ORIGINAL ARTICLE

Brain Responses to Propofol in Advance of Recovery from Coma and Disorders of Consciousness

A Preliminary Study

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Abstract

Rationale: Predicting recovery of consciousness in unresponsive, brain-injured individuals has crucial implications for clinical decision-making. Propofol induces distinctive brain network reconfiguration in the healthy brain as it loses consciousness. In patients with disorders of consciousness, the brain network's reconfiguration to propofol may reveal the patient's underlying capacity for consciousness.

Objectives: To design and test a new metric for the prognostication of consciousness recovery in disorders of consciousness.

Methods: Using a within-subject design, we conducted an anesthetic protocol with concomitant high-density EEG in 12 patients with a disorder of consciousness after a brain injury. We quantified the reconfiguration of EEG network hubs and directed functional connectivity before, during, and after propofol exposure and obtained an index of propofol-induced network reconfiguration: the adaptive reconfiguration index. We compared the index of patients who recovered consciousness 3 months after EEG ($n = 3$) to that of patients who did not recover or remained in a chronic disorder of consciousness ($n = 7$) and conducted a logistic regression to assess prognostic accuracy.

Measurements and Main Results: The adaptive reconfiguration index was significantly higher in patients who later recovered full consciousness (U value = 21, $P = 0.008$) and able to discriminate with 100% accuracy whether the patient recovered consciousness.

Conclusions: The adaptive reconfiguration index of patients who recovered from a disorder of consciousness at 3-month follow-up was linearly separable from that of patients who did not recover or remained in a chronic disorder of consciousness on the single-subject level. EEG and propofol can be administered at the bedside with few contraindications, affording the adaptive reconfiguration index tremendous translational potential as a prognostic measure of consciousness recovery in acute clinical settings.

Keywords: consciousness; coma; prognosis; anesthesia; EEG

Assessing conscious awareness and establishing a prognosis for recovery in the absence of behavioral responsiveness are fundamental shortcomings of clinical practice. Recent advances in the neuroscience of consciousness and machine learning have produced highly accurate diagnostic and prognostic indices in patients with a disorder of consciousness (1–7). The majority of these indices, however, rely on specialized technologies, such as functional magnetic resonance imaging and

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At a Glance Commentary

Scientific Knowledge on the Subject: Prognosticating recovery of consciousness in unresponsive, brain-injured patients is currently limited by a patient's ability and willingness to respond to commands/stimuli or expensive medical equipment that is difficult to integrate into everyday clinical environments. Anesthesia causes loss of consciousness accompanied by specific patterns of brain network reconfiguration, such as anteriorization of α network hubs and neutralization of feedback-dominant connectivity.

What This Study Adds to the Field: This study introduces an entirely new metric for prognostication of consciousness recovery in coma and disorders of consciousness, the adaptive reconfiguration index, which quantifies brain network reconfiguration in response to propofol using EEG. In this preliminary study, the adaptive reconfiguration index was able to identify patients who recovered consciousness within 3 months of the EEG recording with an accuracy of 100%. The adaptive reconfiguration index had the same accuracy when calculated using 18 EEG channels on a single hemisphere, highlighting its translatability to a clinical-grade EEG system. This study suggests that the EEG network response to propofol may be used to predict recovery of consciousness in unresponsive, brain-injured patients, which has crucial implications for clinical management and decision-making.

positron emission tomography (PET), which have contraindications that exclude many patients with disorders of consciousness and are challenging to integrate into everyday clinical environments, preventing their widespread adoption for the assessment of patients with disorders of consciousness (4, 6, 8, 9). Here we develop a translational index that aims to overcome these problems.

The healthy brain undergoes an organized functional reconfiguration as it loses consciousness in response to propofol, a widely used intravenous general anesthetic (10). Propofol induces distinctive brain network alterations, such as anteriorization of α network hubs and neutralization of feedback-dominant connectivity (11–14). Our approach is based on the hypothesis that unresponsive, brain-injured patients who undergo these network reconfigurations in response to propofol— indicating loss of some residual consciousness—currently possess consciousness despite being unresponsive and/or have the capacity to recover.

EEG measures the electrical activity of cortical neurons using scalp electrodes. It is significantly less expensive than other imaging technologies, has fewer contraindications, and can be used at the bedside. An EEG is used to calculate the perturbational complexity index, a data-driven metric that can discriminate the level of consciousness in single subjects across several altered states of consciousness, including disorders of consciousness. The perturbational complexity index measures the complexity of the brain's early reaction to a cortical perturbation induced by transcranial magnetic stimulation (1). Although it is a robust measure of consciousness (9), the perturbational complexity index is limited in its translational potential because of its reliance on transcranial magnetic stimulation, which is not commonly available in most acute and chronic facilities with patients with disorders of consciousness.

This preliminary study introduces a translational index that aims to overcome these problems: the adaptive reconfiguration index. The adaptive reconfiguration index measures the brain's response to a neurophysiological perturbation by propofol anesthesia, using EEG. Because propofol anesthesia specifically affects network hubs and directed functional connectivity (11–14), we calculated the reconfiguration of these two metrics and combined them to create the adaptive reconfiguration index. Our central hypothesis was that propofol anesthesia would provoke a reconfiguration of the brain functional network (i.e., a high adaptive reconfiguration index) in patients in a coma and with disorders of consciousness with the capacity for consciousness. Using a within-subject design, we investigated the diagnostic and prognostic value of the adaptive reconfiguration index in a case series of patients in a coma and with disorders of consciousness (i.e., unresponsive wakefulness syndrome and minimally conscious state). Some of the results of these studies have been reported previously in the form of abstracts (15–18).

Methods

Participants

We recruited 12 adults in a coma or with a disorder of consciousness after acquired brain injury (*see* Table 1 and the online supplement for details). Patients in a coma were in a deep state of unconsciousness, lacking both wakefulness and awareness, and had no responses to stimulation and pain. Patients with a disorder of consciousness had preserved ability to awaken but no confirmed signs of awareness; these patients had unresponsive wakefulness syndrome or a minimally conscious state. With unresponsive wakefulness syndrome (also known as a vegetative state), eye opening is present, but patients show no behavioral signs of being aware of themselves or their surroundings, lacking oriented or willful behaviors (19, 20). Therefore, patients with unresponsive wakefulness syndrome are

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Table 1. Demographic and Clinical Characteristics of the 12 Patients Who Underwent Anesthetic Perturbation

ID	Age	Sex	Brain Injury	Time Since Injury	Phase after Injury	CRS-R at Study	Diagnosis at Study	Recovery of Consciousness 90 d after Study
1	42	F	Stroke	21 d	Acute	3	UWS	Yes
2	29	M	TBI	58 d	Acute	4	UWS	Yes
3	50	F	Stroke	25 d	Acute	4	UWS	Yes
4	40	M	Stroke	6 d	Acute	0	Coma	Suspected LIS prior to WOT*
5	74	F	Anoxic	10 d	Acute	0	Coma	NDD*
6	75	F	Stroke	10 d	Acute	5	UWS	No
7	18	F	TBI	21 d	Acute	5	UWS	No
8	24	M	Anoxic	8 yr	Chronic	5	UWS	No
9	53	F	Anoxic	9 mo	Chronic	5	UWS	No
10	28	F	Anoxic	1 yr	Chronic	6	UWS	No
11	28	M	TBI	11 yr	Chronic	10	MCS	No
12	36	F	TBI	2 yr	Chronic	11	MCS	No

Definition of abbreviations: CRS-R = Coma Recovery Scale–Revised; LIS = locked-in syndrome; MCS = minimally conscious state; NDD = neurological determination of death; TBI = traumatic brain injury; UWS = unresponsive wakefulness syndrome; WOT = withdrawal of life-sustaining treatment.
*Withdrawal of treatment or support took place prior to the 90-day follow-up.

considered to be unconscious. A minimally conscious state presents with eye opening and some reproducible but minimal oriented and/or willful behaviors (e.g., visual tracking and inconsistent command following) (21).

Seven of the 12 participants were acute patients (i.e., ⩽6 months after injury) receiving treatment in an intensive care unit; five participants were chronic patients (i.e., >6 months after injury) who were living in the community. The chronic cases were treated as negative controls for the adaptive reconfiguration index. In other words, we expected low adaptive reconfiguration index values, reflecting a low likelihood of recovery, in chronic cases and used them as a benchmark for assessing the prognostic adaptive reconfiguration index values in the acute participants.

Participants were excluded if they had continuous sedation or active vasopressor therapy, elevated intracranial pressure, hepatic or renal failure and/or hemodynamic instability, neurosurgical intervention within 72 hours prior to the study, previous open-head injury, or an allergy to propofol or were deemed medically unsuitable by their attending physician.

Experimental Design

Participants were given propofol in target infusion mode at the predicted target effect site concentration of 2.0 μg/ml using the Marsh pharmacokinetic model (22). Resting-state high-density EEG (hd-EEG) was acquired for 5 minutes at baseline (*pre-anesthesia*), during exposure to propofol anesthesia (*anesthesia*), and after recovery from anesthesia (*post-anesthesia*) (Figure 1A). EEG signals were collected from the scalp using a 128-channel ($n = 10$) or 64-channel ($n = 2$) electrode net (*see* online supplement for details).

We assessed patients' current level of consciousness using the Coma Recovery Scale–Revised (23) immediately preceding the anesthesia protocol (24). Three months after the study, participants were deemed to have recovered full consciousness if they were able to consistently follow commands and/or respond verbally in an appropriate manner to conversation (i.e., if functional/accurate communication or functional object use was present, denoting emergence from a disorder of consciousness, according to criteria of the Coma Recovery Scale–Revised). Of the 12 patients included in his case series, three recovered full consciousness, seven did not recover, one had life-sustaining treatment withdrawn, and another physiological support removed after neurological determination of death. The participant who had life-sustaining treatment withdrawn had a clinical suspicion of complete locked-in syndrome in the 48 hours prior to withdrawal of treatment.

Functional Connectivity of the EEG Network

Network hubs. Network hubs are densely connected nodes within the network. To calculate network hubs, we constructed functional networks using the weighted phase lag index in the α (8–14 Hz) frequency band of all pairwise combinations of electrode channels on 10-second windows (25). Average weighted phase lag index matrices were generated for all three recordings, and network hubs were calculated through the topographic distribution of node degree (i.e., the number of connections a single node has to all other nodes within the network) (Figure 1A).

Directed functional connectivity. The directed phase lag index (dPLI) was calculated across 10-second windows and averaged within each analysis epoch in the α frequency band to generate representative directed functional connectivity matrices for all three recordings (Figure 1A) (26).

Quantifying network reconfiguration in response to anesthesia. We quantified the reconfiguration of network hubs (Hub_R) and dPLI ($dPLI_R$) by calculating differences in the topography of node degree and directed functional connectivity, respectively, between pre-anesthesia, anesthesia, and post-anesthesia epochs (Figure 1B). Hub_R and $dPLI_R$ were then standardized by removing the mean and scaling to unit variance, becoming Hub_{RS} and $dPLI_{RS}$ (Figure 1C) (27).

The Adaptive Reconfiguration Index

The adaptive reconfiguration index is the sum of Hub_{RS} and $dPLI_{RS}$ and represents the amount of topographic reconfiguration exhibited by EEG networks when perturbed by propofol (Figure 1D). We did not calculate the adaptive reconfiguration index for one of the 12 participants because their Hub_R and $dPLI_R$ could not be computed in the post-anesthesia EEG owing to excessive noise.

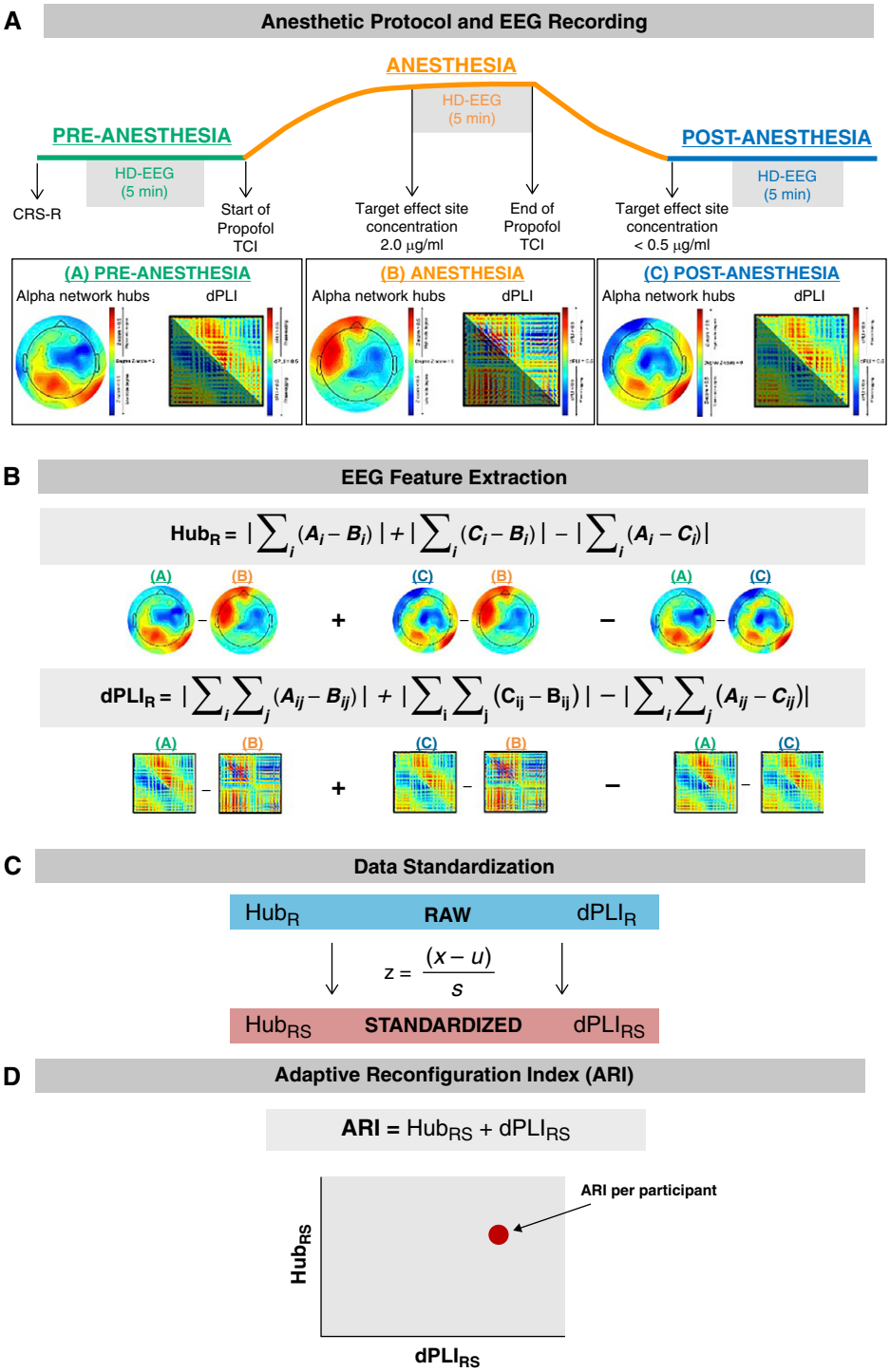

Figure 1. Study protocol and analytic approach. (*A*) Patients underwent propofol anesthesia with a target effect site concentration of 2.0 μg/ml, with concomitant high-density EEG recording. Five-minute epochs of high-density EEG were extracted from *pre-anesthesia* (green), *anesthesia* (orange), and *post-anesthesia* (blue) epochs. The beginning of the recovery (post-anesthesia) period was defined as the moment when the predicted effect site concentration decreased below 0.5 μg/ml. Whole-brain α network hubs and directed phase lag index (dPLI) were calculated in all three epochs. (*B*) The reconfiguration of EEG network hubs (Hub_R) was calculated by contrasting node degree between pre-anesthesia and anesthesia, post-anesthesia and anesthesia, and pre-anesthesia and post-anesthesia recordings. The reconfiguration of dPLI ($dPLI_R$) was calculated by contrasting connectivity matrices between pre-anesthesia and anesthesia, post-anesthesia and anesthesia, and pre-anesthesia and post-anesthesia recordings. (*C* and *D*) Hub_R and $dPLI_R$ were standardized, yielding Hub_{RS} and $dPLI_{RS}$ (*C*), which were then summed to yield the adaptive reconfiguration index (*D*). CRS-R = Coma Recovery Scale–Revised; HD = high-density; TCI = target-controlled infusion.

Statistical analyses. We investigated the association between the adaptive reconfiguration index and *1*) current level of consciousness (diagnosis) and *2*) recovery of full consciousness (prognosis). We conducted one-tailed Mann-Whitney *U* tests to determine whether the adaptive reconfiguration index and its components (Hub_R and $dPLI_R$) were higher in patients with favorable diagnosis (i.e., patients in a minimally conscious state showing some signs of consciousness) and prognosis (i.e., patients who later recovered consciousness within 90 d). We then conducted a logistic regression (scikit learn implementation, L2 penalty) to assess the diagnostic and prognostic separability of the adaptive reconfiguration index. We classified true/false positives/negatives based on the side of the decision boundary on which each data point fell, according to our *a priori* hypothesis (i.e., strong reconfiguration to propofol is associated with favorable diagnosis and prognosis). Diagnostic and prognostic sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were then calculated. The area under the receiver operating characteristic curve (ROC AUC) was also calculated when sensitivity and specificity were above 50%. Patients who had life-sustaining treatment or physiologic support withdrawn were not included in the prognostic analyses. The patient who had a clinical suspicion of complete locked-in syndrome prior to withdrawal of treatment, despite presenting as being in a coma according to the Coma Recovery Scale–Revised, was also removed from group diagnostic analyses. To assess the translational potential of the adaptive reconfiguration index to a clinical EEG system, we recalculated the adaptive reconfiguration index with a selection of 18 electrodes (10–20 placement) across patients' healthiest hemisphere and reran statistical analyses. Given the one-tailed nature of the statistical tests, results were considered statistically significant at $P < 0.025$.

Results

The Adaptive Reconfiguration Index Heralds Recovery within 90 Days

We determined whether patients recovered full consciousness within 3 months after assessment of their adaptive reconfiguration index. We expected that patients with high propofol-induced network reconfiguration (i.e., a high adaptive reconfiguration index) would recover full consciousness at the 3-month follow-up.

Four individual examples of propofol-induced network reconfiguration can be found in Figure 2 (*see* Figure E1 in the online supplement for all cases). On an individual level, a high adaptive reconfiguration index was indicative of favorable prognosis (Figures 2 and 3). When taken separately, the Hub_R and $dPLI_R$ were higher in patients who later recovered full consciousness than in those who did not, reaching statistical significance for Hub_R (Hub_R *U* value = 21, one-tailed $P = 0.008$; $dPLI_R$ *U* value = 19, one-tailed $P = 0.033$) (Figures 4A and 4B). This indicated greater reconfiguration in response to propofol in patients with the capacity to recover. Patients who recovered full consciousness could be separated on an individual subject level from those who did not recover; the minimum Hub_R and $dPLI_R$ values in recovered patients were above the maximum values of those who did not recover (Figures 4A and 4B).

In the three patients who later recovered full consciousness, the network hub topography mirrored that of healthy individuals (anterior during exposure to propofol; posterior otherwise) (Figure 2A; Figure E1, cases 1–3) (11). In the same three patients who later recovered consciousness, the directed functional connectivity patterns also paralleled those of healthy individuals (feedforward-dominant or neutral dPLI during exposure to propofol; feedback-dominant dPLI otherwise) (Figure 2A; Figure E1, cases 1–3) (12–14). In contrast, patients who did not go on to recover full consciousness within the follow-up period showed minimal hub reconfiguration during propofol exposure (e.g., Figure 2B; Figure E1, cases 6, 7, and 12), or random, incoherent shifts in hub structure that did not return to baseline configuration during the post-anesthesia recording (e.g., Figure 2C; Figure E1, cases 8 and 9). The same patients who did not go on to recover consciousness also showed little to no reconfiguration in directed functional connectivity in response to propofol or pathological patterns (e.g., Figures 2B and 2C; Figure E1, cases 6–12).

The adaptive reconfiguration index was significantly higher in patients who later recovered full consciousness (*U* value = 21, one-tailed $P = 0.008$) (Figure 4C). Strikingly, the logistic regression was able to linearly separate patients according to whether they would recover full consciousness with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, and a ROC AUC of 1 (Figure 5).

The adaptive reconfiguration index for all chronic patients was low, as expected, reflecting their low likelihood of recovery. Our results confirmed that these cases were a viable benchmark for patients in an acute coma and with disorder of consciousness because the adaptive reconfiguration index values of all acute patients who did not recover full consciousness were in the same range as these negative controls.

Importantly, the patient (case 4) who was suspected to have complete locked-in syndrome immediately prior to withdrawal of life-sustaining treatment had a high adaptive reconfiguration index, within the range of patients who later recovered full consciousness (Figures 2D and 3). Although the consciousness status of this patient could not be confirmed prior to withdrawal of treatment, the adaptive reconfiguration index would have classified this patient as having the potential for consciousness even though he presented with a behavioral diagnosis of coma at the time of the adaptive reconfiguration index calculation.

The Adaptive Reconfiguration Index Has Low Diagnostic Accuracy

The patients' current level of consciousness was assessed using the Coma Recovery Scale–Revised immediately preceding the anesthesia protocol (23). We expected participants with "some signs of consciousness" (i.e., a minimally conscious state) to have a higher adaptive reconfiguration index than those with "no signs of consciousness" (i.e., coma and unresponsive wakefulness syndrome). However, no group differences were found on the Hub_R (one-tailed $P = 0.911$) and $dPLI_R$ (one-tailed $P = 0.733$), the adaptive reconfiguration index did not differ between groups (one-tailed $P = 0.800$), and the logistic regression indicated that the adaptive reconfiguration index could not meaningfully separate participants according to their currently diagnosed level of consciousness (sensitivity = 0%, specificity = 62.5%, positive predictive value = 0%, negative predictive value = 71.4%, accuracy = 50%) (Figure 6). Contrarily to adaptive reconfiguration index's high prognostic value, its

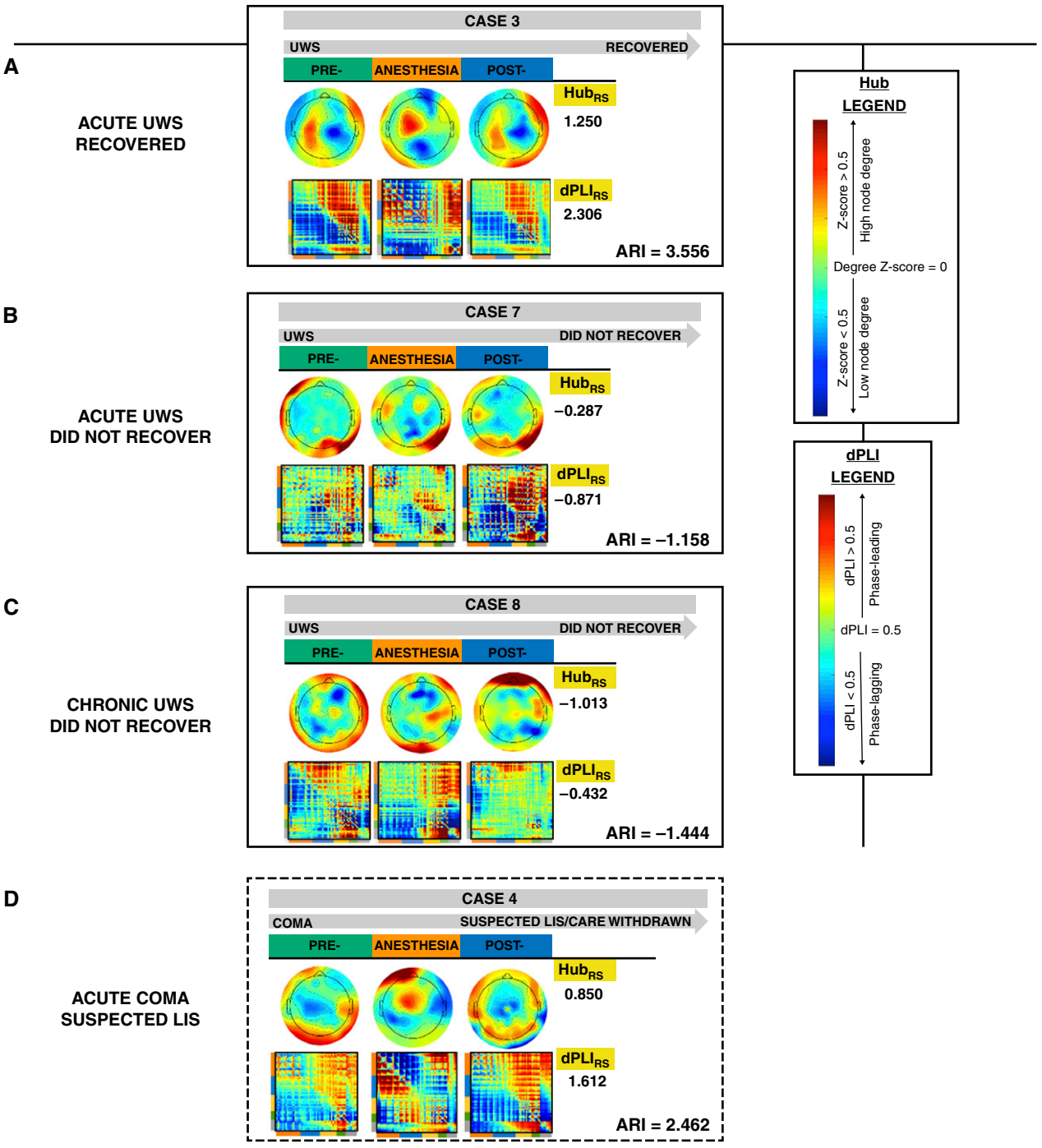

Figure 2. Four individual cases depicting the α network's response to propofol administration. For each case presented, topographic maps of the node degree of α EEG networks and matrices of functional connectivity are presented across *pre-anesthesia* (green), *anesthesia* (orange), and *post-anesthesia* (blue) epochs. For hubs, the color map represents the z-score of the normalized node degree for each electrode. For the directed phase lag index dPLI, for visualization purposes, each matrix depicts a single brain hemisphere per participant (in cases of focal lesions, the hemisphere with the least severe neuronal damage; in cases of diffuse brain injury, the hemisphere with the healthiest reconfiguration pattern). Electrodes are ordered per region, represented by the color bar bordering each matrix: frontal (orange), central (blue), parietal (yellow), occipital (green), and temporal (gray). The color map represents the strength of lead–lag relationships for each electrode pair; red depicts phase leading, and blue represents phase lagging. The standardized values of the hub and dPLI reconfiguration are depicted in the right column of each panel (yellow), and the adaptive reconfiguration index is indicated in the bottom right corner of each case. (*A*) Case 3, who had acute unresponsive wakefulness syndrome, showed strong reconfiguration of hubs and dPLI (high adaptive reconfiguration index) and recovered full consciousness within 90 days of the study. (*B*) Case 7, who had acute unresponsive wakefulness syndrome, showed an absent reconfiguration to propofol anesthesia (low adaptive reconfiguration index) and did not recover consciousness at follow-up. (*C*) Case 8, who had

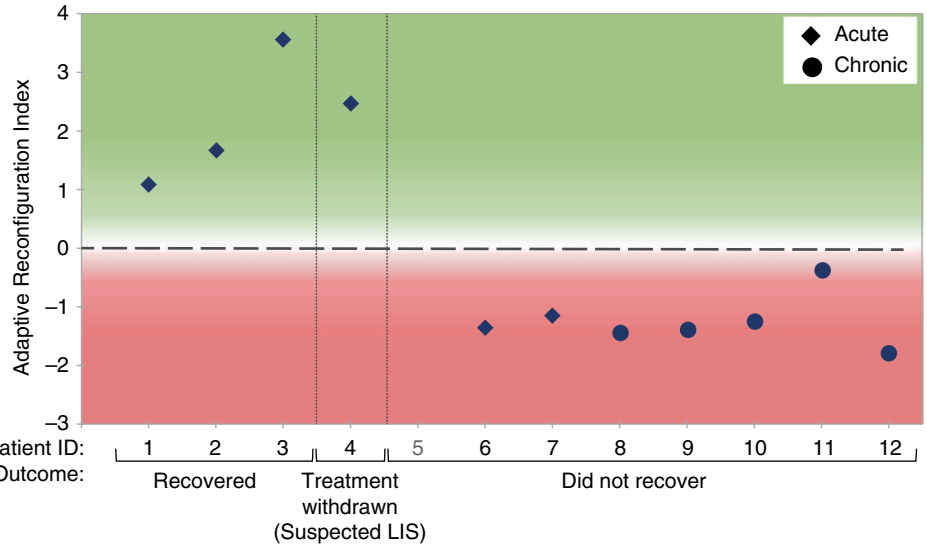

Figure 3. Adaptive reconfiguration index value per patient. Individual adaptive reconfiguration index values are depicted as diamonds for acute patients and circles for chronic patients. Patients are organized by outcome at 90-day follow-up, indicated at the bottom of the *x*-axis. Patients who recovered full consciousness had an adaptive reconfiguration index value above 0, whereas patients who did not recover full consciousness had an adaptive reconfiguration index value below 0. Patient 4 had life-sustaining treatment withdrawn, with a suspicion of complete locked-in syndrome prior to treatment withdrawal. Patient 5 had no *post-anesthesia* recording and could not be included in the adaptive reconfiguration index calculation. LIS = locked-in syndrome.

diagnostic value was not confirmed in this case series.

Translatability of the Adaptive Reconfiguration Index to Clinical EEG

Given that hd-EEG systems are not widely available in acute care settings, we assessed translatability by recalculating the adaptive reconfiguration index with a subset of electrodes common to clinical EEG systems. Using 18 channels across patients' healthiest hemisphere, Hub_R and $dPLI_R$ were significantly higher in patients who recovered full consciousness by the 3-month follow-up (Hub_R *U* value = 21, one-tailed $P = 0.008$; $dPLI_R$ *U* value = 19, one-tailed $P = 0.033$) (Figures 7A and 7B). The adaptive reconfiguration index was also significantly higher in patients who later recovered full consciousness (*U* value = 21, one-tailed $P = 0.008$) (Figure 7C), and both prognostic groups (i.e., "recovered" versus "did not recover") were linearly separable, with a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 100%, and a ROC AUC of 1 (Figure 7D). That is, with only 18 channels, the adaptive reconfiguration index could still discriminate with 100% accuracy whether the patient later recovered from a coma or disorder of consciousness.

Discussion

In this case series, we introduced and tested a novel measure for the prognosis of recovery from coma and disorders of consciousness: the adaptive reconfiguration index. The adaptive reconfiguration index quantifies the reconfiguration of the brain network in response to perturbation with propofol anesthesia. In this small sample, the adaptive reconfiguration index accurately predicted recovery from a coma or disorders of consciousness at 3-month follow-up at the single-subject level. Importantly, we were able to validate that the adaptive reconfiguration index retained its prognostic value even with only 18 EEG channels placed on a single hemisphere, highlighting its translational potential to equipment that is commonly available in critical care environments.

The adaptive reconfiguration index is a novel measure that overcomes the limitations of existing methods for prognostication of coma and disorders of consciousness (*see* online supplement). EEG and propofol anesthesia can be administered at the bedside with limited patient distress or contraindications, affording the adaptive reconfiguration index tremendous translational potential for acute clinical settings. The approach does not require individuals to perform any sensory, motor, or cognitive tasks and is thus independent of the individual's capability or willingness to react to external stimuli or commands. Our approach also does not rely on statistical comparisons between the neurophysiological data of pathologically unresponsive patients and conscious responsive individuals (28); rather, we

Figure 2. (*Continued*). chronic unresponsive wakefulness syndrome, showed a minimal response to propofol, with a pathological response in the post-anesthesia recording (low adaptive reconfiguration index). This patient did not recover consciousness at follow-up. (*D*) Case 4 was in an acute coma and had life-sustaining treatment withdrawn. Within 48 hours of withdrawal of treatment, the attending physician indicated a suspicion of complete locked-in syndrome and potentially preserved awareness. Although the diagnosis of locked-in syndrome was not confirmed, this patient showed a strong reconfiguration to propofol (high adaptive reconfiguration index), which is consistent with the clinical suspicion of complete locked-in syndrome. ARI = adaptive reconfiguration index; dPLI = directed phase lag index; $dPLI_{RS}$ = standardized reconfiguration of the dPLI; HUB_{RS} = standardized hub reconfiguration; LIS = locked-in syndrome; UWS = unresponsive wakefulness syndrome.

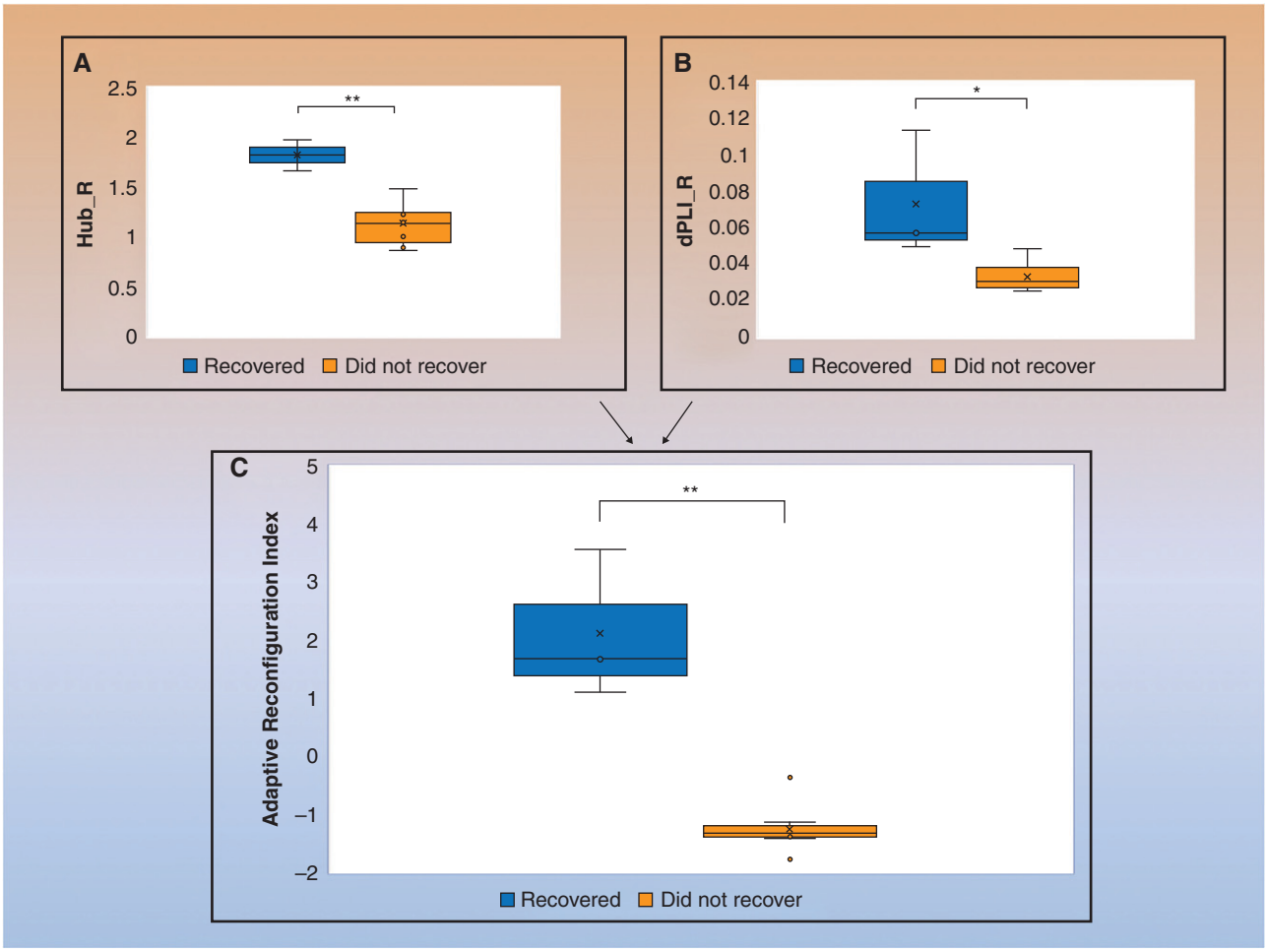

Figure 4. The adaptive reconfiguration index was significantly higher in patients who later recovered consciousness. (*A–C*) Hub reconfiguration (Hub_R) (*A*), directed phase lag index reconfiguration ($dPLI_R$) (*B*), and adaptive reconfiguration index (*C*) values are depicted per group. Patients who recovered full consciousness within 90 days of the study constitute the "recovered" group ($n = 3$) (blue), whereas those who did not recover full consciousness within 90 days constitute the "did not recover" group (orange) ($n = 7$). One-tailed Mann-Whitney *U* test results showed higher Hub_R, $dPLI_R$, and adaptive reconfiguration index in the recovered group, indicating that patients in the recovered group had higher Hub_R and $dPLI_R$ values when these indices were taken separately and higher adaptive reconfiguration index values, indicating stronger reconfiguration to propofol perturbation. Results were statistically significant at $P < 0.025$ for Hub_R (one-tailed $P = 0.008$) and the adaptive reconfiguration index (one-tailed $P = 0.008$), and showed a trend toward significance for $dPLI_R$ (one-tailed $P = 0.033$). *$P < 0.05$ and **$P < 0.025$.

employ a within-subject design that is sensitive to the particular neural activity associated with consciousness in each brain-injured individual (24). The index is simple and transparent without any transformations aside from standardization. The adaptive reconfiguration index accurately predicted recovery of consciousness at 3-month follow-up in a small sample of patients with various etiologies of brain injury and across diagnoses ranging from coma to a minimally conscious state. This naturalistic study sample was reflective of the heterogeneity of individuals in a coma or with a disorder of consciousness, suggesting its potential applicability across diverse brain-injured populations. Finally, unlike other prognostic measures that rely on global or event-related brain signals, the adaptive reconfiguration index focuses on resting-state brain signals that are attenuated by the effects of general anesthesia, which putatively include those associated with conscious awareness. Thus, the adaptive reconfiguration index is low when there is little change in network configuration upon exposure to anesthesia and when brain networks do not return to their baseline configuration after exposure to anesthesia. This aspect is relevant because 50% of our participants who did not recover full consciousness showed baseline patterns associated with conscious awareness (e.g., feedback-dominant connectivity). It is the *inability* of these network patterns to reconfigure upon exposure to anesthesia that reflects the patient's capacity for recovery rather than the baseline patterns alone (*see* online supplement and Figure E2). In other words, anesthetic perturbation of brain networks was necessary to correctly classify patients who had seemingly healthy resting-state patterns (*see* online supplement).

Although the adaptive reconfiguration index showed promising preliminary results

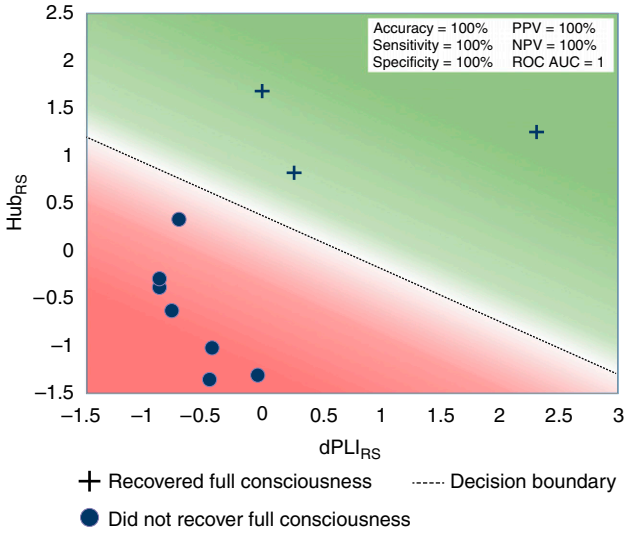

Figure 5. The adaptive reconfiguration index predicts 90-day recovery of consciousness. The standardized reconfiguration of hubs (*y*-axis) and the standardized reconfiguration of the directed phase lag index (*x*-axis) are plotted per participant in a two-dimensional feature space, yielding the adaptive reconfiguration index. Adaptive reconfiguration index value per participant is depicted with circles ("did not recover") and crosses ("recovered") according to recovery status at 90-day follow-up. The logistic regression decision boundary (dashed line) accurately separated both groups according to their 90-day outcome. $dPLI_{RS}$ = standardized reconfiguration of the directed phase lag index; Hub_{RS} = standardized reconfiguration of hubs; NPV = negative predictive value; PPV = positive predictive value; ROC AUC = area under the receiver operating characteristic curve.

as a prognostic tool for consciousness recovery, it showed no association with a patient's current behavioral level of consciousness. This could reflect the limitations of relying on behavioral responses to infer the presence or absence of consciousness. Indeed, behavioral assessment of consciousness may be unfit to capture covert consciousness when it is present, as may have been the case at the time of the study in the three patients who later recovered (cases 1–3). The adaptive reconfiguration index's lack of diagnostic accuracy may also be due to factors affecting the accuracy of the single Coma Recovery

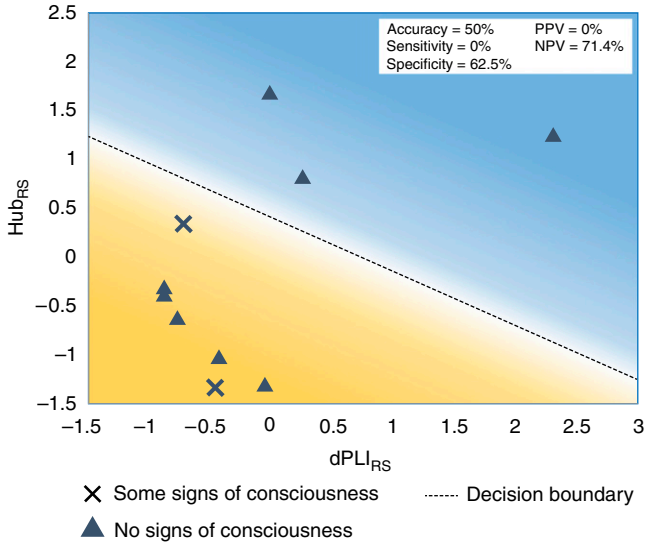

Figure 6. The adaptive reconfiguration index cannot predict current level of consciousness. The standardized reconfiguration of hubs (*y*-axis) and the standardized reconfiguration of the directed phase lag index (*x*-axis) are plotted per participant in a two-dimensional feature space, yielding the adaptive reconfiguration index. Adaptive reconfiguration index value per participant is depicted with triangles ("No signs of consciousness") and X's ("Some signs of consciousness") based on diagnosed level of consciousness at the time of the study according to the Coma Recovery Scale–Revised. The logistic regression decision boundary did not accurately separate both groups according to their current level of consciousness, yielding low accuracy, sensitivity, and positive predictive values. $dPLI_{RS}$ = standardized reconfiguration of the directed phase lag index; Hub_{RS} = standardized reconfiguration of hubs; NPV = negative predictive value; PPV = positive predictive value.

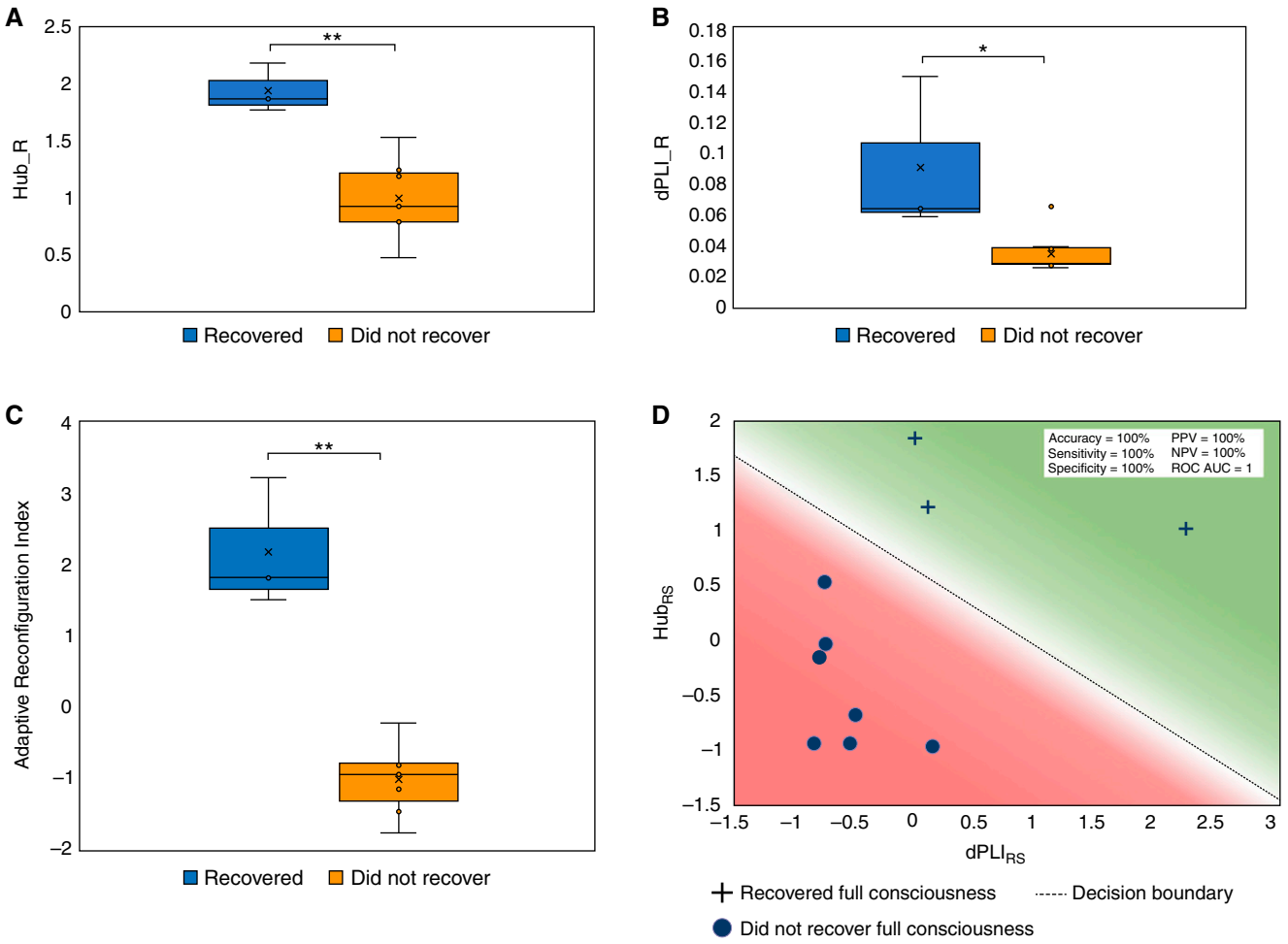

Figure 7. The adaptive reconfiguration index calculated using 18-channel EEG predicts recovery of consciousness within 90 days. (*A–C*) Hub reconfiguration (Hub_R) (*A*), directed phase lag index (dPLI) reconfiguration ($dPLI_R$) (*B*), and adaptive reconfiguration index values (*C*) calculated using 18-channel EEG are depicted for patients who recovered full consciousness within 90 days of the study (i.e., "recovered") (blue) and those who did not recover full consciousness within 90 days (i.e., "did not recover") (orange). Hub_R (*A*), $dPLI_R$ (*B*), and the adaptive reconfiguration index (*C*) were higher in the recovered group. Results were statistically significant at $P < 0.025$ for Hub_R (one-tailed $P = 0.008$) and the adaptive reconfiguration index (one-tailed $P = 0.008$) and showed a trend toward significance for $dPLI_R$ (one-tailed $P = 0.033$). (*D*) The standardized reconfiguration of hubs (*y*-axis) and the standardized reconfiguration of the dPLI (*x*-axis) are plotted per participant in a two-dimensional feature space, yielding the adaptive reconfiguration index. Adaptive reconfiguration index value per participant is depicted by circles ("did not recover") and crosses ("recovered") according to recovery status 90 days after the study. The logistic regression decision boundary (dashed line) accurately separated both groups according to their 90-day outcome. $^*P < 0.05$ and $^{**}P < 0.025$. $dPLI_{RS}$ = standardized reconfiguration of the dPLI; Hub_{RS} = standardized reconfiguration of hubs; NPV = negative predictive value; PPV = positive predictive value; ROC AUC = area under the receiver operating characteristic curve.

Scale–Revised assessment (29), such as pain, reflexive motor activity, fatigue, and psychoactive medication, which are known to affect the level of consciousness (30, 31). However, these factors are common to all investigations that use the Coma Recovery Scale–Revised score as the gold standard for consciousness assessment, many of which have achieved high classification accuracy. For example, the participation coefficient of brain network graphs constructed from hd-EEG of patients in a disorder of consciousness was 79% accurate in distinguishing unresponsive wakefulness syndrome from a minimally conscious state (2), and expert assessment of PET images was 82% accurate in distinguishing the same categories (4). The perturbational complexity index has also been shown to detect a minimally conscious state with a sensitivity of 94% and to identify patients with unresponsive wakefulness syndrome with high brain complexity who may have higher odds of recovery (9). Such techniques and classifications should be used instead of the adaptive reconfiguration index for the diagnosis of disorders of consciousness.

Given the difference between the adaptive reconfiguration index's performance for diagnosis and prognosis of disorders of consciousness, it is possible that the adaptive reconfiguration index captures the plasticity of the brain's functional networks rather than current information content and integration (32). The brain network's response to propofol perturbation may therefore indirectly reflect the brain's preserved ability for self-organization (30).

When the brain has operated in a coma or disorder of consciousness for an extensive period, as in a persistent (chronic) disorder of consciousness, individuals may gradually lose the self-organizing ability of neural networks (33), translating to a loss of reconfiguration capacity altogether. It is well-established that brain organization and plasticity are different in the acute and chronic phases after a brain injury and that cognitive recovery is faster in the first few months to years after a severe brain injury (34, 35). Although the present study did not investigate the network capacity for self-organization, our results confirmed our hypothesis that patients in a chronic coma or disorder of consciousness would have a low adaptive reconfiguration index, which may reflect a decrease in plastic and self-organizing neural processes.

The primary limitation of this study is its small sample size. This case series is intended to introduce the adaptive reconfiguration index and its potential clinical application and translational potential and to highlight its potential to aid in prognostication of patients in a coma or disorder of consciousness on a single-subject level. The prognostic accuracy of the adaptive reconfiguration index will need to be prospectively validated in a larger sample, and its clinical value will need to be assessed by comparing its prognostic accuracy to the prognosis made by the treating team. A second limitation of our study is that it is impossible to confirm whether a target effect size concentration of 2 μg/ml was sufficient to induce a state of anesthesia or whether it only induced a state of deep sedation. Given that all patients were unresponsive to begin with, we cannot confirm whether they were, in fact, anesthetized by the propofol they received. However, given that a brain injury and/or an American Society of Anesthesiologists status of 3 or greater is known to make patients more vulnerable to the effects of anesthesia, this target effect site concentration was recommended by our team of neuroanesthesiologists because they deemed it sufficient to induce a perturbation of the brain network. This concentration was also deemed safest to avoid airway collapse and hypertension and could therefore be administered without breathing support to patients who were breathing spontaneously. Another study limitation is our follow-up assessment of consciousness recovery, performed 90 days after our study. This does not account for time since injury or recovery beyond this 90-day period. However, our approach ensured that all acute participants were in a similar state at the time of testing: they were medically stable, had been weaned off continuous sedation, and remained unresponsive. In addition, withdrawal of life-sustaining treatment also confounded our assessment of one patient's outcome because it was impossible to determine whether the patient could have recovered within 90 days if treatment had been maintained. This patient (case 4) presented as being in a coma at the time of the study but was later suspected to be in a complete locked-in syndrome. Although the attending physician's suspicion could not be confirmed prior to withdrawal of life-sustaining treatment, this participant's adaptive reconfiguration index supported the clinical suspicion of complete locked-in syndrome and highlights the clinical relevance of our proposed index in such a context, where consciousness is suspected but unconfirmed (*see* online supplement for additional details).

This study presented a translational index that has the potential to be used in critical care settings to predict recovery of consciousness in unresponsive patients currently in a coma or disorder of consciousness. The adaptive reconfiguration index is rooted in the idea that the complexity of the brain's response to a perturbation is indicative of its ability to sustain consciousness. In this case series, by combining EEG with propofol anesthesia and capturing the anesthesia-induced reconfiguration of α network hubs and directed functional connectivity, the adaptive reconfiguration index discriminated with 100% accuracy patients who recovered within 3 months after the study. This accessible method of predicting consciousness recovery could have significant implications for clinical management and decision-making. ■

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