



# Finally, Some Neurophysiologic Good News—Favorable Prognosis in Coma

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

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**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 dissociation between commanded motor behavior and brain activation in the first few days after brain injury is 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 1–8, with higher levels indicating better outcomes). **Results:** A total of 16 (15%) of 104 unresponsive patients had brain activation detected by EEG at a median of 4 days after injury. The condition in 8 (50%) of these 16 patients and in 23 (26%) of 88 patients without brain activation improved such that they were able to follow commands before discharge. At 12 months, 7 (44%) of 16 patients with brain activation and 12 (14%) of 84 patients 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: 1.2–17.1). **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).

## Commentary

Families of patients in coma often feel that their loved ones can hear them, even if medical professionals find no outward signs of such sensory perception. There are many news reports of patients “waking up” after weeks or months of coma and confirming that they could hear harrowing conversations of their own condition. Such reports have fueled the desire to have better and more accurate tools for coma prognostication.

Although the clinical neurologic examination is one of the most important tools used to prognosticate coma outcome, the value of clinical neurophysiology cannot be overstated. For many decades, neurophysiologic tests have been used to augment the clinical examination. These tests are often very useful in predicting futility and an unfavorable outcome. While this is very helpful, the ability to predict good outcome would be very welcome as well. Encouraging neurophysiological tests would help clinicians provide families with appropriate encouragement about their loved ones.

A recent study by Claassen and colleagues evaluated patients in various stages of coma to determine whether they had “cognitive motor dissociation” and whether this would

predict outcomes.<sup>1</sup> Cognitive motor dissociation is a coma state in which a patient is able to perceive sensory input without the ability to demonstrate it with motor output. They evaluated 104 patients with acute brain injury admitted to their neurologic intensive care unit who were in coma of varying severity and undergoing electroencephalography (EEG) monitoring. All patients were unresponsive to spoken commands, but some could localize painful stimuli or track visual stimuli. The patients were administered standard auditory stimuli (various commands), and the EEG was analyzed quantitatively for activation. Eight (50%) of 16 patients in whom brain activation was detected (ie, cognitive motor dissociation present) and 23 (26%) of 88 patients in whom it was not able to follow commands before discharge (odds ratio [OR]: 2.8; 95% confidence interval [CI]: 1.0–8.4). After 12 months, 7 (44%) of 16 patient with cognitive motor dissociation and 12 (14%) of 84 patients without brain activation to auditory stimulation were capable of functioning independently (OR: 4.6; 95% CI: 1.2–17.1).<sup>1</sup>

The study by Claassen and colleagues demonstrates that verbal command–induced brain activation, as detected by sophisticated quantitative EEG analysis, is a favorable



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prognostic indicator in comatose patients. Such patients with cognitive motor dissociation are considerably more likely than those without brain activation to have meaningful recovery. Having a reliable neurophysiologic marker for favorable outcome from coma is a welcome addition.

The clinical neurophysiologist has several tests that can assist with unfavorable and favorable prognosis from coma. Many of these have been evaluated in anoxic coma, and most have been reappraised after the widespread use of therapeutic hypothermia (TH).<sup>2</sup> One of the most widely used and reliable neurophysiologic tests used for predicting poor outcome from coma is median somatosensory-evoked potentials (SEPs). Bilateral absence of cortical N20 waveforms of the median SEP study as early as 24 hours after onset of coma is highly correlated with a poor outcome (0%-5% false-positive rate [FPR]); with the use of TH, this reliability has not changed.<sup>2,3</sup> Brainstem auditory-evoked potentials (BAEP) have also been evaluated in anoxic coma but have been found to have limited value in prognosticating poor outcomes.<sup>4</sup>

Electroencephalography, obtained continuously or serially, can also have indicators of poor prognosis.<sup>5,6</sup> The absence of EEG reactivity to painful stimulation is highly suggestive of poor prognosis during TH (FPR 1%-7%) and after (FPR 0%-3%).<sup>2</sup> Other EEG features indicative of a poor prognosis include a suppressed EEG with amplitude <20  $\mu$ V (FPR 0%-7%), prolonged epileptiform activity (FPR 0%-6%), and a burst suppression pattern with identical bursts after TH (FPR 0%).<sup>7,8</sup> A recent study has challenged the association of prolonged status epilepticus with poor prognosis in patients undergoing TH. In this study, 54% of patients with status epilepticus were alive at 6 months and 43% had a good outcome.<sup>9</sup> Burst suppression during TH is not strongly associated with poor prognosis, and some of these patients can make a full recovery.<sup>10</sup> Several other EEG features that are often associated with a poor prognosis, but lack as much data, are  $\alpha/\theta$  coma, spindle coma, generalized periodic discharges, and stimulus-induced rhythmic, periodic, or ictal discharges.<sup>11</sup>

A few EEG features have also been associated with a favorable prognosis. Early reactivity to painful stimuli and early continuous background have a greater than 70% positive predictive value (PPV).<sup>12</sup> Rhythmic delta activity has also been associated with good outcomes.<sup>11</sup>

Although the absence of cortical waveforms of short latency median SEPs has been used to prognosticate poor prognosis in coma, middle and late latency-evoked potentials have been shown to predict favorable outcomes. These latter evoked potentials likely represent secondary processing of sensory stimuli. The N70 potential, a middle latency potential, normally obtained approximately 70 ms after stimulation of the median nerve at the wrist, if present with a latency of less than 130 ms was associated with a favorable prognosis in 35 (97%) of 36 of patients.<sup>13</sup> Conversely, if the N70 is absent or delayed beyond 130 ms, it is highly associated with a poor prognosis (FPR 15%).<sup>14</sup>

The auditory mismatch negativity (MMN) potential has also shown value in identifying anoxic coma patients with favorable prognosis. In the pre-TH era, patients who had an MMN had a

PPV for favorable outcome of 69.8%; the MMN was a more reliable predictor of favorable outcome than Glasgow Coma Scale and BAEP.<sup>15</sup> With TH, MMN improvement between when the patient is hypothermic to normothermic suggests favorable outcome; 100% of patients with improved MMN survived anoxic coma while only 40% of those without MMN improvement survived.<sup>16</sup>

The novelty P300 potential has also been associated with a favorable prognosis. This potential is obtained approximately 220 to 380 ms after auditory stimulus delivery and is induced in response to a “novel” stimulus, presented at a frequency of less than 5%. This tests higher cognitive processing without active participation by the patient, making use of this test possible in coma. The novel stimulus can be an auditory stimulus that is of different tone and pitch than the usual, or it can be more specific, like the patient’s own name spoken by a loved one. The more specific the novelty stimulus to the patient, the more likely the P300 will be present.<sup>17</sup> The P300 has a high sensitivity (71%), specificity (85%), and PPV (81%) for awakening from anoxic coma.<sup>18</sup>

The auditory stimulus used to determine brain activation in Claassen and colleagues study joins these other neurophysiologic tests in determining prognosis for patients in coma. The EEG changes detected in this study were done with quantitative EEG analysis using a machine learning algorithm. Such tools are likely not readily available in most laboratories, and whether the EEG activation can be seen visually is not certain. Additionally, whether this auditory stimulus-induced brain activation is different than painful stimulus-induced EEG reactivity (something routinely tested in comatose patients) is not clear. These issues notwithstanding, this study does add another very useful tool to help determine prognosis of comatose patients.

With the variety of neurophysiologic tests now available, clinical neurophysiologists are in a position to not only determine poor prognosis but can also estimate favorable outcomes. Continuous EEG (or serial routine EEGs) and median SEP can identify indicators of unfavorable outcome. If no such indicators are present, evaluating the EEG for brain activation in response to auditory stimulus, using novelty auditory stimuli to identify the novelty P300, or using other middle or late latency-evoked potentials may be considered to identify patients who have a high chance of recovery. When appropriate these techniques can be combined with other nonneurophysiologic techniques, such as neuroimaging and serologic testing, used for prognostication.<sup>2</sup> It should be remembered that most prognostic evaluations have been studied in anoxic coma, and their applicability to other causes of coma may be limited.

As we improve our ability to identify the coma patient who is likely to make a favorable recovery as well as those who are not, we can offer families more accurate information. We may be able to validate that their loved one can “hear” them or we may be able to more convincingly assure them that they cannot. Indeed, as important as caring for the comatose patient is managing the family’s expectations.



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