

Objective Neurophysiologic Markers of Cognition After Pediatric Brain Injury

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Abstract

Background and Objectives

Following brain injury, clinical assessments of residual and emerging cognitive function are difficult and fraught with errors. In adults, recent American Academy of Neurology (AAN) practice guidelines recommend objective neuroimaging and neurophysiologic measures to support diagnosis. Equivalent measures are lacking in pediatrics—an especially great challenge due to the combined heterogeneity of both brain injury and pediatric development. Therefore, we aim to establish quantitative, clinically practicable measures of cognitive function following pediatric brain injury.



Methods

Participants with and without brain injury were aged 8–18 years, clinically classified according to cognitive recovery state: N = 8 in disorders of consciousness (DoC), N = 7 in confusional state, N = 19 cognitively impaired, and N = 13 typically developing uninjured controls. We prospectively measured electroencephalographic markers of sensory processing and attention in an auditory oddball paradigm, and of covert movement attempts in a command-following paradigm.

Results

In 3 participants with DoC, EEG markers of active attempted command following revealed cognitive function that clinical assessment had failed to detect. These same 3 individuals could also be distinguished from the rest of their group by 2 event-related potentials that correlate with sensory processing and orienting attention in the oddball paradigm. Considered across the whole participant group, magnitudes of these 2 ERP markers significantly increased as cognitive recovery progressed (ANOVA: each $p < 0.001$); viewed jointly, the 2 ERP markers cleanly delineated the 4 cognitive states.

Discussion

Despite heterogeneity of brain injuries and brain development, our objective EEG markers reflected cognitive recovery independent of motor function. Two of these markers required no active participation. Together, they allowed us to identify 3 individuals who meet the criteria for cognitive-motor dissociation. To diagnose, prognose, and track cognitive recovery accurately, such markers should be used in pediatrics.

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Brain injury is a leading cause of death and disability among children and adolescents; cognitive impairment is the primary, most persistent, and most disabling sequela. Assessments of emerging and residual cognition are conducted via bedside behavioral examination¹; these are inextricably tied to co-emergence of motor responses. Cognitive recovery, especially in the more severely injured, is characterized by subtle, inconsistent behaviors, further complicated by injury-related motor impairments. Consequently, clinical assessment of cognitive recovery is difficult and fraught with errors.²

Objective brain signal measurements during cognitive tasks have long been used in neuroscience to elucidate cognitive processing and have broad clinical relevance.³⁻⁶ They have been used to diagnose cognitive function in the absence of a positive clinical evaluation, both acutely⁷ and chronically⁶ in adults. In adults, the use of neuroimaging and neurophysiology for detection of covert function has been adopted as a practice guideline by the AAN, American Congress of Rehabilitation Medicine, National Institute on Disability, Independent Living, and Rehabilitation Research,⁸ and European Academy of Neurology.⁹ By contrast, in pediatric brain injury, attempts to improve diagnosis and prognosis via neuroimaging and neurophysiology have been very limited¹⁰⁻¹⁴ and have not reported on brain responses to command following. Thus, there has been insufficient evidence in pediatrics to develop guidelines.¹⁰⁻¹⁴

Our present aim was to characterize cognitive recovery objectively in children and adolescents with brain injury. We included participants across the full spectrum of cognitive recovery¹⁵ including disorders of consciousness (DoC), confusional state (CS), and cognitive impairment, with uninjured controls for comparison. To assess recovery comprehensively, we used well-established event-related EEG markers,^{7,16-18} time-locked to multiple distinct aspects of cognitive processing. In this way, we probed a hierarchy of cognitive functions from basic sensory processing and orienting attention during passive listening, up to sustained, active performance of mental tasks on command. We hypothesized that electrophysiologic markers of cognitive function would track cognitive state in children recovering from brain injury despite the combined heterogeneity arising from the diverse types of brain injury and from the natural variation that occurs along the course of brain development.

Methods

Participants

Participants were 31 children and adolescents with a history of brain injury (Table 1) and 13 typically developing (TD) age-matched controls. The participants were enrolled at a single subacute pediatric rehabilitation center. Participants with brain injury represent a convenience sample of patients admitted either to the inpatient or outpatient rehabilitation service and/or referred to the study by physicians at the

center. Controls were recruited from the same center (limited to patients with injuries not affecting the brain) and the local community. All procedures were approved by the institutional review boards (IRBs) of Weill Cornell Medicine and Blythedale Children's Hospital. Parental consents and participant assents were obtained as per IRB protocols. Participants with a history of brain injury spanned the full spectrum of cognitive function: DoC to CS and cognitive impairment (CI). With 2 exceptions noted in Table 1, participants were tested in a single cognitive state.

Cognitive State Classification

Clinical classification was made by a pediatric clinical neuropsychologist using validated standard clinical measures.^{1,19,20} Disorders of consciousness such as the vegetative state, sometimes known as unresponsive wakefulness syndrome (VS/UWS) or minimally conscious state (MCS), were classified¹⁵ based on the gold standard neurobehavioral assessment, the Coma Recovery Scale-Revised (CRS-R).¹ The lowest level of functioning of participants in this study was VS/UWS, which is characterized by generalized, nonspecific responses to environmental stimuli. Participants were classified as MCS based on the CRS-R criteria.

Emergence from DoC into CS was determined by functional object use or functional communication as per the CRS-R. CS usually follows emergence from MCS and describes a cluster of fluctuating neurobehavioral symptoms that include disturbances of attention, disorientation, disturbance of memory, and emotional/behavioral dysregulation. This designation was based on recent case definition and diagnostic criteria for posttraumatic CS.²¹ In this study, because similar presentations are often observed across etiologies, we have expanded it to broadly apply to all types of brain injury.

Emergence from CS was assessed with an age-appropriate orientation measure (Children's Orientation and Amnesia Test²⁰ or Orientation Log)²² as a proxy for the overall cluster of confusion-related symptoms. CS was considered resolved when a participant obtained 2 consecutive scores above the cutoff for their age on these orientation measures. All participants who emerged from CS were classified as CI because there were no consistent outcome data to specify when and whether complete recovery of all cognitive functions occurred.

Stimuli and Tasks

Auditory Oddball

This EEG paradigm, frequently used in both adults¹⁷ and pediatrics,¹² consists of abrupt, frequent standard and rarer deviant stimuli presented in rapid, randomized sequences. It requires no participation beyond passive listening. Although both sounds trigger event-related potentials (ERPs), the ERPs time-locked to standards and those time-locked to oddballs exhibit robustly detectable differences. (1) In-house version: stimuli were square-wave beeps of 340 ms duration with a fundamental frequency of either 400 Hz (standard) or 575 Hz (deviant), as well as a variety of novel deviant sounds

Table 1 Clinical Characteristics and Session Details

Case #	State	Age at injury	Age at testing	Sex	Etiology	Coma Recovery Scale-Revised (CRS-R)							TTA (days)	Rehab length of stay (days)	Time since injury at testing (mo)	Craniectomies/ cranioplasties	EEG system	Oddball		Motor command following		
						Total	Auditory	Visual	Motor	Oromotor	Communication	Arousal						No. of sessions	No. of sessions	Actual movement	EEG motor response	
1	1(A)	DoC (MCS-)	10	11	F	Hypoxic ischemic encephalopathy	11	2	3	2	2	0	2	45	609	5	—	NeuroCatch and DSI	2	4	—	1/4
2	2(B)	DoC (MCS)	11	12	M	TBI	N/A	N/A	N/A	N/A	N/A	N/A	N/A	17	106	1	—	DSI	N/A	1	—	—
3	3	DoC (MCS-)	4	12	M	Hypoxic ischemic encephalopathy	12	2	1	5	2	0	2	N/A	N/A	96	—	DSI	2	3	—	—
4	4(C)	DoC (MCS-)	9	16	M	TBI	10	2	1	3	2	0	2	309		65	—	DSI and EGI	2	5	—	2/5
5	5	DoC (VS/UWS)	12	17	F	TBI	4	0	0	1	1	0	2	54	1085	67	Craniectomy	DSI	3	3	—	—
6	6(D)	DoC (MCS+)	16	17	M	TBI	14	2	3	5	2	1	1	103	281	4	Cranioplasty	NeuroCatch and DSI	6	N/A	N/A	N/A
7	7(E)	DoC (VS/UWS)	14	18	M	Hypoxic ischemic encephalopathy	6	1	0	1	2	0	2	~90		48	—	DSI and EGI	2	4	—	1/4
8	8	DoC (VS/UWS)	13	17	M	TBI	5	0	1	2	1	0	1	1499	134	54	—	DSI	N/A	1	—	—
—	1(B)	CS	11	12	M	TBI	N/A							17	106	5	—	DSI	6	6	—	—
9	2		11	12	F	TBI								23	51	2	—	DSI	1	1	Yes	—
10	3		12	13	M	TBI								55	243	13	—	DSI	1	1	Left only	—
11	4		13	15	F	Encephalitis								117	670	21	—	DSI	1	1	Yes	—
12	5		15	15	F	Lupus cerebritis								75	35	4	—	DSI	1	1	—	Yes
—	6(D)		16	17	M	TBI								103	281	5	—	NeuroCatch and DSI	8	4	Yes	1/4
13	7		15	18	M	Vascular								27	108	40	Craniectomy, cranioplasty	DSI	1	1	Left only	—
14	1	CI	8	8	M	Acute hydrocephalus								50	126	6	—	DSI	1	1	Yes	Yes
15	2		7	9	M	TBI								12	14	1	—	DSI	1	1	Yes	—
16	3		10	11	M	Lupus cerebritis								24	98	7	—	NeuroCatch and DSI	4	N/A	N/A	N/A
17	4		9	11	M	Encephalitis								12	21	25	—	DSI	1	1	Yes	Yes
18	5		10	11	F	Vascular								54	111	9	—	DSI	1	1	Yes	Yes

Continued

Table 1 Clinical Characteristics and Session Details (continued)

ID	State	Age at injury	Age at testing	Sex	Etiology	Coma Recovery Scale-Revised (CRS-R)						Time since injury at testing (mo)	Craniectomies/cranioplasties	EEG system	Oddball		Motor command following					
						Total	Auditory	Visual	Motor	Oromotor	Communication				Arousal	TTA (days)	Rehab length of stay (days)	No. of sessions	No. of sessions	Actual movement	EEG motor response	
19	6	11	12	M	Vascular									22	74	1	—	NeuroCatch and DSI	2	1	Yes	Yes
—	7(B)	11	12	M	TBI									17	106	9	—	DSI	6	6	Yes	Yes
20	8	11	12	M	Cancer									205	N/A	13	—	DSI	1	1	Yes	Yes
21	9	3	12	M	TBI									122	389	107	—	DSI	1	1	Yes	Yes
22	10	11	12	M	TBI									14	75	18	—	DSI	1	1	Yes	Yes
23	11	11	13	F	Hypoxic ischemic encephalopathy									99	343	27	—	DSI	1	N/A	N/A	N/A
24	12	13	14	M	Encephalitis									83	158	15	—	DSI	1	1	Yes	—
25	13	10	15	M	TBI									48	92	68	—	DSI	1	1	Yes	Yes
26	14	14	15	F	TBI									35	67	9	Craniectomy and cranioplasty	DSI	1	1	Yes	Yes
27	15	14	15	M	Vascular									12	125	12	Craniectomy	DSI	1	N/A	N/A	N/A
28	16	16	16	M	Encephalitis									27	63	3	—	DSI	1	1	Yes	—
29	17	17	18	M	Vascular									19	35	14	—	DSI	1	1	Yes	Yes
30	18	10	11	M	TBI									13	13	13	—	DSI	N/A	1	—	—
31	19	12	14	M	Acute disseminated encephalomyelitis									61	290	30	—	DSI	N/A	1	—	—

Abbreviations: CI = cognitively impaired; CS = confusional state; DoC = disorders of consciousness; DSI = Dry Sensor Interface (Wearable Sensing LLC); MCS = MCS+, minimally conscious state, MCS+, MCS- per published definitions⁵¹; TBI = traumatic brain injury; TTA = time to admission; VS/UWS = vegetative state/unresponsive wakefulness.

The injured group comprised 31 distinct individuals, of whom 2 were followed longitudinally. Letters denote individuals singled out in the figures and discussion: A, C, and E are the participants with DoC who showed detectable brain responses in the attempted movement task; B and D were followed longitudinally, such that B was included in the DoC, CS, and CI groups, and D was included in the DoC and CS groups. Diagnosis for participant B when tested during DoC is confirmed by clinical reports because the CRS-R report is unavailable.

designed to elicit an enhanced P3a component.¹⁷ Each recording session comprised 410 stimuli (270 standard beeps, 80 deviant beeps, and 60 novel deviant sounds) presented in random order in a 1-second repeating rhythm. (2) NeuroCatch: in 4 participants, the NeuroCatch oddball paradigm²³ was used. This paradigm was adapted from previous “brain vital signs” studies that use an oddball paradigm.²³ Each session consisted of two 5-minute runs, for a total of 520 standard (75 dB) and 46 deviant (100 dB) stimuli.

Attempted Motor Command Following

Participants performed a motor command-following (MCF) paradigm previously used in adult brain injury but with fewer trials.⁷ This paradigm required active mental effort and participation. It did not require overt motor responses. Participants heard a prerecorded female voice saying “Keep opening and closing your left hand,” then, “Stop and relax,” then “Keep opening and closing your right hand”, and then “Stop and relax”. Commands were delivered every 15 seconds, allowing 13 seconds to perform or attempt each movement, and the sequence was repeated 8 times for a total of 8 left-hand, 8 right-hand, and 16 rest trials.⁷ Table 1 notes the presence or absence of actual overt hand movement during this task, as well as the number of sessions with positive EEG results.

Data Acquisition

Three EEG systems were used to collect the recordings: (1) Wearable Sensing DSI-24 dry electrode EEG headset (Wearable Sensing LLC) with 19 active electrodes covering frontal, central, parietal, and occipital areas, according to the 10–20 system of the International Federation. Signals were digitized at 300 samples per second after appropriate anti-alias filtering. (2) g.Nautilus system (g.tec Medical Engineering GmbH, Austria; NeuroCatch Inc., Canada) with 3 midline electrodes (Fz, Cz, and Pz, embedded within a cap) and 4 additional electrodes to provide ground, reference, and eye monitoring.²³ The sampling rate was 500 Hz. (3) Geodesic EEG Net Station (Electrical Geodesics Inc.) with the 129-channel Sensor Net. The signals were digitized at 1000 samples per second.

Data Analysis

EEG Data Preprocessing

EEG data were analyzed using custom software and EEGLAB²⁴ in MATLAB (The MathWorks, Inc). EEG signals were high-pass filtered at 1 Hz before 60 Hz line noise removal, anti-alias filtering, and downsampling to 200 Hz. The artifact subspace reconstruction method (ASR)²⁵ was further applied to remove transient high-amplitude artifacts from the continuous EEG data. Smaller artifacts from blinks, cardiac activity, and muscle contractions were removed by rejecting the corresponding sources from an independent component analysis (ICA) decomposition using the Infomax algorithm²⁶ and projecting back into the sensor space.

Analysis of Event-Related Potentials

We derive 3 ERP measures at the vertex electrode: auditory evoked potential (AEP), the P3 and N2.^{16–18} After preprocessing,

trials were segmented into 1100 ms epochs time-locked to the onset of the auditory stimulus (100 ms prestimulus and 1000 ms poststimulus). Analysis then followed standard procedures²⁷: each trial was baseline corrected (by subtracting the mean voltage over the 100 ms prestimulus interval), low-pass filtered at 20 Hz, and averaged time-locked to the stimulus onset. For the analysis of AEPs, this used standard tones only; for the oddball response analysis, a difference wave was computed (average response to deviant stimuli of either kind minus average response to standard tones). We corrected this for the effect of noise by computing a signal-to-noise ratio (SNR), that is, by dividing the mean voltage signal by its own trial-to-trial standard error at each time sample. For the difference waves, this standard error was computed from the variance of differences (i.e., from the sum of the trial-to-trial variances of the deviant-class amplitudes and standard-class amplitudes).²⁸ To obtain a single number reflecting each participant’s AEP, whose latency varies according to age,¹⁶ we computed the largest negative value of the SNR at electrode location Cz in the interval 60–260 ms following stimulus onset. In the oddball difference waveforms, we computed the largest positive SNR at Cz in the interval 200–450 ms to capture the P3 component¹⁷ and the largest negative value in the interval 100–250 ms to capture the N2 (part of which is the mismatch negativity or MMN).¹⁸ The latency of each peak response was also noted.

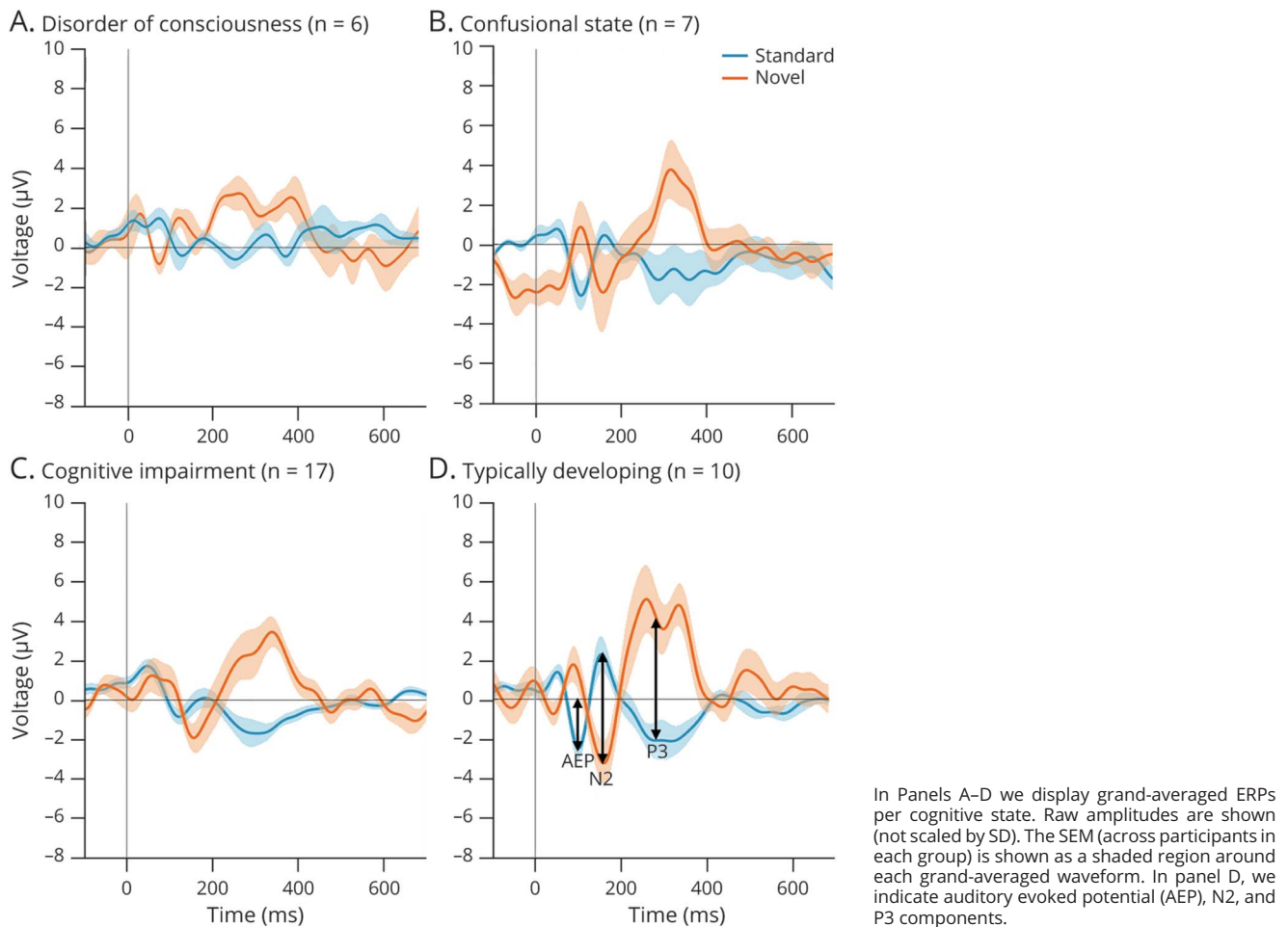
Statistical Tests

A two-way ANOVA was performed separately for the latency and magnitude of each ERP peak. We had a total of 41 ERP measurements from $N = 38$ participants—so, for the participants measured in more than 1 cognitive state, we included only their results from the DoC state. Cognitive state was one explanatory variable (4 levels, corresponding to our 4 groups), and age was the other (binned into 3 roughly equally populated groups, 8–12, 13–16, and 17–18 years).

Analysis of MCF-EEG

After preprocessing, the EEG data were divided into 9-second trials, each trial starting 3 s after the end of the auditory cue. The trials were separated and grouped by condition (move left: $n = 8$; move right: $n = 8$; rest: $n = 16$). Signals were spatially filtered using a Hjorth Laplacian montage,²⁹ and power spectral density estimates were obtained using a multitaper method with 5 tapers, resulting in a frequency resolution of 2 Hz. As in previous work,²⁹ we used the 2-group test³⁰ to determine statistical significance of power spectral differences at each electrode (Chronux toolbox for MATLAB, chronux.org) using a jackknife method with a cutoff of $p \leq 0.05$ before false discovery rate correction. Significant separations between hand movement and rest conditions in the alpha or theta frequency band power were taken as evidence of a response. Furthermore, we boiled down the question of a positive or negative outcome to 2 statistical tests per participant—one for attempted left-hand movement and one for right. For each, we computed the signed coefficient of determination between the bandpower values at each electrode, and a binary variable indicating the instruction (rest or movement), and then subtracted the sum of the values

Figure 1 Grand-Averaged Event-Related Potentials (ERPs) in the Auditory Oddball Paradigm



in contralateral electrodes from the sum of the values in ipsilateral electrodes. A positive net value would be expected in successful command following, as it indicates consistent contralateral event-related desynchronization and/or ipsilateral event-related synchronization³¹; a negative value would indicate the reverse. The significance of the statistic was assessed using a 1-sided permutation test in which the labels (rest and movement) were randomly reassigned to the trials in each of 1,000 repetitions. We considered a participant to have a positive MCF-EEG response if either the left-hand or right-hand *p* value was equal to or less than 0.05.

Data Availability

Data and stimuli from this study are available from the corresponding author on reasonable request.

Results

Demographics and Characteristics

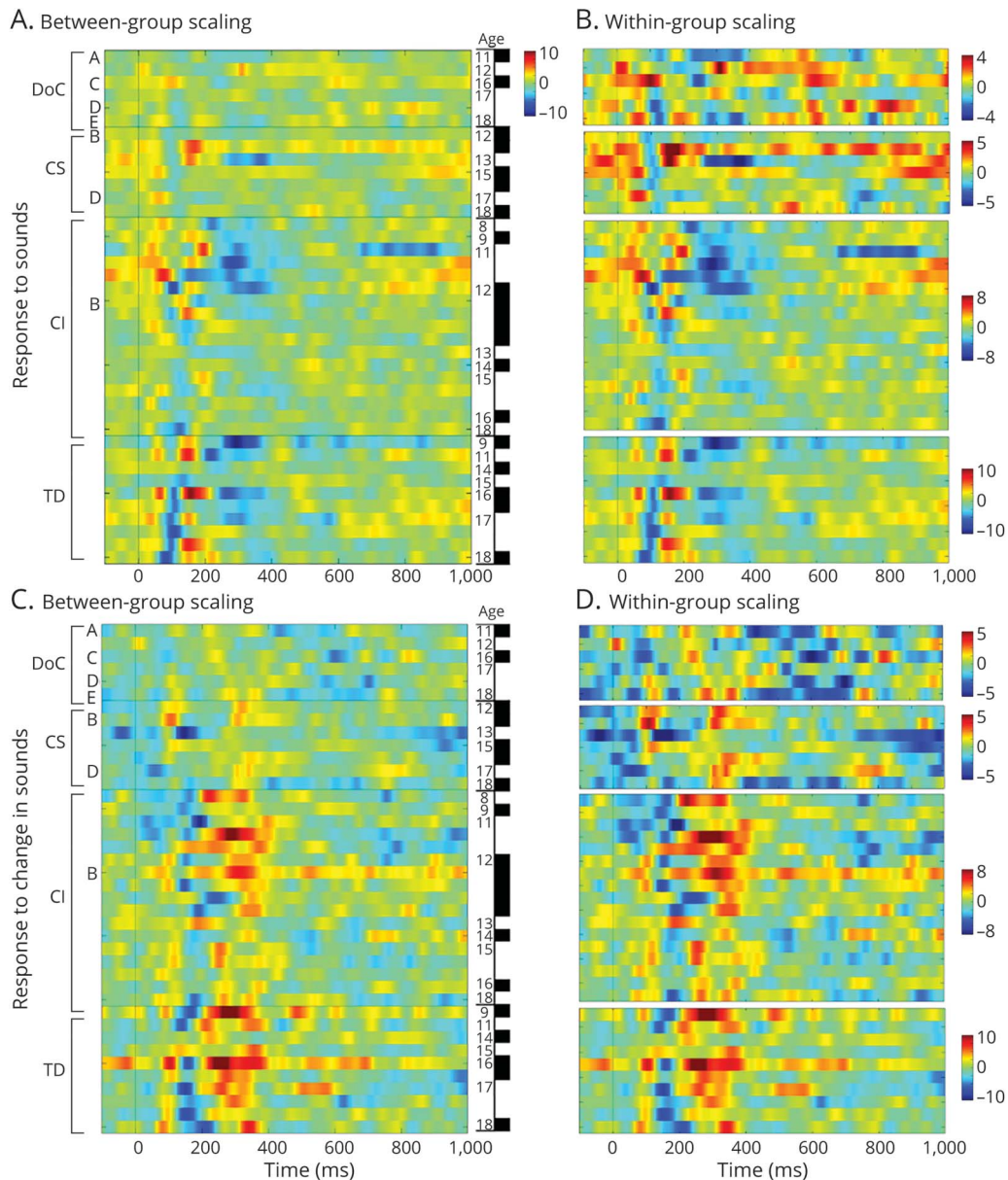
Thirteen TD children and adolescents (9 males) with no history of neurologic disease participated in this study, along

with 31 children and adolescents (23 males) with a history of brain injury (Table 1). Two participants were followed longitudinally: one (marked as B in Table 1 and Figures 2, 3, and 4) was measured in the CS and CI groups; another (marked as D) appears in DoC and CS. The predominant etiology was traumatic brain injury (TBI), accounting for 45% of the injured cohort. Time since injury at date of EEG measurement was widely distributed; 40% were within 12 months.

EEG Correlates of Auditory Stimulus Processing

A traditional groupwise grand-averaged view of the auditory ERP responses is shown in Figure 1, whereas Figure 2 shows the individual results after standardization of each waveform by its own trial-to-trial standard error at each time point. When viewed at the same intensity scaling across all cognitive-state groups in Figure 2A, it is clear that the magnitudes of the AEP responses (blue negative deflections between 60 and 250 ms) increase as cognitive state improves, as is also apparent in Figure 1. The same data, when scaled groupwise in Figure 2B, reveal that AEPs were nonetheless present for most participants in all groups, even when scaling

Figure 2 Raster Plot of Individual Event-Related Potentials From the Oddball Paradigm



In panels A and B, individual participants' response to sounds is displayed with between-group and within-group scaling respectively. In panels C and D, individuals' response to change in sounds is displayed with between-group and within-group scaling respectively. Each row corresponds to a different participant (except where participants B and D are marked as reappearing in multiple cognitive states). The horizontal axis shows time relative to the onset of an auditory stimulus. The color scale is a z-score derived from voltage: it indicates electrical potential, measured at the vertex EEG electrode, standardized by its own trial-to-trial variability. Upper panels: response to standard beep stimuli; lower panels: difference wave between deviant and standard stimuli. Left panels: between-group color scaling—all groups are compared on the same scale. Right panels: within-group scaling—each group is presented with a group-specific scale. Within each group, participants are sorted according to their age at testing—each individual's age, in years, is indicated in the column of numbers down the center of the figure. Certain individuals of interest are denoted by letters in the margin: A, C, and E all showed positive EEG responses to attempted movement while in disorders of consciousness; only B and D were measured longitudinally—B appears in the confusional state and cognitively impaired groups, and D appears in disorders of consciousness and confusional state.

alongside other groups' stronger responses made them invisible in Figure 2A. As expected,¹⁶ AEPs appeared at ~200–250 ms in participants younger than 12 (first few rows of the TD and CI groups), whereas older participants exhibit a 100-ms component similar to the N1 seen in adults.

Individual waveforms from the oddball paradigm are similarly presented in Figure 2C and 2D, this time as difference

waves reflecting the contrast between the EEG response to standard beeps and deviant sounds. In contrast to the AEPs, the change in scaling from a global common scale in Figure 2C to per-group scaling in Figure 2D does not qualitatively change the picture: some participants have a clear N2 (blue negative deflection ~200ms) and P3 (red positive deflection ~300ms), whereas others do not. There is a group-dependent trend in the magnitude and prevalence of

Table 2 Oddball Peak Magnitude and Latency—Mean (SD) and F-Scores From 2-Way ANOVA

	ERP component magnitude and latency by cognitive state: mean (SD) across individuals				F-scores from 2-way ANOVA			
	DoC N = 7 ^a	CS N = 7 ^a	CI N = 19 ^a	TD N = 13	State	Age	State x age	
					F(3,26)	F(2,26)	F(6,26)	
Age (median, range)	16.5 (11–18)	15 (12–18)	12 (8–18)	16 (9–18)				
AEP	Magnitude (z-score)	2.09 (0.54)	1.99 (0.17)	3.78 (1.35)	5.25 (1.33)	16.87***	3.53*	1.14
	Latency (ms)	176 (63.51)	106 (9.72)	157 (56.32)	143 (64.75)	3.15*	9.94***	1.39
N2	Magnitude (z-score)	2.24 (1.09)	4.08 (3.15)	4.24 (2.20)	4.88 (2.91)	2.28	4.82*	2.17
	Latency (ms)	122 (53.07)	137 (82.10)	173 (55.67)	186 (55.34)	2.24	0.19	0.77
P3	Magnitude (z-score)	2.31 (0.50)	2.69 (1.08)	4.80 (1.90)	6.78 (2.90)	6.99**	1.39	0.24
	Latency (ms)	306 (76.61)	290 (48.72)	314 (65.71)	274 (47.12)	0.80	0.44	0.56

Abbreviations: CI = cognitively impaired; CS = confusional state; DOC = disorders of consciousness; ERP = event-related potential; TD = typically developing.
^a The injured group comprised 31 distinct individuals, of whom 2 were followed longitudinally: one (marked as B in other tables and figures) was measured in the CS and CI states; another (marked as D) appears in DoC and CS. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

clear N2 and P3 components, with the DoC group having the fewest and smallest components and the TD group exhibiting a clear P3 in all cases and an N2 in almost all cases. Statistical analysis of the ERP magnitudes and latencies is shown in Table 2.

From our analyses of variance (Table 2), we note a main effect of cognitive state on peak magnitude in both AEPs and P3s ($p < 0.01$ for both). We also found a significant effect of age on AEP and N2 peak magnitude ($p < 0.05$ for both). The AEP latency also showed a main effect of age, as expected: the observed latency decreases ($p < 0.001$) as dominance transitions from a longer-latency component to the adult-like N1 at age 10–12.¹⁶ We found no significant effect of age on N2 or P3 latency and no significant effect of cognitive state on any of the ERP latencies.

EEG Correlates of Attempted Movement to Command

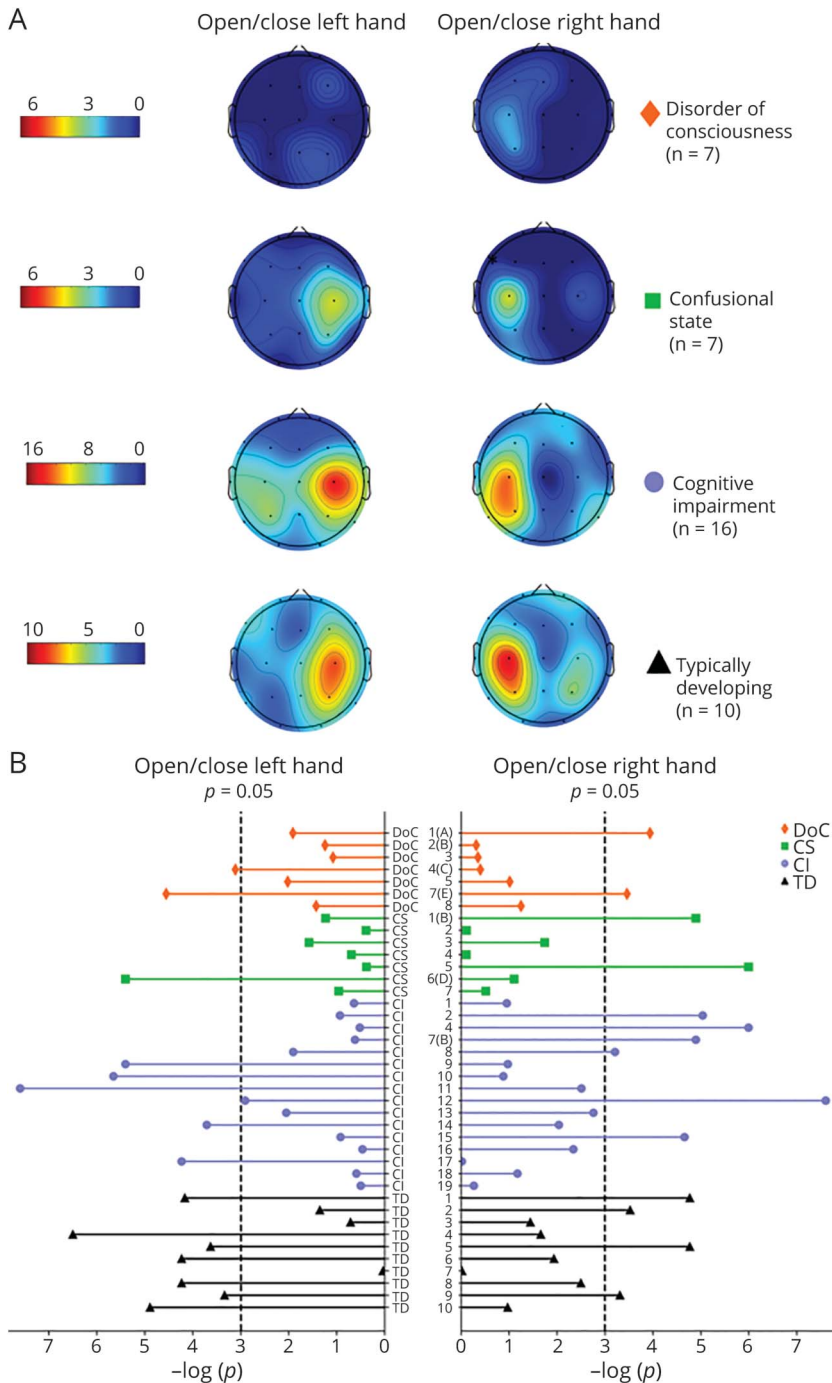
Modulation of EEG bandpower with imagined movement was observed in participants across all recovery states, but the proportion varied across groups (Figure 3). Statistical testing revealed that 80% of participants in the TD group, and 69% in the CI group, showed significant responses contralateral to attempted hand movements. In both CS and DoC groups, 43% showed significant responses. For one particular participant (labeled B in Table 1 and Figures 2, 3, and 4), the response was not significant when tested during DoC but reached significance with the right hand following emergence (in both CS and CI states). As noted in Table 1, 3 participants in the DoC group showed significant responses in at least 1 session (A: 1 of 4 sessions; C: 2 of 5; and E: 1 of 4). These 3 participants with DoC had not shown any clinical signs of command following since their injury.

Toward an Integrated EEG-Based Profile of Cognitive Recovery

The power of the EEG markers emerges clearly when they are plotted together in Figure 4, where each individual's P3 magnitude (response to change in sounds, reflecting higher-level stimulus processing including orienting attentional processes) is plotted against the same individual's AEP magnitude (response to sounds, reflecting lower-level sensory processing of auditory stimuli).

Two participants in the DoC group are clustered together in the lower left corner, with the lowest response magnitudes. In contrast, 3 other participants in the DoC group (marked A, C, and E) show larger responses to both stimuli; these are the same 3 participants who showed significant EEG correlates of attempted motor command following (MCF-EEG positive). Of note, participant D is in this latter cluster, but we cannot corroborate the AEP measurement in this individual as no MCF-EEG test was performed during the time period while they remained in DoC. Several participants in the CS group also show an increase in response to change in sounds (log P3 magnitude >0.4) with intermediate values between those in the DoC group and the CI group in their response to sounds (log AEP values from 0.2 to 0.4). There is both a wide range of responses in the TD and CI groups and considerable overlap between them; however, they are separable from the DoC and CS groups by their larger magnitudes of both AEP and P3. In the 2 participants followed longitudinally (B and D), we note increases in ERP responses as clinical signs demonstrated improving cognition (DoC to CS to CI). We also note a proportion of negative MCF-EEG results in each of our 4 groups. Within each of our groups, the individuals with negative MCF-EEG findings tend to cluster toward the origin of Figure 4, that is, to have smaller AEP and P3 magnitudes than the rest of their group.

Figure 3 Group and Individual Motor Command-Following EEG Results (MCF-EEG)



Panel A displays topographic scalp maps of group results. Within each group, the color scale denotes the number of participants whose EEG response was significant according to the two-group test at each electrode location. Cold colors represent channels where few or no participants responded significantly; hot colors indicate channels where significant responses occurred (greater bandpower in the rest condition than in the attempted hand movement trials). Panel B shows individual statistical test results. Significance values (negative log p values) from permutation tests are shown per participant for attempted left-hand movement on the left side of the panel and attempted right-hand movement on the right side of the panel. Symbol shape and color denote cognitive state, corresponding with Figure 4. Participant numbers and letters on the y axis correspond with the identifiers in Table 1.

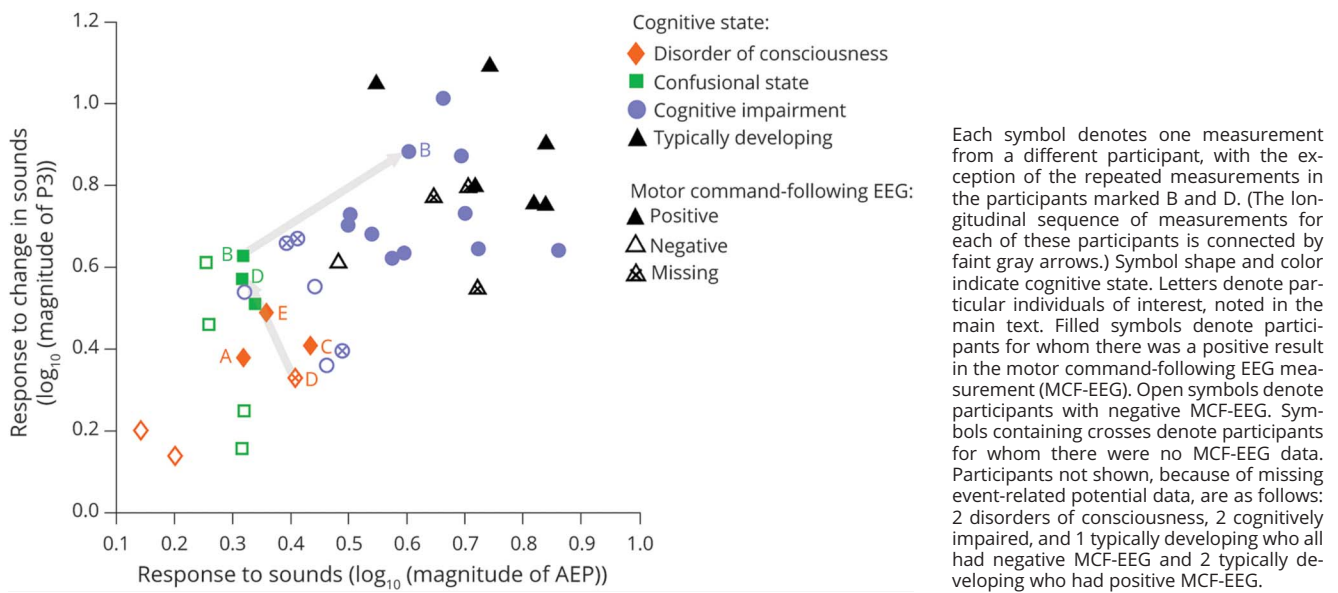
To determine the extent to which cognitive state can be objectively determined from passive ERP biomarkers alone, we conducted an automated classification of cognitive state using a machine learning approach, details of which are provided in eTable 1, links.lww.com/CPJ/A372. The data from participants A, C, and E were excluded from classifier training, on the grounds that their MCF-EEG results rendered their labeling as DoC questionable. This left 37 measurements (37 of the 40 points in Figure 4). Our algorithm detected emergence from

DoC with sensitivity 94.1% and specificity 66.7% (2 of 3). It detected emergence from DoC and CS (considered together) with sensitivity 96.3% and specificity 100% (10 of 10).

Discussion

In a heterogeneous sample of 44 children, clinically feasible hierarchical neurophysiologic assessments yielded objective, non-motor function-dependent biomarkers of cognitive

Figure 4 Two-Dimensional View of Individuals' Event-Related Potential Magnitudes, Inflected According to Motor Command-Following EEG Results



function. Two EEG ERPs, reflecting sensory processing and orienting attention, systematically tracked cognitive recovery following pediatric brain injury. With only 4 exceptions across the cohort, correlates of auditory processing distinguished our DoC and CS groups from each other and from the clinically higher-functioning CI and TD groups. The 4 exceptional participants were clinically categorized in DoC but had higher magnitudes in both ERP components. For 3 of this group, additional EEG measurements verified MCF; we did not measure the fourth on this task. Because the 3 participants exhibit neurophysiologic evidence of command following, but no clinically significant response to commands, they fulfill the construct of cognitive-motor dissociation (CMD).³²

Auditory Stimuli Processing During Cognitive Recovery

The presence of the N1 AEP component (or, for younger children, a negative AEP of longer latency¹⁶ than the N1) is traditionally thought to reflect preattentive perception of sound.³³ However, variation in AEP amplitude has also been linked to arousal and selective attention,³⁴ allowing identification of residual consciousness in severely brain-injured adults.³⁵ In adults, the absence, reduced amplitude, and longer latency of AEPs are associated with poorer outcomes following TBI.³⁶ In the oddball difference wave, 2 components (the N2¹⁸ and P3¹⁷) are considered to be dependent on attention to target discrimination¹⁷ and information processing. In adults, the P3 has been used to improve diagnosis and prognostication in both severe^{3,36} and mild³⁵ brain injury. In pediatrics, P3 amplitude has been shown to be decreased in mild TBI³⁷ and to be correlated with better function in DoC.¹²

Whereas most ERP studies use mean amplitude, we divide our waveforms by the standard error to better reflect signal-to-noise ratio. This improved our results—for example, in allowing us to identify the P3 component more reliably and consistently in the typically developing participants. Consequently, our measures must be interpreted slightly differently: they reflect not only the strength but also the consistency of ERP generators, taking greater account of the extent to which irrelevant brain processes and other noise sources interfere.

All our participants displayed an AEP, albeit with varying magnitude. The presence of an AEP in all our participants with DoC is consistent with previous results from children¹² and adults.³⁸ The magnitude of the AEP separated the groups well: in particular, the CS group was separated almost perfectly from CI and TD where we see larger magnitudes, and from the participants with DoC without motor command-following (MCF) EEG correlates, who had smaller magnitudes. We note a P3 response in almost all our participants but with reduced magnitude in the DoC and CS groups, increasing as cognitive recovery progresses ($p < 0.001$); P3 makes a clearer separation than AEP between the participants with positive and negative MCF-EEG. If such a correlation between markers of orienting attention and markers of higher-order function could be confirmed in a larger sample, the P3 might emerge as a more sensitive indicator of cognitive recovery than current clinical criteria. Our N2 magnitude measurements were not significantly affected by cognitive state (others³⁹ have also found it to be less valuable than the P3). In the CI group, we note a wide range of AEP, P3, and N2 magnitudes, overlapping with the uninjured TD group; this might reflect heterogeneity in

cognitive impairments not captured by gross classifications of recovery.

The latency of the N2 and P3 components did not exhibit significant effects of age or cognitive state. The AEP latency changed with age in the expected way, but we did not find any superimposed trend of latency as a marker of cognitive recovery—a larger sample would be necessary to confirm this and to investigate this apparent failure to replicate findings from adults.³⁶ An exception of particular note is DoC participant C: while a low-amplitude AEP was present, it occurred at ~200 ms, developmentally consistent with age at injury (9 years) and not at the time of testing (16 years). A larger sample of chronic participants would be necessary to determine whether such apparent stunting of brain development is to be expected following severe brain injury.

CMD Following During Cognitive Recovery

fMRI or EEG correlates of attempted movement, temporally consistent with verbal instructions, have been used to detect awareness and motor planning in the absence of overt, purposeful movements.²⁹ Such task-based brain signal analytics can reveal CMD in 15–20% of patients judged unresponsive on clinical examination,² and emerging evidence suggests that acute detection of CMD predicts positive 1-year functional outcomes.² Furthermore, such tasks have also been used to establish simple communication channels for answering yes/no questions.⁴⁰ Negative results should be seen as less conclusive than positive, partly because the appropriate signals are not always measurable even in healthy individuals^{41–43} and partly because the task requires active effort—fluctuation of arousal regulation and mental effort is to be expected in all groups. Studies using small groups of uninjured adult controls have reported false-negative rates ranging from 0 to 30%.^{7,29,31,41,42,44,45} Accordingly, a meta-analysis⁴⁶ demonstrated that passive paradigms (e.g., responses to sounds/change in sounds, as in the current study) may be more effective than active paradigms in diagnosing adults' state of consciousness.

In our own MCF-EEG measurements, the high positive rate in single-session measurements in the TD group (80%) is encouraging evidence that this cognitively demanding task is applicable, even unmodified from the adult paradigm, in children as young as 9 years (youngest positive in our sample). We also note a fairly high response rate (69%) in CI. The response rate drops to 43% in CS—unsurprising given the nature of this cognitive state.⁴⁷ Most notably, we identify positive responses in 3 participants in DoC, who show no clinical evidence of command following; in 2 of these participants, we investigated further using additional cognitive tasks and imaging modalities and obtained positive results that corroborate the findings here.⁴⁸

Limitations

(1) Despite being the largest cognitive ERP study of pediatric brain injury, our sample is still small and heterogeneous. This limits the generalizability of our results due to potential outlier effects. Etiologies and severity are not equally distributed across cognition groups. (2) The lack of detailed cognitive assessments

prevents finer stratification of our results by degree of cognitive impairment, especially within the CI group. (3) Our test sample only extends down to 8 years of age; we are unable to conclude how well our findings might generalize to younger children. (4) We cannot draw strong conclusions about individual recovery trajectories as we have very few longitudinally repeated measurements. (5) A larger cohort of healthy controls across a wider age range would help to establish more-precise quantitative expectations as a function of developmental age. (6) Although our SNR methodology helped in standardizing the results across EEG systems, a cleaner picture might emerge from using a single manufacturer. (7) Larger prospective cohorts would be necessary to link our EEG findings with structural patterns of injury or with effects of particular types of medication. (8) Caution is urged before concluding that patients, especially those tested in a single session, have negative MCF-EEG or lack overt voluntary movement given the high rate (up to 30%) of false negatives noted even in healthy adults.^{41–43} Ideally, we would perform multiple assessments over several days and times, as in behavioral assessments of adult DoC.⁴⁹ (9) Finally, this study, in common with the previous studies reviewed above, uses only a small subset of the possible EEG components that reflect different aspects of cognition.⁵⁰ Pediatric adaptations of additional paradigms, including passive language paradigms,^{10,11} may further broaden and enrich the cognitive profile provided by a few minutes of bedside EEG measurement.

Recent practice guidelines for DoC⁸ identified the lack of evidence supporting an understanding of the natural history of individual pediatric brain injuries as a crucial gap in knowledge. Our results provide a quantitative framework that can be applied to track the natural history of pediatric brain injuries prospectively across the full spectrum of cognitive recovery. Our EEG markers show precise quantification of cognitive recovery at the individual level without relying on motor function. These findings go beyond previous work in that they reflect multiple levels of a cognitive hierarchy, allowing us to consider each measure separately and illustrate the unique way in which it characterizes recovery. Where previous (adult) studies relied on active command following alone to reveal covert cognition, we assessed EEG in both active and passive tasks and illustrated the potential of passive responses alone to achieve this goal. For our participants in DoC, active and passive measures were in agreement. Our results should be validated across larger cohorts and in a more extensive set of within-subject longitudinal assessments. Most importantly, we were able to identify 3 individuals in DoC with evidence of sustained purposeful intent unrevealed by behavioral testing. These 3 participants fulfill the construct of cognitive-motor dissociation,³² identification of which has been associated (in adult populations) with critical differences in natural history and clinical outcome.²

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TAKE-HOME POINTS

- Following pediatric brain injury, diagnosing residual and recovering cognitive function is difficult.
- In a convenience sample of 44 children with and without brain injury, we demonstrate that neurophysiologic measures of sensory processing, orienting attention, and imagined action can track recovery and identify covert cognitive abilities.
- Our direct measurements of brain activity reveal features of cognitive recovery that transcend both the heterogeneity of brain injury and the variation across different stages of brain development.
- Objective measurements of brain responses during cognitive activity can and should be used in children to diagnose cognitive impairment and track recovery.

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Disclosure

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William Watson, PhD	Blythedale Children's Hospital, Valhalla, New York	Drafting/revision of the manuscript for content, including medical writing for content; additional contributions: conducted clinical assessments and wrote the report

Appendix (continued)

Name	Location	Contribution
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N. Jeremy Hill, DPhil	National Center for Adaptive Neurotechnologies, Stratton VA Medical Center, Albany, New York	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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