow Outcome Scale–Extended (GOS-E; levels range from 1 to 8, with higher levels indicating better outcomes).

#### RESULTS

A total of 16 of 104 unresponsive patients (15%) had brain activation detected by EEG at a median of 4 days after injury. The condition in 8 of these 16 patients (50%) and in 23 of 88 patients (26%) without brain activation improved such that they were able to follow commands before discharge. At 12 months, 7 of 16 patients (44%) with brain activation and 12 of 84 patients (14%) without brain activation had a GOS-E level of 4 or higher, denoting the ability to function independently for 8 hours (odds ratio, 4.6; 95% confidence interval, 1.2 to 17.1).

#### CONCLUSIONS

A dissociation between the absence of behavioral responses to motor commands and the evidence of brain activation in response to these commands in EEG recordings was found in 15% of patients in a consecutive series of patients with acute brain injury. (Supported by the Dana Foundation and the James S. McDonnell Foundation.)

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**C**LINICALLY UNRESPONSIVE PATIENTS can have electroencephalographic (EEG) or magnetic resonance imaging (MRI) evidence of brain activation in response to spoken commands.<sup>1-4</sup> A meta-analysis has reported that 14% of chronically unresponsive patients may have a dissociation between behavior and brain activation (cognitive–motor dissociation<sup>5</sup>) months or years after injury.<sup>6</sup> However, the prevalence and prognostic relevance of this dissociation, if detected in the days soon after brain injury, are not well understood. The absence of an ability to follow commands shortly after brain injury may have an effect on decisions regarding the withdrawal of life-sustaining therapies.<sup>7,8</sup>

We studied the prevalence and prognostic importance of brain activation detected by EEG in response to spoken commands to perform a motor task. We used a machine-learning technique<sup>3</sup> to analyze EEG recordings obtained at the bedside in a prospective cohort of unresponsive patients with acute brain injury in a single intensive care unit (ICU).

## METHODS

### PATIENTS

From July 2014 through September 2017, we prospectively screened all patients who were admitted with acute brain injury to the neuroscience ICU of our hospital; screening was performed within 3 days after admission. Patients were screened for the absence of the ability to follow spoken commands — for example, “stick out your tongue” or “show me two fingers with your right hand” (details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). In keeping with our routine practice and in accordance with guidelines regarding EEG monitoring of patients in the ICU,<sup>9</sup> unresponsive patients either were monitored by continuous EEG or were anticipated to be connected to monitoring within 12 hours after screening, unless imminent death was expected. We enrolled all patients who were in a coma, vegetative state, or minimally conscious state–minus (defined as unresponsiveness with preserved visual fixation, visual pursuit, or localization to noxious stimuli); who had an acute brain injury of any type; and who were undergoing or were expected to undergo imminent con-

tinuous EEG monitoring. The presence of the minimally conscious state–minus was determined with the use of the Coma Recovery Scale–Revised (CRS-R,<sup>10</sup> a six-dimension, 23-point scale of hierarchically arranged items [with no cutoff score used for enrollment]), which we assessed among patients who were not receiving deep sedation or neuromuscular blockade. The exclusion criteria were an age of less than 18 years, a preexisting disorder of consciousness before the onset of the acute brain injury that resulted in the current admission, pregnancy, deafness before the acute brain injury, clinical recovery of the ability to follow commands before enrollment, patients or families who did not want to participate in the study, or logistic reasons (details are provided in the Supplementary Appendix).

Patients, families, and treating physicians were unaware of the results of the EEG recordings, and these results were not made available to treating clinicians in relation to decisions regarding the withdrawal of care. Demographic data and data on complications that occurred during the hospital stay and on outcomes were prospectively collected. In addition, we recorded EEGs from 10 healthy volunteers with a mean age of 31 years, using the same EEG protocol as in the patients (see the Supplementary Appendix).

### STUDY OVERSIGHT

The study was approved for patients and healthy volunteers by the local institutional review board. Written informed consent was obtained from the patients’ surrogates and from the healthy volunteers; patients who recovered consciousness were given the opportunity to withdraw from the study.

The first and last authors are responsible for the study design and drafting of the manuscript. There was no industry involvement in or support for the study. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.<sup>11</sup>

### STUDY PROCEDURES

Daily neurologic examinations, including a clinical assessment of the ability or inability of the

patient to follow spoken commands (“stick out your tongue,” “show me two fingers with your right hand,” and “wiggle your toes”), were performed during morning rounds, and the results were recorded.<sup>12</sup> Each EEG assessment was preceded by a clinical examination that included the CRS-R<sup>10</sup> in order to categorize the clinical state of consciousness at the time of the recording (details are provided in the Supplementary Appendix).

Functional outcome was assessed with the Glasgow Outcome Scale–Extended (GOS-E; levels range from 0 to 8, with higher levels indicating better outcomes), with data obtained in a structured telephone interview at 12 months after the injury.<sup>13,14</sup> Both the patient and the interviewer who performed the outcome assessments were unaware of the results of the above-noted examinations during routine rounds and were unaware of the EEG categorization. Outcomes were dichotomized at a GOS-E level of 4, a level that signifies the ability to be left up to 8 hours during the day without assistance.

At the time of the EEG and clinical assessments, all patients were evaluated to ensure the absence of the following complications: seizures, hyperglycemia (serum glucose level, >11.1 mmol per liter [ $>200$  mg per deciliter]), hyponatremia or hypernatremia (serum sodium level <133 and >150 mmol per liter, respectively), and renal or fulminant liver failure. For the daily neurologic assessment, sedated patients underwent interruption or reduction of sedation if it was deemed safe by the attending physician during rounds.<sup>15</sup> Both the behavioral and the EEG assessments were performed during interruption of sedation whenever possible. To account for cases in which stopping sedation was unsafe, during the study we developed a post hoc method to explore the effect of sedative and analgesic medications on EEG responses by collecting information on the doses of administered medications at the time of the assessments as well as the cumulative doses received within the two preceding elimination half-lives of each agent.<sup>3</sup> Sedation was categorized as “minimal” for discontinuous (e.g., single-push) administration and as “low” or “moderate” according to the cumulative doses administered through continuous drip during the two previous half-lives (details are provided in Table S3 in the Supplementary Appendix).

#### MOTOR COMMAND PROTOCOL

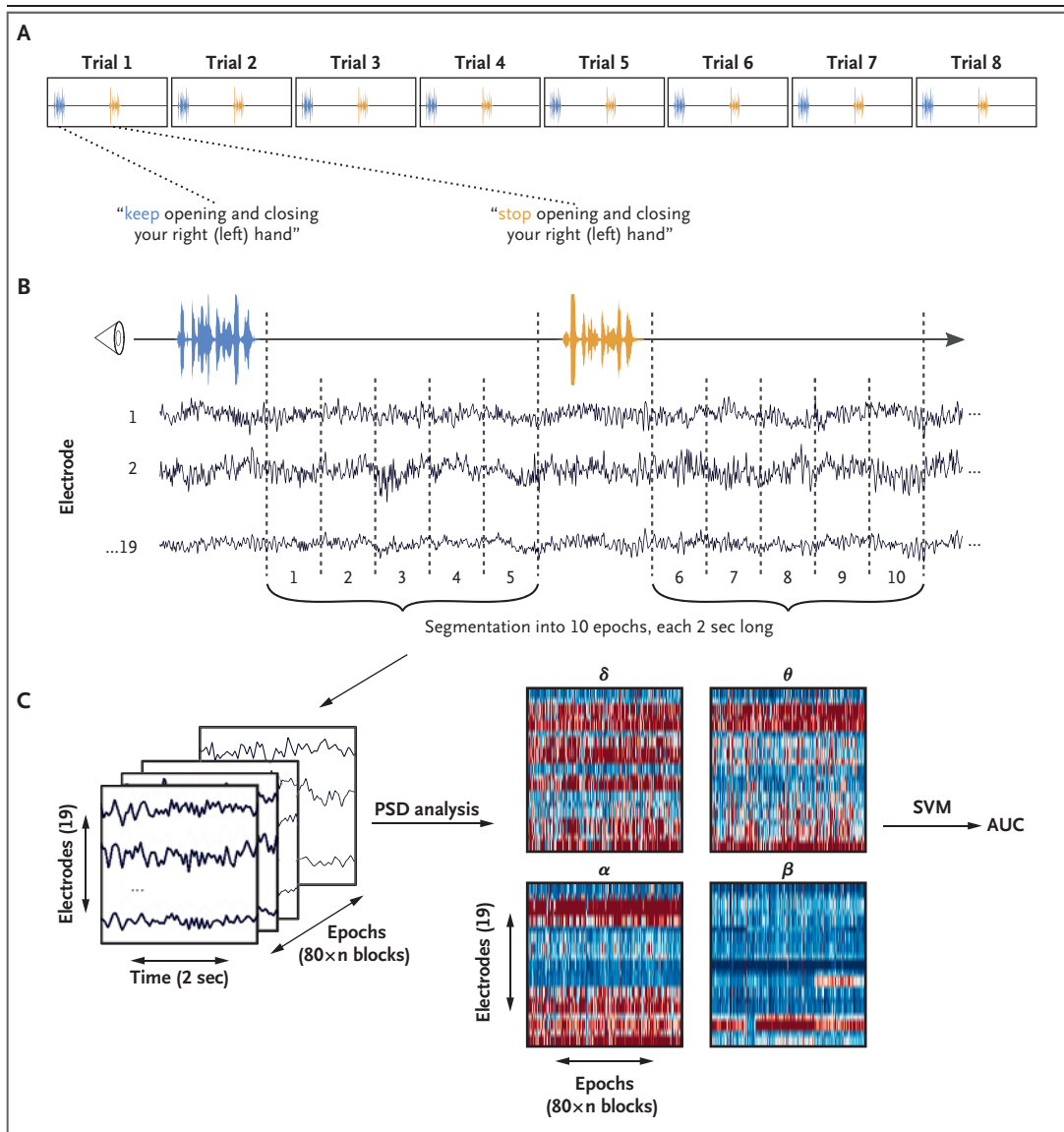
Spoken command instructions during EEG recording alternated between “keep opening and closing your right hand” and “stop opening and closing your right hand.”<sup>16</sup> A total of six blocks each with eight consecutive trials of “keep opening . . .” and “stop opening . . .” commands were recorded (Fig. 1A). For each patient, we recorded three blocks in which the patient was asked to move the right hand and three blocks in which the patient was asked to move the left hand (recordings of the right-hand and left-hand blocks were alternated; see the Supplementary Appendix). The total duration of the motor command session was approximately 25 minutes.

#### EEG ACQUISITION AND PROCESSING

Digital bedside EEG monitoring was performed with a standard 21-electrode montage.<sup>9</sup> EEG recording quality (e.g., lead maintenance and movement artifact) was determined by bedside visual observation at the time of recording in addition to twice-daily lead maintenance by EEG technicians (see the Supplementary Appendix). For each EEG recording, power in predefined frequency ranges was calculated<sup>3,12,17</sup> and used to train a machine-learning algorithm (support vector machine [SVM] with a linear kernel) to distinguish between the EEG responses that followed the commands “keep opening . . .” and “stop opening . . .”

#### STATISTICAL ANALYSIS

The performance of the machine-learning algorithm for each EEG recording was estimated as the area under the receiver-operating-characteristic curve (AUC). To evaluate the significance of the AUC, a one-tailed permutation test was performed (training and evaluation of the classifier 500 times after random shuffling of the “keep opening . . .” and “stop opening . . .” commands<sup>18,19</sup>). Recordings were considered to show evidence of brain activation that was temporally concordant with spoken commands if the AUC was significantly greater than 0.5 (corresponding to the level that would be expected by chance), after application of the Benjamini–Hochberg false-discovery-rate method in cases of multiple recordings in a given patient.<sup>20,21</sup> All EEG analyses were performed with the use of open-source packages, including MNE-Python (www.martinos



**Figure 1. Motor Command Protocol and Data Processing.**

Each block in the motor command protocol consisted of eight trials alternating between the instructions “keep opening and closing your right (left) hand” and “stop opening and closing your right (left) hand” (Panel A). The 10 seconds of electroencephalographic (EEG) recording after the instructions were given were extracted and segmented in five epochs, each 2 seconds long, for further analysis (Panel B). This procedure resulted in 480 epochs in patients (5 epochs×2 instructions×8 trials×6 blocks) and 240 epochs in controls (5 epochs×2 instructions×8 trials×3 blocks). Power spectral density (PSD) analysis was applied to the obtained EEG matrix in four frequency bands ( $\delta$  [1 to 3 Hz],  $\theta$  [4 to 7 Hz],  $\alpha$  [8 to 13 Hz], and  $\beta$  [14 to 30 Hz]) (Panel C). The resulting features were used to train and test a support vector machine (SVM). The classification performance of the SVM for a given recording was assessed as the area under the receiver-operating-characteristic curve (AUC).

.org/mne/stable/index.html)<sup>22</sup> and Scikit-learn (http://scikit-learn.org/stable/index.html).<sup>23</sup>

Categorical variables were expressed as numbers and percentages and were compared with

the use of Fisher’s exact or ordinal chi-square tests, as appropriate. Continuous variables were expressed as medians and interquartile ranges or as means and standard deviations, as appro-



appropriate, and were compared with the use of Wilcoxon signed-rank tests. All tests (other than the permutation test applied on the SVM output) were two-sided. Statistical analyses were performed with R statistical software, version 3.4.1 (R Project for Statistical Computing).<sup>24</sup>

## RESULTS

### PATIENTS AND VOLUNTEERS

A total of 401 unresponsive patients with acute brain injury were screened, and 104 met the criteria for inclusion and were enrolled (Table 1 and Fig. 2). Enrolled patients were similar to those who were not enrolled with respect to age, sex, and admission Glasgow Coma Scale score (Table S1 in the Supplementary Appendix).

The healthy volunteers all had EEG evidence of brain activation in response to motor commands. We obtained a total of 240 EEG recordings from the 104 patients (median number of recordings per patient, 2; interquartile range, 1 to 3) a median of 6 days (interquartile range, 3 to 10) after the injury. Of the 240 EEG recordings, 126 (52%) were acquired while patients were comatose, 54 (22%) while patients were in the vegetative state, and 60 (25%) while patients were in the minimally conscious state—minus category.

Of the 104 patients, 16 (15%) had cognitive–motor dissociation detected on at least one recording. This dissociation was detected at a median of 4.0 days (interquartile range, 2.0 to 5.3) after admission to the ICU. Among these 16 patients, the causes of the acute brain injury were subarachnoid hemorrhage (5 patients), traumatic brain injury (3), intracerebral hemorrhage (4), cardiac arrest (2), neurosarcoidosis (1), and bupropion overdose (1) (Table 2). The group-classification performance of the machine-learning algorithm among patients and healthy volunteers over time is shown in Figure 3.

The condition in 8 (50%) of the patients with cognitive–motor dissociation improved such that they were able to follow the spoken commands used during the daily clinical assessment by the time of hospital discharge, 6.0 days (interquartile range, 4.5 to 8.3) after cognitive–motor dissociation was first documented by EEG (Table S2 in the Supplementary Appendix). The condition in 2 additional patients (12%) with cognitive–motor dissociation improved after hospital

**Table 1. Characteristics of the 104 Patients.\***

| Characteristic   | Value    |
|--|----------|
| Age — yr   | 61±17    |
| Female sex — no. (%)   | 46 (44)  |
| Cause of acute brain injury — no. (%)  |          |
| Cardiac arrest   | 33 (32)  |
| Intracerebral hemorrhage   | 26 (25)  |
| Traumatic brain injury or subdural hematoma  | 15 (14)  |
| Subarachnoid hemorrhage  | 13 (12)  |
| Other  | 17 (16)  |
| Behavioral assessments   |          |
| Median Glasgow Coma Scale score at admission (interquartile range)†                          | 6 (4–8)  |
| Median Coma Recovery Scale–Revised score (interquartile range)‡                              |          |
| Median   | 2 (0–5)  |
| Worst  | 1 (0–3)  |
| Best   | 3 (1–6)  |
| EEG recordings   |          |
| Median EEG recordings per patient (interquartile range) — no.                                | 2 (1–3)  |
| Median time from onset of acute brain injury to first recording (interquartile range) — days | 6 (3–10) |
| Median time from ICU admission to first recording (interquartile range) — days               | 3 (2–6)  |
| Patient's primary language   |          |
| English  | 93 (89)  |
| Spanish  | 11 (11)  |

\* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. EEG denotes electroencephalographic, and ICU intensive care unit.

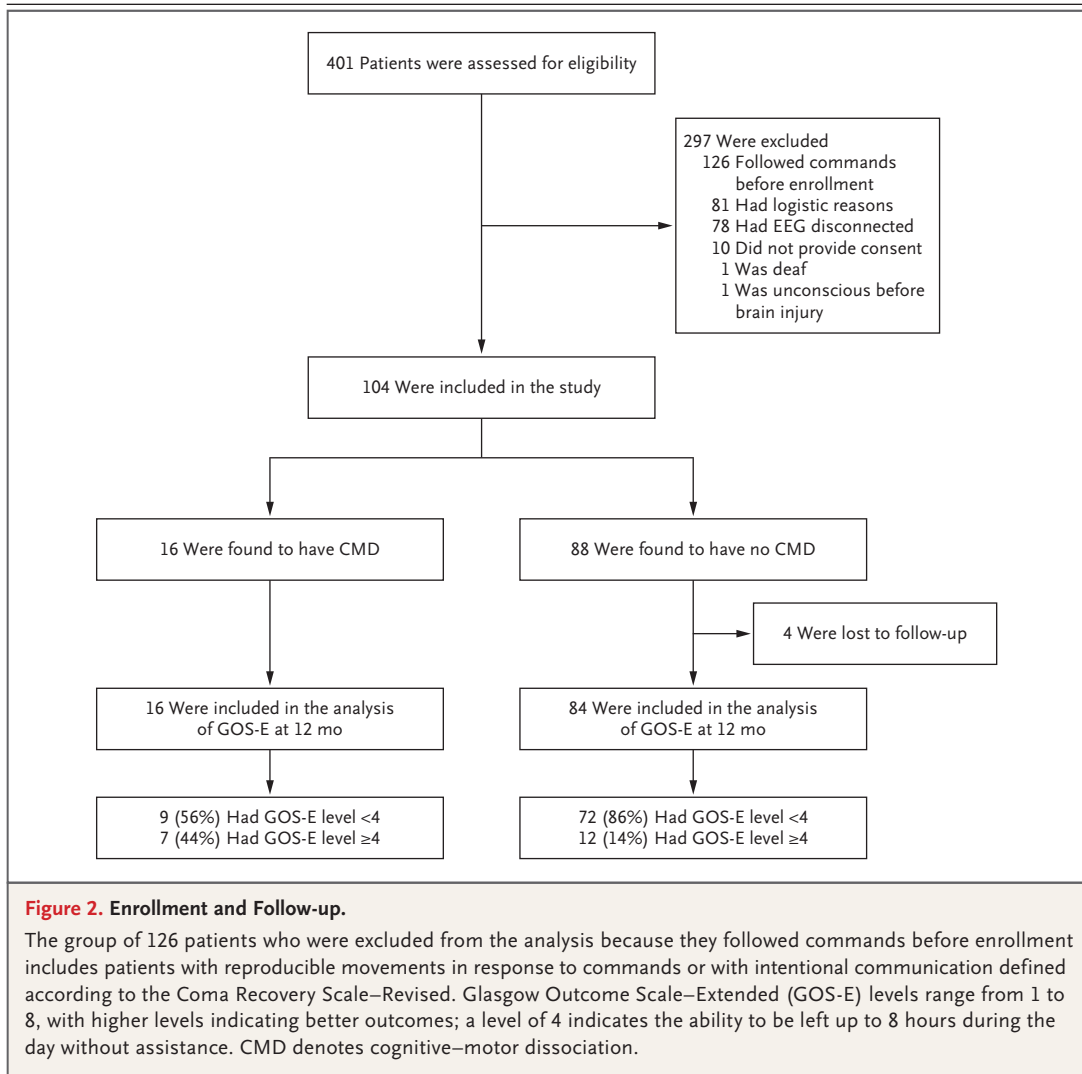
† Scores on the Glasgow Coma Scale range from 3 to 15, with higher scores indicating less neurologic dysfunction.

‡ Scores on the Coma Recovery Scale–Revised range from 0 to 23, with higher scores indicating a higher level of consciousness.

discharge such that they were able to follow the spoken commands used during the daily clinical assessment. In comparison, 26% of the patients who did not have cognitive–motor dissociation (23 patients) were able to follow commands before hospital discharge (median ICU day, 12.0; interquartile range, 9.5 to 19.5).

### OUTCOMES

The GOS-E level at 12 months after the acute brain injury was obtained for 100 of the 104 patients (4 patients were lost to follow-up). A total of 7 of 16 patients (44%) with and 12 of 84



patients (14%) without cognitive–motor dissociation had a GOS-E level of 4 or greater (odds ratio, 4.6; 95% confidence interval [CI], 1.2 to 17.1), and 6 (38%) with cognitive–motor dissociation and 50 (60%) without cognitive–motor dissociation were dead at 12 months. Among the 6 patients with cognitive–motor dissociation who were dead at 12 months, 4 had died in the context of withdrawal of life-sustaining therapy (Table 2, and Table S2 in the Supplementary Appendix). After the 28 patients who underwent withdrawal of life-sustaining therapy were removed from the analysis, cognitive–motor dissociation remained predictive of a GOS-E level of 4 or greater (odds ratio, 5.4; 95% CI, 1.2 to 26.0).

## DISCUSSION

We found that 15% of patients in a consecutive series of patients with acute brain injury who were clinically unresponsive — some of whom had motor localization to pain stimuli, visual fixation, or visual tracking — had evidence of brain activation in response to spoken motor commands, as determined on the basis of EEG activity. This dissociation between behavior and EEG responses to spoken motor commands has been referred to as cognitive–motor dissociation.<sup>5</sup> In our study, this state was seen more frequently in patients with trauma or brain hemorrhages than in patients with hypoxic–ischemic

**Table 2. Comparison of Patients According to Cognitive–Motor Dissociation Status.\***

| Characteristic   | Cognitive–Motor Dissociation |                  | Odds Ratio (95% CI)† |
|--|------------------------------|------------------|----------------------|
|  | Present<br>(N=16)            | Absent<br>(N=88) |                      |
|  | <i>no. of patients (%)</i>   |                  |                      |
| Age >63 yr   | 5 (31)                       | 40 (45)          | 0.5 (0.1–1.9)        |
| Female sex   | 7 (44)                       | 39 (44)          | 1.0 (0.3–3.3)        |
| Cause of acute brain injury                                      |                              |                  |                      |
| Subarachnoid hemorrhage  | 5 (31)                       | 8 (9)            | 4.5 (1.0–19.0)       |
| Intracerebral hemorrhage   | 4 (25)                       | 22 (25)          | 1.0 (0.2–3.8)        |
| Traumatic brain injury or subdural hematoma                      | 3 (19)                       | 12 (14)          | 1.5 (0.2–6.5)        |
| Cardiac arrest   | 2 (12)                       | 31 (35)          | 0.3 (0.0–1.3)        |
| Other  | 2 (12)                       | 15 (17)          | 0.7 (0.1–3.6)        |
| Behavioral assessments   |                              |                  |                      |
| Glasgow Coma Scale score at admission <8                         | 12 (75)                      | 58 (66)          | 1.5 (0.4–7.1)        |
| Median Coma Recovery Scale–Revised score ≥2                      | 10 (62)                      | 47 (53)          | 1.4 (0.4–5.3)        |
| Worst Coma Recovery Scale–Revised score ≥1                       | 10 (62)                      | 56 (64)          | 1.0 (0.3–3.5)        |
| Best Coma Recovery Scale–Revised score ≥3                        | 11 (69)                      | 49 (56)          | 1.7 (0.5–6.9)        |
| Behavioral category at enrollment                                |                              |                  |                      |
| Coma   | 8 (50)                       | 48 (55)          | 0.8 (0.2–2.8)        |
| Unresponsive wakefulness syndrome                                | 3 (19)                       | 20 (23)          | 0.8 (0.1–3.3)        |
| Minimally conscious state–minus                                  | 5 (31)                       | 20 (23)          | 1.5 (0.4–5.5)        |
| Mechanical ventilation   | 15 (94)                      | 81 (92)          | 1.3 (0.1–62.3)       |
| EEG studies  |                              |                  |                      |
| No. of recordings ≥3‡  | 8 (50)                       | 28 (32)          | 2.1 (0.6–7.3)        |
| Time from onset of acute brain injury to first recording ≥6 days | 6 (38)                       | 50 (57)          | 0.5 (0.1–1.5)        |
| Time from ICU admission to first recording ≥3 days               | 7 (44)                       | 52 (59)          | 0.5 (0.2–1.8)        |
| Length of stay   |                              |                  |                      |
| ICU stay ≥13 days  | 11 (69)                      | 43 (49)          | 2.3 (0.7–9.1)        |
| Hospital stay ≥14 days   | 11 (69)                      | 41 (47)          | 2.5 (0.7–10.0)       |
| Outcomes   |                              |                  |                      |
| Following clinical commands before discharge                     | 8 (50)                       | 23 (26)          | 2.8 (1.0–8.4)        |
| Withdrawal of life-sustaining therapy                            | 4 (25)                       | 24 (27)          | 0.9 (0.2–3.3)        |
| Death before discharge   | 6 (38)                       | 32 (36)          | 1.0 (0.3–3.5)        |
| Glasgow Outcome Scale–Extended level ≥4 at 12 months§            | 7 (44)                       | 12 (14)¶         | 4.6 (1.2–17.1)       |

\* Percentages may not total 100 because of rounding. CI denotes confidence interval.

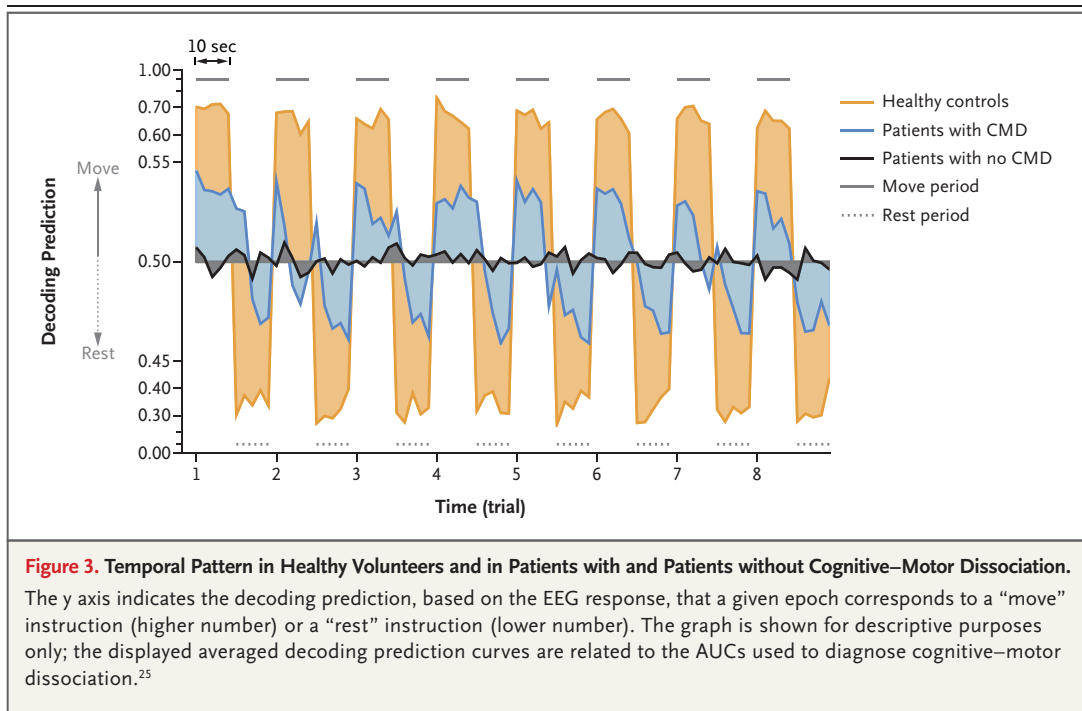
† Odds ratios for the categorical variables were computed using Fisher's exact test. Data for continuous and ordinal variables were split according to the median.

‡ A median of 3 EEG studies (interquartile range, 1 to 4) per patient was performed in the group of patients with cognitive–motor dissociation, and a median of 2 EEG studies (interquartile range, 1 to 3) was performed in the group of patients without cognitive–motor dissociation.

§ Glasgow Outcome Scale–Extended levels range from 1 to 8, with higher levels indicating better outcomes. A level of 4 indicates the ability to be left up to 8 hours during the day without assistance.

¶ Outcomes were missing for 4 patients.





injury, but it was detected in patients with other acute brain injuries and, in some instances, in patients who had been lightly sedated. The frequency of cognitive–motor dissociation and the prognostic associations in our single-center descriptive study require validation in larger, multi-center studies that are powered to detect differences in long-term outcomes.

Our findings support those of previous studies that have shown that EEG or functional MRI can in some cases reflect activation of parts of the brain in response to spoken commands in unresponsive patients,<sup>1,4,26</sup> but whether the detected signal represents recognition or comprehension of commands is uncertain. Patients who had an EEG response to spoken commands more often had later recovery than those who did not have this pattern. It is possible that these patients had overall greater functional integrity of the brain stem, thalamus, and cortex and of the connections among these structures, similar to findings in previous studies in which metabolic measurements such as fluorodeoxyglucose positron-emission tomography were used.<sup>27</sup>

In chronic brain injury, cognitive–motor dissociation has been studied most often in patients with traumatic brain injury<sup>2,4,16,17,28,29</sup> and has been

estimated to have a prevalence of 14%.<sup>6</sup> Our study shows that cognitive–motor dissociation can be detected in the ICU early after brain injury in a similar percentage of patients.<sup>3</sup> The use of methods such as functional MRI to detect cognitive–motor dissociation may result in more frequent detection than EEG, but functional MRI is challenging to perform in a critical care setting.<sup>30</sup>

Limitations of our study include the varied causes of brain injuries among the patients. In addition, the withdrawal of life-sustaining therapies confounds studies of the natural history of acute brain injury.<sup>31</sup> However, even after the exclusion of patients who underwent withdrawal of life-sustaining therapy, our study continued to show a difference in long-term functional outcomes between patients with and patients without cognitive–motor dissociation. We did not perform in-person 12-month follow-up assessments but recorded functional outcomes (GOS-E) by telephone. Sedation is a potential confounder in the classification of patients as being in a comatose, vegetative, or minimally conscious state; however, we were able to detect brain activation in response to motor commands in some lightly sedated patients.

In conclusion, early after brain injury, 15% of clinically unresponsive patients who did not follow commands had EEG evidence of brain activation in response to spoken motor commands recorded at the bedside in the ICU.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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details are provided in the Supplementary Appendix). Dr. Rohaut received postdoctoral grants from Amicale des Anciens Internes des Hôpitaux de Paris and Syndicat des Chefs de Cliniques et Assistants des Hôpitaux de Paris, Assistance Publique-Hôpitaux de Paris, and the Philippe Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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