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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.

Objective: 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 in a disorder of consciousness following 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 post-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.

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Introduction

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 (fMRI) and positron-emission tomography (PET), which have contraindications that exclude many patients in disorders of consciousness and are challenging to integrate into everyday clinical environments, preventing their widespread adoption for the assessment of patients in 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 alpha network hubs and neutralization of feedback-dominant connectivity (11-14). Our approach is founded on the hypothesis that unresponsive, brain-injured patients who undergo these network reconfigurations in response to propofol— indicating the loss of some residual consciousness—currently possess consciousness, despite being unresponsive, and/or have the capacity to recover.

Electroencephalography (EEG) measures the electrical activity of cortical neurons using scalp electrodes. It is significantly less expensive than other imaging technologies, has fewer patient contraindications, and can be used at the bedside. EEG is used to calculate the Perturbational Complexity Index, a data-driven metric that can discriminate 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). While it is a robust measure of consciousness (9), the Perturbational Complexity Index is limited in its translational potential due to its reliance on transcranial magnetic stimulation, which is not commonly available in most acute and chronic facilities with patients in 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. Since 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 coma and 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 coma and disorders of consciousness (i.e., unresponsive wakefulness syndrome, and minimally conscious state). Some of the results of these studies have been previously reported in the form of a abstracts (15-18).

Methods

Participants

We recruited 12 adults in a coma or a disorder of consciousness following acquired brain injury (see Table 1 and Online Data 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 in a disorder of consciousness had preserved ability to awaken, but no confirmed signs of awareness: these patients were either in an unresponsive wakefulness syndrome or a minimally consciousness state. In unresponsive wakefulness syndrome (also known as vegetative state), eye opening is present, but patients show no behavioral signs of being aware of themselves or their surroundings, therefore lacking oriented or wilful behaviors (19,20). As such, patients in unresponsive wakefulness syndrome are considered to be unconscious. Minimally conscious state presents with eye opening and some reproducible, though minimal, oriented and/or willful behaviors (e.g. visual tracking, inconsistent command following) (21).

Seven of the 12 participants were acute patients (i.e., ≤ 6 months post-injury) receiving treatment in an intensive care unit; five participants were chronic patients (i.e., > 6 months post-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 low likelihood of recovery – in the 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 72h prior to the study, previous open-head injury, allergy to propofol, or were deemed medically unsuitable by their attending physician.

Experimental design

Participants were given propofol in target-infusion mode at 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*) (Fig. 1a). EEG signals were collected from the scalp using a 128-channel (n = 10) or 64-channel (n = 2) electrode net (see Online Data Supplement for details).

We assessed patients' current level of consciousness using the Coma Recovery Scale-Revised (23), immediately preceding the anesthetic protocol (24). Three months following 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 were present, denoting emergence from a disorder of consciousness, as per criteria from 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 had removal of physiological support following neurological determination of death. The participant who had life sustaining treatment withdrawn had a clinical suspicion of complete locked-in syndrome in the 48h prior to the 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 (wPLI) in the alpha (8-14 Hz) frequency band of all pairwise combinations of electrode channels on 10-second windows (25). Average wPLI matrices were generated for all three recordings, and network hubs were calculated through the topographic distribution of node degree (i.e. number of connections a single node has to all other nodes within the network) (Fig. 1a).

Directed functional connectivity

The directed phase lag index (dPLI) was calculated across 10-second windows and averaged within each analysis epoch in the alpha frequency band to generate representative directed functional connectivity matrices for all three recordings (Fig. 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* (Fig. 1b). Hub_R and $dPLI_R$ were then standardized by removing the mean and scaling to unit variance, becoming Hub_{RS} and $dPLI_{RS}$ (Fig. 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 (Fig. 1d). We did not calculate the Adaptive Reconfiguration Index for one of the 12 participants, as their Hub_R and $dPLI_R$ could not be computed in the *post-anesthesia* EEG due to excessive noise.

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 if 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 days). 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, accuracy were then calculated. Area under the receiver operating characteristic curve (ROC AUC) was also calculated if 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 as per 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 re-ran statistical analyses. Given the one-tailed nature of the statistical tests, rResults 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 three months following assessment of their Adaptive Reconfiguration Index. We expected that patients with high propofol-induced network reconfiguration (i.e., high Adaptive Reconfiguration Index) would recover full consciousness at the three-month follow-up.

Four individual examples of propofol-induced network reconfiguration can be found in Fig. 2 (see Fig. E1 for all cases). On an individual level, a high Adaptive Reconfiguration Index was indicative of favorable prognosis (Fig. 2, Fig. 3). When taken separately, the reconfiguration of network hubs (Hub_R) and directed functional connectivity ($dPLI_R$) were significantly higher in

patients who later recovered full consciousness than those who did not, reaching statistical significance for Hub_R (Hub_R U-value = 21, one-tailed p-value = 0.008; $dPLI_R$ U-value = 19, one-tailed p-value~~p~~ = 0.033) (Fig. 4A, 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 both above the maximum values of those who did not recover (Fig. 4A, 4B).

In the three patients who later recovered full consciousness, network hub topography mirrored that of healthy individuals (anterior during exposure to propofol; posterior otherwise) (Fig. 2A, Fig. S1 Cases 1-3) (11). In these 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) (Fig. 2A, Fig. S1 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. Fig. 2B, Fig. S1 Cases 6, 7, 12), or random, incoherent shifts in hub structure that did not return to baseline configuration during the *post-anesthesia* recording (e.g. Fig. 2C, Fig. S1 Cases 8, 9). These same patients who did not go on to recover consciousness also either showed little to no reconfiguration in directed functional connectivity in response to propofol or pathological patterns (e.g. Fig 2B, 2C, and Fig. S1 Cases 6-12).

The Adaptive Reconfiguration Index was significantly higher in patients who later recovered full consciousness (U-value = 21, one-tailed p-value~~p~~ = 0.008) (Fig. 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 (Fig. 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 acute coma and disorder of consciousness patients, as the Adaptive Reconfiguration Index 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 be in a 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 (Fig 2D, Fig 3). Though 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

Patients' current level of consciousness was assessed using the Coma Recovery Scale-Revised immediately preceding the anesthetic protocol (23). We expected participants with "some signs of consciousness" (i.e., 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-value = 0.911) and $dPLI_R$ (one-tailed p-value = 0.733, ~~(U-values ≤ 13, p-values > 0.05~~), the Adaptive Reconfiguration Index did not differ between groups (~~U-value = 11,~~ one-tailed p-value~~p~~ = 0.~~27~~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 diagnostic value was not confirmed in this case series.

Translatability of Adaptive Reconfiguration Index to clinical EEG

Given that high-density 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-value = 0.008; $dPLI_R$ U-value = 19, one-tailed p-value = 0.033) (Fig. 7A, 7B). The Adaptive Reconfiguration Index was also significantly higher in patients who later recovered full consciousness (U-value = 21, one-tailed p-value = 0.008) (Figure 7C), and both prognostic groups (i.e., "recovered" vs. "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 (Fig. 7D). That is, with only 18 channels, the Adaptive Reconfiguration Index could still discriminate with 100% accuracy whether or not 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 the prognostication of coma and disorders of consciousness (see Online Data 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 for 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 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 aetiologies of brain injury, and across diagnoses ranging from coma to minimally conscious state. This naturalistic study sample was reflective of the heterogeneity of individuals with a coma or 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 that did not recover full consciousness showed baseline patterns associated with conscious awareness (e.g., feedback-dominant connectivity). It is the *inability* for 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 Data 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 Supplemental Discussion).

Though the Adaptive Reconfiguration Index showed promising preliminary results as prognostic tool for consciousness recovery, it showed no association to 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 Come Recovery Scale-Revised assessment (29), such as pain, reflexive motor activity, fatigue and psychoactive medication, which are known to affect 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 accuracies. 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 minimally conscious state

(2), and expert assessment of PET images was 82% accurate in distinguishing these same categories (4). The Perturbational Complexity Index was also shown to detect minimally conscious state with a sensitivity of 94%, and to identify unresponsive wakefulness syndrome patients 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 the propofol perturbation may therefore indirectly reflect the brain's preserved ability for self-organization (30). When the brain has operated in a come 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 following a brain injury, and that speed of cognitive recovery is faster in the first few months to years following a severe brain injury (34,35). Though 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 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, its potential clinical application and translational potential, and to highlight to potential for the Adaptive Reconfiguration Index to aid in the

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 the prognostic accuracy of the Adaptive Reconfiguration Index to the prognosis made by the treating team. A second limitation to 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 if they were in fact anesthetized by the propofol received. However, given that a brain injury and/or an American Society of Anesthesiologists status ≥3 is known to make patients more vulnerable to the effects of anesthesia, this target effect site concentration was recommended by our team of neuroanesthesiologists, as 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 in patients who were breathing spontaneously. Another study limitation is our follow-up assessment of consciousness recovery, carried out 90 days following 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, as 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. Though the attending physician's suspicion could not be confirmed prior to the 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 Data 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 anesthetic-induced reconfiguration of alpha network hubs and directed functional connectivity, the Adaptive Reconfiguration Index discriminated with 100% accuracy patients who recovered within three months following the study. This accessible method of predicting consciousness recovery could have significant implications for clinical management and decision-making.

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Figure Legends

Figure 1. Study protocol and analytic approach.
Patients underwent propofol anesthesia with a target effect-site concentration of 2.0 μg/mL, with concomitant high-density EEG (hd-EEG) recording. Five-minute epochs of hd-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 the predicted effect site concentration decreased below 0.5 μg/mL. Whole-brain alpha 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) The Hub_R and $dPLI_R$ were standardized, yielding the Hub_{RS} and $dPLI_{RS}$, which (d) were then summed to yield the Adaptive Reconfiguration Index.

Figure 2. Four individual cases depicting the alpha network's response to propofol administration. .
For each case presented, topographic maps of the node degree of alpha EEG networks and matrices of functional connectivity are presented across *pre-anesthesia* (green), *anesthesia* (orange) and *post-anesthesia* (blue) epochs. For hubs, the colormap represents the Z-score of the normalized node degree for each electrode. For 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 colorbar bordering each matrix: frontal (orange), central (blue), parietal (yellow), occipital (green), and temporal (grey). The colormap 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 (Hub_{RS} and $dPLI_{RS}$) are depicted in the right-hand column of each panel (yellow), and the Adaptive Reconfiguration Index is indicated in the bottom right-hand corner of each case. A) Case 3, who was in an 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 was in an 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 was in a 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 48h of withdrawal of treatment, the attending physician indicated a suspicion of complete locked-in syndrome and potentially preserved awareness. Though 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.

Figure 3. Adaptive Reconfiguration Index value per patient.
Individual Adaptive Reconfiguration Index values are depicted by 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, while 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.

Figure 4. The Adaptive Reconfiguration Index was significantly higher in patients who later recovered consciousness.
(A) Hub reconfiguration (Hub_R), (B) dPLI reconfiguration ($dPLI_R$) and (C) Adaptive Reconfiguration Index values are depicted per group. Patients who later recovered full consciousness within 90 days of the study constitute the "Recovered" group (n = 3) (blue), while 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 ~~significant differences between groups for~~higher Hub_R, $dPLI_R$, and ~~the~~ Adaptive Reconfiguration Index in the Recovered group, indicating that patients in the Recovered group had higher hub and dPLI reconfiguration when these indices were taken separately, and had 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-value = 0.008) and the Adaptive Reconfiguration Index (one-tailed p-value = 0.008), and showed a trend toward significance for $dPLI_R$ (one-tailed p-value = 0.033).
*: $p < 0.05$; **: $p < 0.025$~~1~~

Figure 5. The Adaptive Reconfiguration Index predicts 90-day recovery of consciousness.
The standardized reconfiguration of hubs (Hub_{RS}) (y-axis) and the standardized reconfiguration of the dPLI ($dPLI_{RS}$) (x-axis) are plotted per participant in a two-dimensional feature space, yielding the ARI. ARI 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.

Figure 6. The Adaptive Reconfiguration Index cannot predict current level of consciousness.
The standardized reconfiguration of hubs (Hub_{RS}) (y-axis) and the standardized reconfiguration of the dPLI ($dPLI_{RS}$) (x-axis) are plotted per participant in a two-dimensional feature space, yielding the ARI. ARI value per participant is depicted with X's ("No signs of consciousness") and circles ("Some signs of consciousness") according to diagnosed level of consciousness at the time of the study, as per 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.

Figure 7. The Adaptive Reconfiguration Index calculated on 18 EEG channels predicts recovery of consciousness within 90 days.

(A) Hub reconfiguration (Hub_R), (B) dPLI reconfiguration ($dPLI_R$) and (C) Adaptive Reconfiguration Index values calculated on 18-channel EEG are depicted for patients who later 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). Mann-Whitney U-test results showed significant differences between groups for 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-value = 0.008) and the Adaptive Reconfiguration Index (one-tailed p-value = 0.008), and showed a trend toward significance for $dPLI_R$ (one-tailed p-value = 0.033). ($p < 0.05$), and Adaptive Reconfiguration Index ($p < 0.01$). In panel (D), The standardized reconfiguration of hubs (Hub_{RS}) (y-axis) and the standardized reconfiguration of the dPLI ($dPLI_{RS}$) (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 90 days following the study. The logistic regression decision boundary (dashed line) accurately separated both groups according to their 90-day outcome.

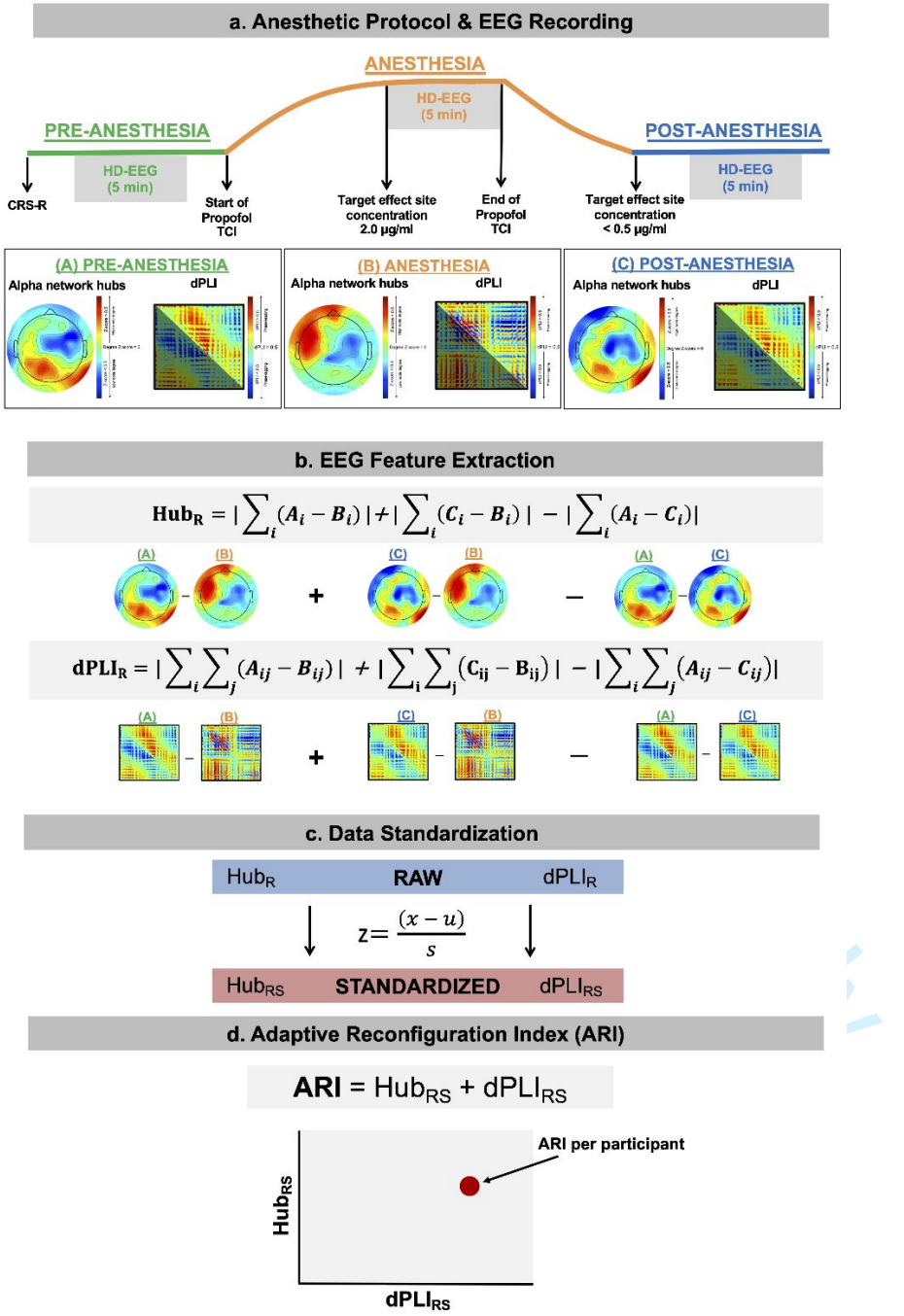
*: $p < 0.05$; **: $p < 0.025$1

Table 1. Demographic and clinical characteristics of the 12 patients who underwent anesthetic perturbation

ID	Age	Sex	Brain injury	Time since injury	Phase post-injury	CRS-R at study	Diagnosis at study	Recovery of consciousness 90 days post-study
1	42	F	Stroke	21 days	Acute	3	UWS	YES
2	29	M	TBI	58 days	Acute	4	UWS	YES
3	50	F	Stroke	25 days	Acute	4	UWS	YES
4	40	M	Stroke	6 days	Acute	0	Coma	Suspected LIS prior to WOT*
5	74	F	Anoxic	10 days	Acute	0	Coma	NDD*
6	75	F	Stroke	10 days	Acute	5	UWS	NO
7	18	F	TBI	21 days	Acute	5	UWS	NO
8	24	M	Anoxic	8 years	Chronic	5	UWS	NO
9	53	F	Anoxic	9 months	Chronic	5	UWS	NO
10	28	F	Anoxic	1 year	Chronic	6	UWS	NO
11	28	M	TBI	11 years	Chronic	10	MCS	NO
12	36	F	TBI	2 years	Chronic	11	MCS	NO

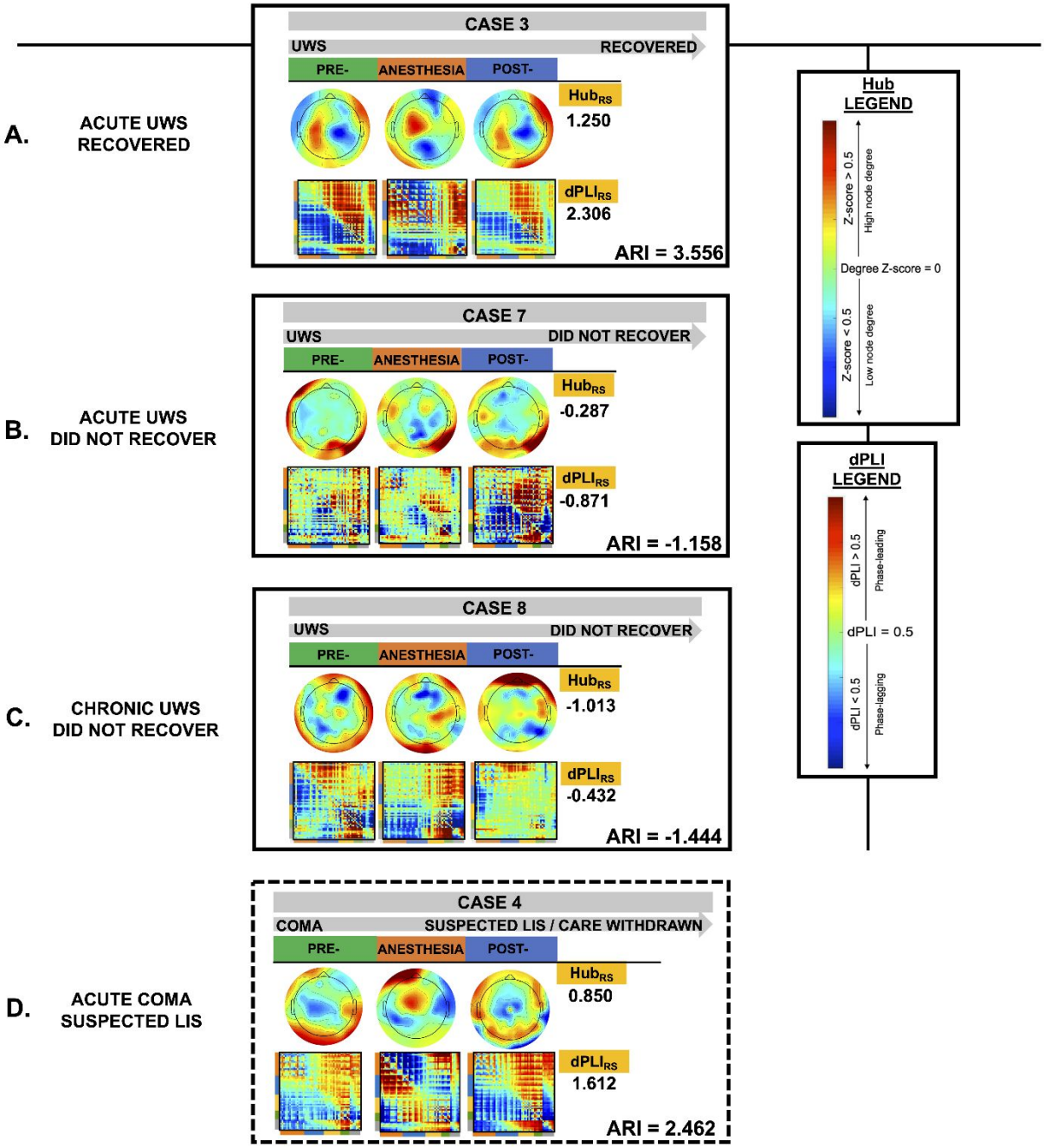
* Withdrawal of treatment or support took place prior to the 90-day follow-up.
CRS-R: Coma Recovery Scale-Revised; DOC: disorder of consciousness; EEG: electroencephalography; LIS: locked-in syndrome; MCS minimally conscious state; NDD: neurological determination of death; TBI traumatic brain injury;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

Figure 1. Study protocol and analytic approach.



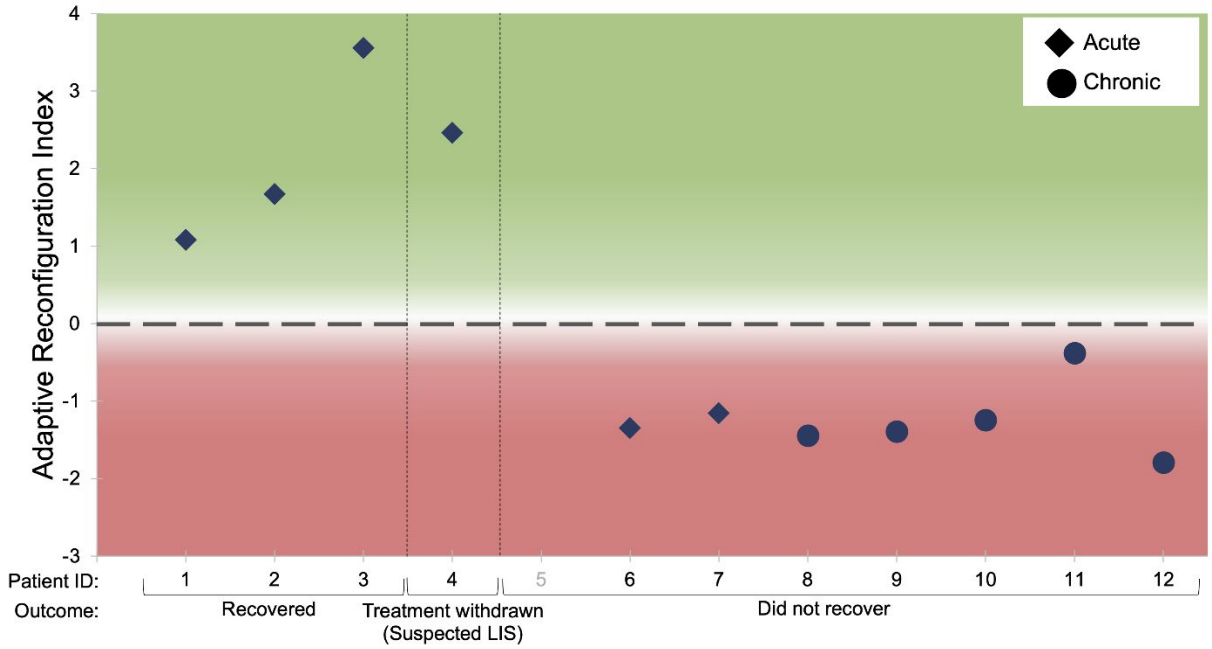
ARI: adaptive reconfiguration index. EEG: electroencephalography; dPLI: directed phase lag index; $dPLI_R$: reconfiguration of the directed phase lag index; $dPLI_{RS}$: standardized reconfiguration of the directed phase lag index; HD-EEG: high density electroencephalography; HUB_R: hub reconfiguration; HUB_{RS}: standardized hub reconfiguration; TCI: target-controlled infusion.

Figure 2. Four individual cases depicting the alpha network's response to propofol administration.



dPLI: directed phase lag index; $dPLI_{RS}$: standardized reconfiguration of the directed phase lag index; HUB_{RS}: standardized hub reconfiguration; LIS: locked-in syndrome; UWS: unresponsive wakefulness syndrome

Figure 3. Adaptive Reconfiguration Index values per patient



LIS: locked-in syndrome

Figure 4. The Adaptive Reconfiguration Index was significantly higher in patients who later recovered consciousness.

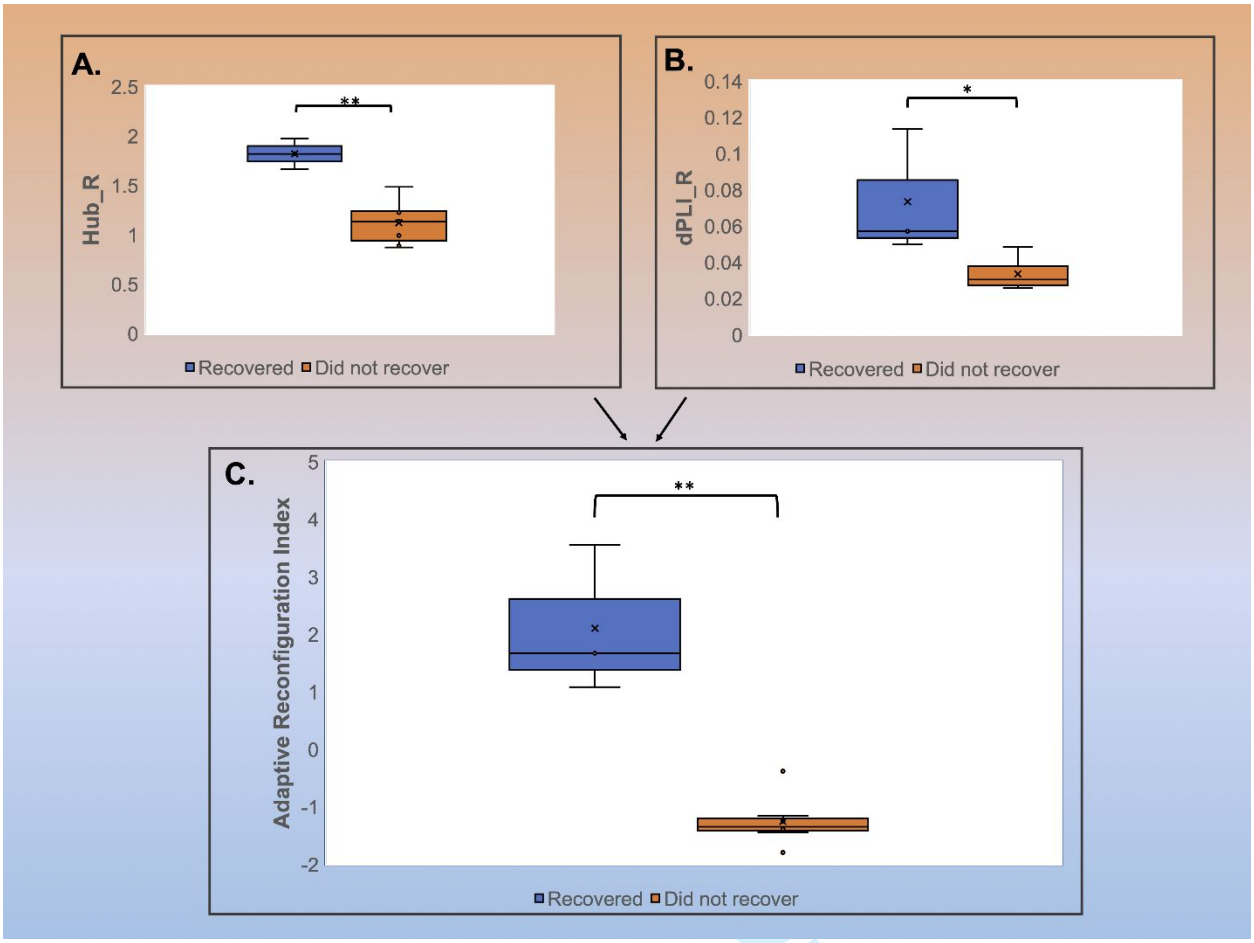


Figure 5. The Adaptive Reconfiguration Index predicts 90-day recovery of consciousness.

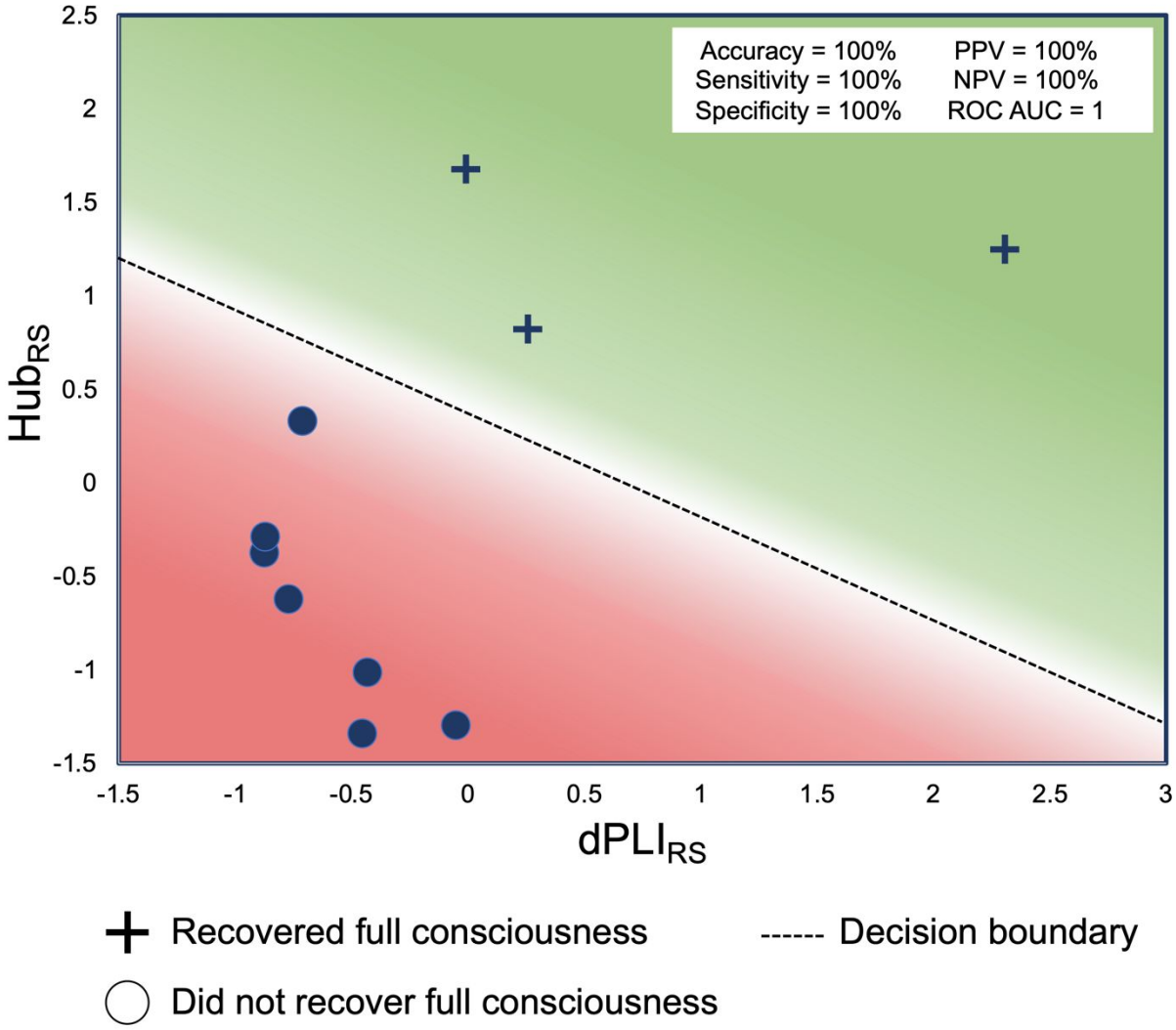


Figure 6. The Adaptive Reconfiguration Index cannot predict current level of consciousness.

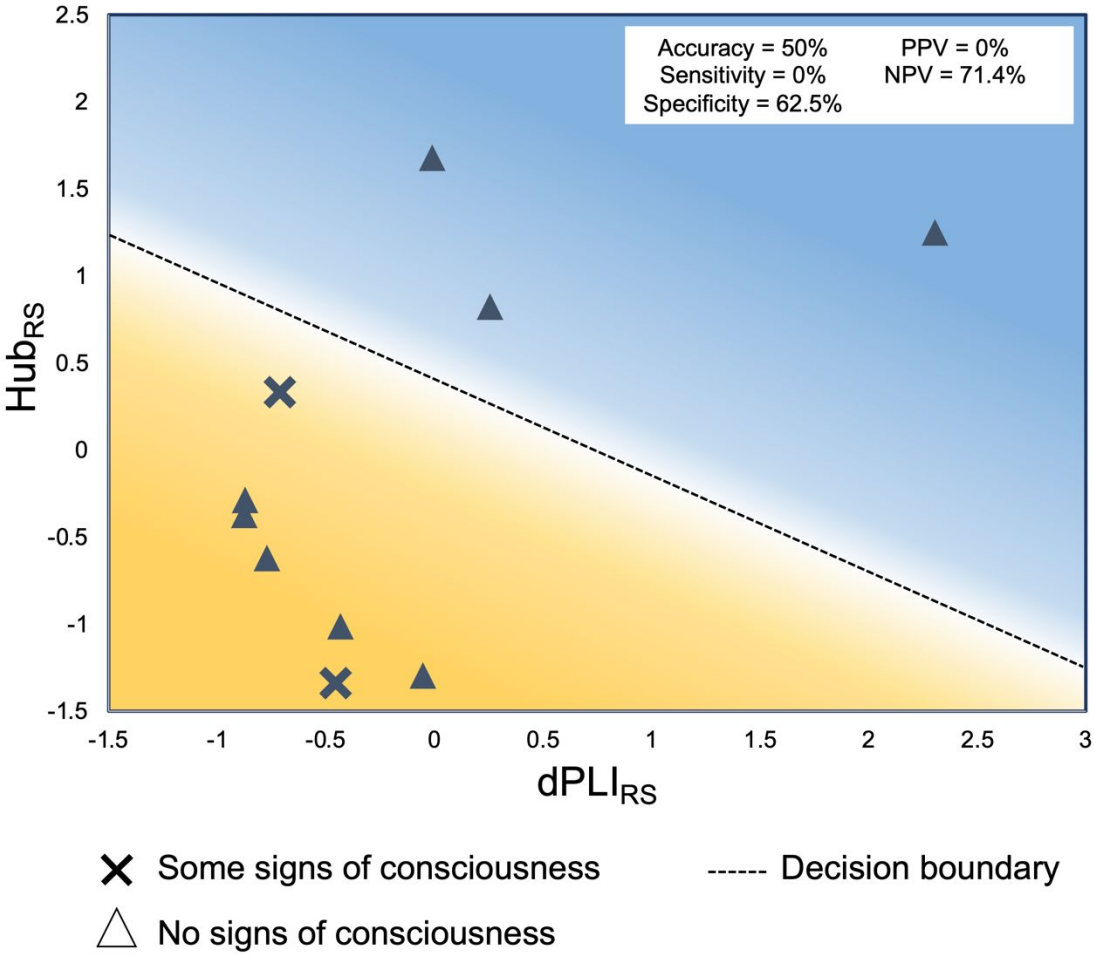
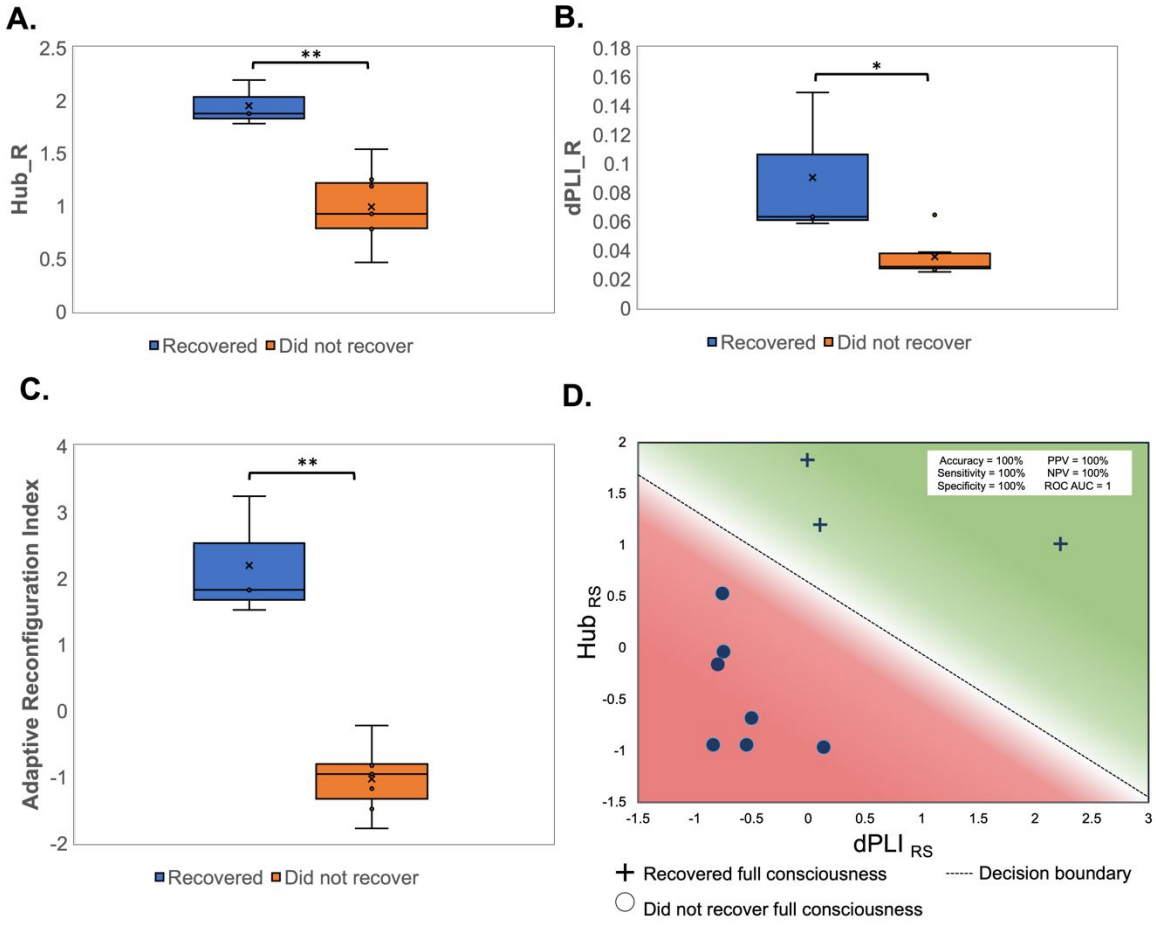


Figure 7. The Adaptive Reconfiguration Index calculated on 18 EEG channels predicts recovery of consciousness within 90 days.



Brain responses to propofol in advance of recovery in coma and disorders of consciousness: a preliminary study

Catherine Duclos, Charlotte Maschke, Yacine Mahdid, Danielle Nadin, Alexander Rokos, Caroline Arbour, Mohamed Badawy, Justin Létourneau, Adrian M. Owen, Gilles Plourde, Stefanie Blain-Moraes

Online Data Supplement

Supplemental Methods

Participants

Participants were recruited from the McGill University Health Centre (n = 6), from a long-term care facility in greater Montreal (n = 1), and through brain injury and consciousness-related patient support networks in Ontario (n = 5). Participants not currently hospitalized were admitted to the Montreal Neurological Hospital for the study protocol. Next of kin provided written informed consent. The study was approved by the McGill University Health Center Research Ethics Board (15-996-MP-CUSM).

Propofol anesthesia

Guidelines of the Canadian Anesthesiologists' Society were followed, including pre-anesthetic assessment, fasting, and monitoring. Propofol was administered by an anesthesiologist or intensivist in the Intensive Care Unit (ICU) or in the operating room (when no ICU bed was available). A respiratory therapist was present during the procedure and prepared to provide rescue ventilation. Constant nurse monitoring was maintained for 2 h following the end of propofol administration. An effect-site concentration of 2.0 μg/mL was targeted for the *anesthesia* condition. Though the ED50 concentration to prevent response to verbal command is 2.35 μg /mL in healthy adults, for the purposes of this study, the lower concentration of 2 μg /mL was recommended by a team of neuroanesthesiologists because of the patients' pre-existing conditions. Indeed, as per the product monograph (1) propofol use in "debilitated and/or adult patients in American Society of Anesthesiologists Physical Status Classes III and IV" is recommended to be approximately 50% that of healthy adults (i.e. 1.0 to 1.5 μg /mL), "as these patients may be more sensitive to the effects of propofol", while propofol should be kept between 1.0 and 2.0 μg /mL in neurosurgical patients. This concentration was also deemed safest to avoid airway collapse and hypertension, and could

therefore be administered without breathing support in patients who were breathing spontaneously. Target effect-site concentration was attainted and maintained using an Alaris PK Carefusion target-controlled infusion pump (Carefusion, Switzerland). When the pump was not available (n = 2), a Marsh PK/PD model comprising boluses and infusions was designed using the TivaTrainer (2), and propofol was administered intravenously following a rigorous timeline. Effect-site concentration was held constant for the duration of the anesthetic exposure, which ranged from 10 to 40 min (only the first 5 minutes of this anesthetic period were used for analysis in this study). Prior to the anesthetic protocol, participants were breathing spontaneously either through an endotracheal tube or a tracheostomy tube, or were breathing independently. There were no complications.

Assessment of recovery of full consciousness

Patients were considered to have recovered full consciousness if they were able to consistently follow commands and/or to respond verbally in an appropriate manner to conversation (i.e. emergence from a disorder of consciousness), and to have not recovered full consciousness if they were unable to consistently follow commands (i.e. coma, unresponsive wakefulness syndrome, minimally conscious state) or remained unresponsive when life-sustaining care was withdrawn. For non-hospitalized participants, command-following and verbal responses were assessed by phone interviews with next of kin. If any change in level of responsiveness was reported, a member of the study team proceeded with targeted questions to enable assessment and consistency of command-following and verbal responses. For hospitalized participants, command-following and verbal responses were assessed through chart reviews, which included nursing logs/notes, attending physician notes, and reports from occupational therapists and

neuropsychologists when available. If phone interviews or chart reviews were inconclusive, a trained experimented conducted the Coma Recovery Scale-Revised at bedside (3).

Electroencephalographic data acquisition and preprocessing

EEG signals were collected from the scalp using a 128-channel electrode net (Electrical Geodesics, Inc., Eugene, OR, USA) (n = 10) or a 64-channel electrode net (BrainProducts, Gilching, Germany) (n = 2) referenced to Cz. Electrode impedances were kept below 50 kΩ. The data were bandpass filtered from 0.1 to 50 Hz, and non-scalp channels were discarded. Upon visual inspection by a trained experimenter, noisy epochs and channels, as well as muscle and non-physiological artifacts, were removed. The data were then re-referenced to an average reference. Five-minute segments of continuous EEG were extracted during three analysis epochs: pre-anesthesia, anesthesia and post-anesthesia.

Weighted phase lag index (wPLI)

The wPLI between two channels was computed as:

$$wPLI_{ij} = \frac{|E\{\Im(C_{ij})\}|}{E\{|\Im(C_{ij})|\}} = \frac{|E\{|\Im(C_{ij})|sgn(\Im(C_{ij}))\}|}{E\{|\Im(C_{ij})|\}}$$

where $\Im(C_{ij})$ is the imaginary part of the cross-spectrum C_{ij} between i and j, and sgn is the signum function (4). When one signal consistently leads the other, the wPLI is close to 1, with a value of 1 indicating perfect phase locking between signals. When there is no phase relationship between the signals, the wPLI is equal to 0. We controlled for the effects of spurious phase relationships through a surrogate analysis, where signal i remained fixed while the phase time-series of signal j was scrambled, abolishing the phase relationship between the signals while maintaining their other properties. We then compared the wPLI values against a distribution of the means of 20 surrogate analyses. wPLI values were then retained if they were significantly different than the surrogate distribution ($p < 0.05$ level). Non-significant connections were set to 0.

We then constructed a binary adjacency matrix Aij using a custom threshold for each participant: if the wPLIij value of nodes i and j were above the custom threshold, Aij = 1; otherwise, Aij = 0. The custom threshold was determined for each participant by identifying the lowest threshold enabling a minimally-spanning graph during the pre-anesthesia recording. The threshold established for the pre-anesthesia network was also used for constructing the networks in the anesthesia and post-anesthesia epochs.

Directed phase lag index (dPLI)

A Hilbert transform yielded the instantaneous phase time series for each channel, and the phase difference $\Delta\phi_{ij}$ between all pairs of signals i and j was calculated. Directed functional connectivity were calculated with the directed phase lag index (dPLI), defined as:

$$dPLI_{ij} = \frac{1}{N}\sum_{t=1}^{N} H(\Delta\phi_{ij})$$

where N is the length of the analysis segment and t is a given time point (5). H is the Heaviside step function, such that when i leads j, the dPLI is between 0.5 and 1; when j leads i, the dPLI is between 0 and 0.5; and, when there is no phase relationship between the signals, the dPLI is equal to 0.5. We compared the dPLI values against a distribution of the means of 20 surrogate analyses. As described above, for each surrogate signal i remained fixed while the phase time-series of signal j was scrambled, abolishing the phase relationship between the signals while maintaining their other properties. dPLI values were retained if they were significantly different than the surrogate distribution ($p < 0.05$ level), and non-significant connections were set to 0.5.

Reconfiguration of network hubs (Hub_R)

The Hub_R captures differences in node degree across epochs, as per the following formula:

$$Hub_{DRI} = |\sum_i (A_i - B_i)| \; + \; |\sum_i (C_i - B_i)| \; - \; |\sum_i (A_i - C_i)|$$

where A is a vector of network degree pre-anesthesia, B is a vector of network degree during anesthesia, C is a vector of network degree post-anesthesia, and *i* is the index corresponding to a given electrode. In networks with high reconfiguration in response to anesthesia, $|\sum_i(A_i - B_i)|$ and $|\sum_i(C_i - B_i)|$ are expected to be high, as they contrast anesthesia with a non-anesthetic epochs, whereas $|\sum_i(A_i - C_i)|$ is expected to be low, as it contrasts pre- and post-anesthesia epochs.

Reconfiguration of dPLI ($dPLI_R$)

The $dPLI_R$ captures differences in node degree across epochs, as per the following formula:

$$dPLI_{DRI} = |\sum_i\sum_j (A_{ij} - B_{ij})| \; + \; |\sum_i\sum_j (C_{ij} - B_{ij})| \; - \; |\sum_i\sum_j (A_{ij} - C_{ij})|$$

Where A is the dPLI matrix pre-anesthesia, B is the dPLI matrix anesthesia, and C is the dPLI matrix post-anesthesia, and *i* and *j* are indices representing individual electrodes. In a network with high reconfiguration in response to anesthesia, $|\sum_i\sum_j(A_{ij} - B_{ij})|$ and $|\sum_i\sum_j(C_{ij} - B_{ij})|$ are expected to be high, and the difference between non-anesthesia epochs, $|\sum_i\sum_j(A_{ij} - C_{ij})|$ is expected to be low.

Differences between anesthesia and non-anesthesia epochs are high when there is strong anesthetic-induced network reconfiguration and low when there is limited reconfiguration. Differences between pre- and post-anesthesia epochs are expected to be low if the EEG network returns to its baseline configuration after propofol has been ceased.

Translational potential of Adaptive Reconfiguration Index with clinical EEG (18 channels)

We re-calculated the Adaptive Reconfiguration Index on a subset of 18 EEG channels to assess its translatability for critical care settings. For focal injuries, the healthiest hemisphere was defined as the least-injured hemisphere, according to the CT scan. For diffuse injuries, the

healthiest hemisphere was selected based on the scalp's condition (i.e., side with absence of wounds, patches, drains, etc.). If the scalp was intact, the left hemisphere was selected by default. Significant results with hd-EEG were re-analyzed with 18-channel EEG for the 10 patients in a coma or disorder of consciousness.

***Post hoc* analysis of baseline EEG data, without propofol perturbation**

To assess the diagnostic and prognostic value of alpha network hubs and directed connectivity measured at baseline alone, we conducted a *post hoc* analysis on the pre-anesthesia EEG recording only, for the 11 previously described patients (Case 4, with suspected LIS, was excluded), and an additional 14 participants who underwent a baseline EEG recording as described above, but did not receive anesthesia.

Of the 14 additional participants included in this analysis of baseline EEG data only, six did not provide consent for the anesthesia portion of the study, and the other eight were participants from another study included in previous publications (7-10), which was reviewed by the Western University Health Science Research Ethics Board (Project ID 100628). We also obtained approval from the McGill University Health Center Research Ethics Board to add these 8 participants to our study. EEG data acquisition and preprocessing, as well as computation of alpha network hubs and directed functional connectivity were carried out as described above.

Hub Posteriority Ratio: We quantified the anterior vs. posterior dominance of network hubs through the hub posteriority ratio:

$$Hub\ posteriority\ ratio = \frac{E(d_P)}{E(d_A)}$$

where E() denotes the expected value, d_P represents the degree of posterior electrodes (along and posterior to midline) and d_A represents the degree of anterior electrodes (along and anterior to midline). A hub posteriority ratio above 1 indicates a posterior-dominant hub location, whereas a

ratio below 1 indicates an anterior-dominant hub location. Given that alpha network hubs are located in the posterior regions of the brain in healthy conscious individuals (11), we expected the hub posterior ratio to be higher in individuals with a higher current level of consciousness or capacity to recover consciousness.

Feedback Dominance Index: We quantified the feedback dominance of directed phase-based functional connectivity using the feedback dominance index. This index is calculated from a dPLI matrix with the electrode regions ordered as follows: frontal, central, temporal, parietal, and occipital. The index sums the upper diagonal of the average dPLI matrix for each EEG recording, and was computed for each participant:

$$Feedback\ Dominance\ Index = \sum_{i=1}^{n}\sum_{j=i}^{n}(dPLI_{ij} - 0.5)$$

Where i and j are indices representing given electrodes and n is the total number of electrodes. Feedback-dominant connectivity yields a positive Feedback Dominance Index, whereas feedforward-dominant connectivity yields a negative Feedback Dominance Index. Given that healthy conscious individuals show feedback-dominant connectivity when awake (12-14), we expected higher feedback dominance index values in individuals with a higher current level of consciousness or capacity to recover consciousness.

Baseline EEG association with current levels of consciousness and recovery of consciousness

We tested the ability for the baseline EEG recording without anesthesia to classify current level of consciousness and eventual recovery of full consciousness by applying a logistic regression (scikit learn implementation, L2 penalty) on Hub Posteriority Ratio and Feedback Dominance Index data standardized and combined into a two-dimensional feature space (6). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were then calculated from the results of the logistic regression. We hypothesized that baseline EEG alone, without

anesthetic perturbation, would yield low accuracy, sensitivity, specificity, positive predictive value and negative predictive value for both current level of consciousness (i.e. “no signs of consciousness” (i.e. coma and unresponsive wakefulness syndrome) vs. “some signs of consciousness” (i.e. minimally conscious state)) and eventual recovery of consciousness (“recovered full consciousness" (i.e. emergence from a disorder of consciousness within 90 days following the EEG) vs. “did not recover full consciousness”).

Supplemental Results

Anesthesia is necessary for the prediction of consciousness recovery

Mann-Whitney U tests confirmed that hub posteriority ratio and feedback dominance index, when taken individually, did not differ between patient groups, whether in terms of current behavioral diagnosis (hub posteriority ratio: one-tailed p-value = 0.965; feedback dominance index one-tailed p-value = 0.907) or eventual recovery of consciousness (hub posteriority ratio: one-tailed p-value = 0.390; feedback dominance index one-tailed p-value = 0.195~~p-values ≥ 0.05~~). A logistic regression was applied to assess the linear separability of the data and its concordance with (i.e. “no signs of consciousness" (n = 20) and “some signs of consciousness” (n = 5)) and eventual recovery of consciousness (i.e. “recovered full consciousness” (n = 5) and “did not recover full consciousness” (n = 19)). The decision boundary of the logistic regression did not accurately separate patients according to their current diagnosis, yielding an accuracy of only 20% (Fig E2A). As for prognostic separability, the logistic regression decision boundary was not able to separate the data in a way rendered possible the subsequent calculate accuracy, sensitivity, specificity, positive predictive value and negative predictive value (i.e., the decision boundary did not separate the data points) (Fig E2B). These results illustrate that the hub and directed functional connectivity patterns of baseline EEG alone (without propofol perturbation) is insufficient to distinguish current

level of consciousness or eventual recovery of consciousness in disorder of consciousness patients, highlighting the pivotal role of anesthetic perturbation to the Adaptive Reconfiguration Index.

Supplemental Discussion

Currently, methods for prognostication in patients in a coma or disorder of consciousness can be divided into 4 broad categories: 1) clinical and neurological evaluations; 2) neuroimaging techniques; 3) response to sensory stimuli; and 4) biological markers. Clinical and neurological variables, such as motor response, re-appearance with proper timing of spontaneous motility, eye tracking and oculo-cephalic reflex, have been highly correlated with patient prognosis, particularly in acute unresponsive wakefulness syndrome (previously known as vegetive state) (15). However, these variables are generally assessed in the presence of confounding factors such as sedation, metabolic disturbances, and organ dysfunction, and they have been shown to be less effective in the prognostication of recovery than other neuroimaging or neurophysiological techniques (16,17). Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have also shown a strong prognostic value in disorder of consciousness patients, with accuracies up to 88% (16,18-21), though clinical use of these techniques remains sparse. Their accessibility, expense, and the multiple contraindications for their use in critical care patients are important barriers to their use for early prognosis of consciousness recovery. Interpreting neuroimaging findings has also been challenged by their reliance on comparisons to healthy brains. EEG has been extensively explored for its ability to predict patient outcome, with features such as spectral power ratios, reactivity, frequency, coherence, and approximate entropy revealing strong associations with eventual improvements in level of consciousness (22-26). Brain network characteristics and graph theoretical features of EEG networks have also been explored for their ability to predict outcome in disorders of consciousness

(25,27-30). While EEG studies have highlighted the value of this technique in the prediction of consciousness improvements or recovery in disorders of consciousness, a perpetual shortcoming of these studies is their inability to achieve a sufficient balance between prognostic accuracy, specificity and sensitivity to be clinically useful. Studies investigating responses to sensory stimuli, whether using neuroimaging (EEG, fMRI) (31-33), assessing event-related potentials (ERPs) (33-37), or even, more recently, leveraging the sniff response (38), have shown great promise as predictors of recovery from a disorder of consciousness. However, these approaches rely heavily on an individual's ability or willingness to respond to the sensory or cognitive stimulus, and can be affected by damage to specific neural pathways enabling the sensory processing of these stimuli (39). Finally, biological markers such as serum neuron-specific enolase (NSE) and S100B, have been associated with brain damage and patient outcome (40-44), but more studies are needed to assess their role in consciousness recovery specifically, and to determine their usefulness as prognostic, rather than diagnostic markers. Overall, a recent meta-analysis of prognostic models of prolonged disorders of consciousness revealed that predictive accuracies vary from 60 to 90%, leading the authors to conclude that the integration of multiple techniques has the potential to improve prognostication in disorders of consciousness (45). This review also confirmed that predictive accuracy of prognostic models has not improved as a function of year of publication, suggesting that the prognostication of disorders of consciousness remains in an exploratory phase.

A pivotal finding of this study is that propofol anesthesia can induce a network perturbation sufficient to detect an unresponsive individual's ability to recover consciousness. Previous studies using graph theory and connectivity analyses to investigate the functional architecture of the brain have shown that anesthesia effectively disrupts cortical networks (11,13,46). Globally, network neuroscience has shown that a healthy brain adaptively reconfigures the functional interactions of its network under anesthesia, to maintain essential properties that enable it to then regain

consciousness when anesthesia is discontinued. Our approach was rooted in these principles: a brain that has the capacity for consciousness will also undergo network alterations in response to anesthesia, and will revert to its pre-anesthesia state when anesthesia is stopped. Propofol anesthesia is a widely available tool that intensivists and anesthesiologists are familiar with, and that can easily be used at a patient's bedside. The approach used within this study therefore has high potential for translatability to clinical assessments of the capacity to recover consciousness in unresponsive patients.

The present study should be interpreted in light of several limitations. 1) Patients were classified as "recovered" or "non-recovered" based on their level of responsiveness three months following the EEG. Two limitations are associated with this decision. First, this classification does not account for the time since injury, which significantly predicts a patient's likelihood of recovery. However, given the heterogeneity of our sample, ranging from days to over 20 years post-injury, our classification was made in order to standardize the time window for prognostication across all participants. Second, studies have shown that recovery of consciousness and cognitive functions can occur up to years following an injury (47-50). It is therefore possible that some participants from the non-recovered group may have recovered full consciousness after our 90-day follow-up. This may in turn imply that the Adaptive Reconfiguration Index identifies individuals with potential for rapid recovery of full consciousness, rather than slower recovery trajectories. 2) In the entire sample (n = 26), a total of three participants had life-sustaining treatment withdrawn following our study. The patient in suspected locked-in syndrome was excluded from all group analyses, and the other two participants were classified as "did not recover full consciousness," but it is impossible to know if they would have recovered consciousness within three months of the EEG. 3) The wPLI matrix was binarized using a custom threshold for each participant: the minimum number of the highest functional connectivity values that created a

minimally-spanning graph during the pre-anesthesia recording. This threshold was maintained for the anesthesia and post-anesthesia epochs. While this decision was driven by theoretical considerations (assuming the pre-anesthesia state is the most naturalistic, ensuring the graph has no isolated nodes, minimal network wiring cost (51), it is well-established that the threshold used to generated brain networks affects the properties of the resulting graph, which may in turn influence our results. 4) Finally, the Adaptive Reconfiguration Index combined only two functional network measures. Other network measures, such as power-law distribution and markers of criticality, could prove relevant to the quantification of the network's capacity for adaptive reconfiguration. Future studies could investigate these network features and their responses to an anesthetic perturbation in individuals in a coma or disorder of consciousness.

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Figure Legends

Figure E1. Reconfiguration of alpha network hubs and directed functional connectivity before, during and after an anesthetic perturbation of the brain network.
For each case presented, topographic maps of the node degree of alpha EEG networks and matrices of functional connectivity are presented across *pre-anesthesia* (green), *anesthesia* (orange) and *post-anesthesia* (blue) epochs. For hubs, the colormap represents the Z-score of the normalized node degree for each electrode. For 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 colorbar bordering each matrix: frontal (orange), central (blue), parietal (yellow), occipital (green), and temporal (grey). The colormap 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 (Hub_{RS} and $dPLI_{RS}$) are depicted in the right-hand column of each panel (yellow), and Adaptive Reconfiguration Index values are reported at the bottom right-hand corner of each case. Cases 1-3 were acute patients who recovered full consciousness within 90 days of the study, and showed strong reconfiguration of hubs and dPLI. Cases 4 and 5 had life-sustaining treatment withdrawn prior to 90-day follow-up. Case 4 had a suspected complete locked-in syndrome prior to withdrawal of treatment, while Case 5 had a neurological determination of death prior to withdrawal of treatment. Cases 6 and 7 (acute) and Cases 8-12 (chronic) did not recover full consciousness within 90 days. All patients who did not later recover showed weak reconfiguration of network hubs and dPLI, yielding lower Hub_{RS} and $dPLI_{RS}$ values.

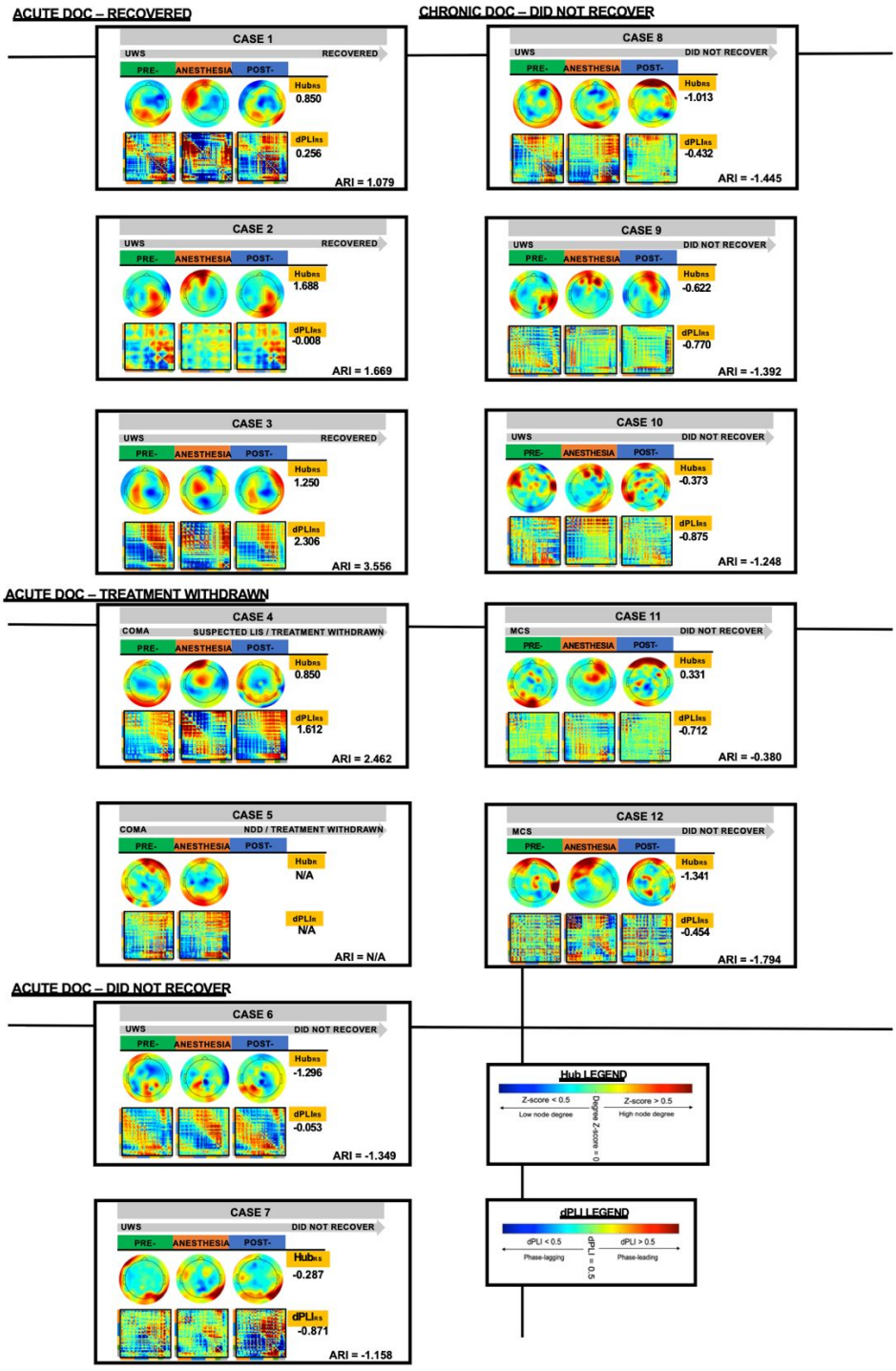
Figure E2. Baseline EEG alone cannot predict current level of consciousness or recovery of consciousness.
Baseline hub posteriority index per participant (y-axis) and feedback dominance index per participant (x-axis) are plotted in a two-dimensional feature space. Panel A represents the classification of the logistic regression based on currently diagnosed level of consciousness, as per the Coma Recovery Scale-Revised (diagnosis). Panel B represents the classification of the logistic regression algorithm based on recovery of full consciousness within 90 days (prognosis). In Panel A, patients with some signs of consciousness (i.e. minimally conscious state) are depicted by the red triangles, whereas patients with no signs of consciousness (i.e., coma and unresponsive wakefulness syndrome) are depicted by blue triangles. In Panel B, red circles depict patients who recovered consciousness at 90-day follow-up ("recovered full consciousness") and blue circles are patients who did not recover consciousness by 90-day followup ("did not recover full consciousness"). The logistic regression decision boundary (dashed line) did not accurately separate groups according to their current diagnosis or their recovery status at 90-day follow-up. In fact, in Panel B, the decision boundary is located outside the boundaries depicted in the figure (did not cross the data points), which indicates that the logistic regression was unable to separate the data points into two groups.

Table E1. Demographic and clinical characteristics of patients who did not undergo anesthetic perturbation (only included in *post hoc* analysis)

ID	Age	Sex	Brain injury	Time since injury	Phase post-injury	CRS-R at study	DOC	Recovery of consciousness within 90 days of EEG
13	36	M	Anoxic	14 years	Chronic	6	UWS	NO
14	27	M	TBI	5 years	Chronic	6	UWS	NO
15	32	M	TBI	6 years	Chronic	8	MCS	NO
16	19	M	Anoxic	10 weeks	Acute	7	UWS	YES
17	20	M	Anoxic	3. years	Chronic	6	UWS	NO
18	52	F	Hypoxic	6years	Chronic	5	UWS	NO
19	35	M	TBI	3years	Chronic	5	UWS	NO
20	65	M	Anoxic	1 year	Chronic	4	UWS	NO
21	45	M	Anoxic	7 years	Chronic	6	UWS	WOT
22	35	F	Stroke	46 days	Acute	12	MCS	YES
23	26	M	TBI	36 days	Acute	16	MCS	YES
24	54	M	Anoxic	21 years	Chronic	8	UWS	NO
25	56	M	Stroke	10 days	Acute	0	Coma	NDD
26	56	M	Anoxic	6 days	Acute	5	UWS	WOT

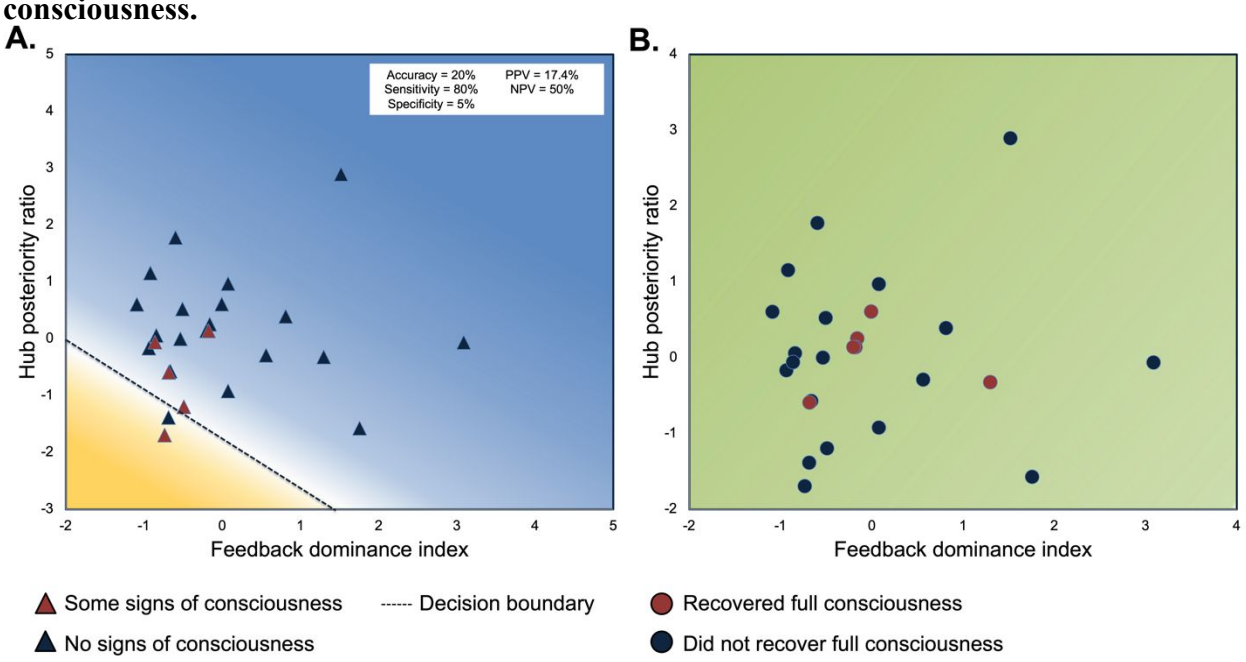
CRS-R: Coma Recovery Scale-Revised; DOC: disorder of consciousness; EEG: electroencephalography; MCS minimally conscious state; NDD: Neurological Determination of Death; TBI traumatic brain injury; UWS: unresponsive wakefulness syndrome; WOT: withdrawal of life-sustaining treatment

Figure E1. Reconfiguration of alpha network hubs and directed functional connectivity before, during and after an anesthetic perturbation of the brain network.



ARI: adaptive reconfiguration index; DOC: disorder of consciousness; dPLI: directed phase lag index: $dPLI_{RS}$: standardized reconfiguration of the directed phase lag index; MCS: minimally conscious state; NDD: Neurological Determination of Death; UWS: unresponsive wakefulness syndrome

Figure E2. Baseline EEG alone cannot predict current level of consciousness or recovery of consciousness.



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.

Objective: 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 in a disorder of consciousness following 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 post-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.

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Introduction

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 (fMRI) and positron-emission tomography (PET), which have contraindications that exclude many patients in disorders of consciousness and are challenging to integrate into everyday clinical environments, preventing their widespread adoption for the assessment of patients in 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 alpha network hubs and neutralization of feedback-dominant connectivity (11-14). Our approach is founded on the hypothesis that unresponsive, brain-injured patients who undergo these network reconfigurations in response to propofol— indicating the loss of some residual consciousness—currently possess consciousness, despite being unresponsive, and/or have the capacity to recover.

Electroencephalography (EEG) measures the electrical activity of cortical neurons using scalp electrodes. It is significantly less expensive than other imaging technologies, has fewer patient contraindications, and can be used at the bedside. EEG is used to calculate the Perturbational Complexity Index, a data-driven metric that can discriminate 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). While it is a robust measure of consciousness (9), the Perturbational Complexity Index is limited in its translational potential due to its reliance on transcranial magnetic stimulation, which is not commonly available in most acute and chronic facilities with patients in 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. Since 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 coma and 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 coma and disorders of consciousness (i.e., unresponsive wakefulness syndrome, and minimally conscious state). Some of the results of these studies have been previously reported in the form of a abstracts (15-18).

Methods

Participants

We recruited 12 adults in a coma or a disorder of consciousness following acquired brain injury (see Table 1 and Online Data 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 in a disorder of consciousness had preserved ability to awaken, but no confirmed signs of awareness: these patients were either in an unresponsive wakefulness syndrome or a minimally consciousness state. In unresponsive wakefulness syndrome (also known as vegetative state), eye opening is present, but patients show no behavioral signs of being aware of themselves or their surroundings, therefore lacking oriented or wilful behaviors (19,20). As such, patients in unresponsive wakefulness syndrome are considered to be unconscious. Minimally conscious state presents with eye opening and some reproducible, though minimal, oriented and/or willful behaviors (e.g. visual tracking, inconsistent command following) (21).

Seven of the 12 participants were acute patients (i.e., ≤ 6 months post-injury) receiving treatment in an intensive care unit; five participants were chronic patients (i.e., > 6 months post-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 low likelihood of recovery – in the 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 72h prior to the study, previous open-head injury, allergy to propofol, or were deemed medically unsuitable by their attending physician.

Experimental design

Participants were given propofol in target-infusion mode at 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*) (Fig. 1a). EEG signals were collected from the scalp using a 128-channel (n = 10) or 64-channel (n = 2) electrode net (see Online Data Supplement for details).

We assessed patients' current level of consciousness using the Coma Recovery Scale-Revised (23), immediately preceding the anesthetic protocol (24). Three months following 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 were present, denoting emergence from a disorder of consciousness, as per criteria from 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 had removal of physiological support following neurological determination of death. The participant who had life sustaining treatment withdrawn had a clinical suspicion of complete locked-in syndrome in the 48h prior to the 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 (wPLI) in the alpha (8-14 Hz) frequency band of all pairwise combinations of electrode channels on 10-second windows (25). Average wPLI matrices were generated for all three recordings, and network hubs were calculated through the topographic distribution of node degree (i.e. number of connections a single node has to all other nodes within the network) (Fig. 1a).

Directed functional connectivity

The directed phase lag index (dPLI) was calculated across 10-second windows and averaged within each analysis epoch in the alpha frequency band to generate representative directed functional connectivity matrices for all three recordings (Fig. 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* (Fig. 1b). Hub_R and $dPLI_R$ were then standardized by removing the mean and scaling to unit variance, becoming Hub_{RS} and $dPLI_{RS}$ (Fig. 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 (Fig. 1d). We did not calculate the Adaptive Reconfiguration Index for one of the 12 participants, as their Hub_R and $dPLI_R$ could not be computed in the *post-anesthesia* EEG due to excessive noise.

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 if 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 days). 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, accuracy were then calculated. Area under the receiver operating characteristic curve (ROC AUC) was also calculated if 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 as per 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 re-ran 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 three months following assessment of their Adaptive Reconfiguration Index. We expected that patients with high propofol-induced network reconfiguration (i.e., high Adaptive Reconfiguration Index) would recover full consciousness at the three-month follow-up.

Four individual examples of propofol-induced network reconfiguration can be found in Fig. 2 (see Fig. E1 for all cases). On an individual level, a high Adaptive Reconfiguration Index was indicative of favorable prognosis (Fig. 2, Fig. 3). When taken separately, the reconfiguration of network hubs (Hub_R) and directed functional connectivity ($dPLI_R$) were higher in patients who

later recovered full consciousness than those who did not, reaching statistical significance for Hub_R (Hub_R U-value = 21, one-tailed p-value = 0.008; $dPLI_R$ U-value = 19, one-tailed p-value = 0.033) (Fig. 4A, 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 both above the maximum values of those who did not recover (Fig. 4A, 4B).

In the three patients who later recovered full consciousness, network hub topography mirrored that of healthy individuals (anterior during exposure to propofol; posterior otherwise) (Fig. 2A, Fig. S1 Cases 1-3) (11). In these 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) (Fig. 2A, Fig. S1 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. Fig. 2B, Fig. S1 Cases 6, 7, 12), or random, incoherent shifts in hub structure that did not return to baseline configuration during the *post-anesthesia* recording (e.g. Fig. 2C, Fig. S1 Cases 8, 9). These same patients who did not go on to recover consciousness also either showed little to no reconfiguration in directed functional connectivity in response to propofol or pathological patterns (e.g. Fig 2B, 2C, and Fig. S1 Cases 6-12).

The Adaptive Reconfiguration Index was significantly higher in patients who later recovered full consciousness (U-value = 21, one-tailed p-value = 0.008) (Fig. 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 (Fig. 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 acute coma and disorder of consciousness patients, as the Adaptive Reconfiguration Index 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 be in a 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 (Fig 2D, Fig 3). Though 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

Patients' current level of consciousness was assessed using the Coma Recovery Scale-Revised immediately preceding the anesthetic protocol (23). We expected participants with "some signs of consciousness" (i.e., 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-value = 0.911) and $dPLI_R$ (one-tailed p-value = 0.733), the Adaptive Reconfiguration Index did not differ between groups (one-tailed p-value = 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 diagnostic value was not confirmed in this case series.

Translatability of Adaptive Reconfiguration Index to clinical EEG

Given that high-density 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-value = 0.008; $dPLI_R$ U-value = 19, one-tailed p-value = 0.033) (Fig. 7A, 7B). The Adaptive Reconfiguration Index was also significantly higher in patients who later recovered full consciousness (U-value = 21, one-tailed p-value = 0.008) (Figure 7C), and both prognostic groups (i.e., "recovered" vs. "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 (Fig. 7D). That is, with only 18 channels, the Adaptive Reconfiguration Index could still discriminate with 100% accuracy whether or not 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 the prognostication of coma and disorders of consciousness (see Online Data 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 for 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 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 aetiologies of brain injury, and across diagnoses ranging from coma to minimally conscious state. This naturalistic study sample was reflective of the heterogeneity of individuals with a coma or 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 that did not recover full consciousness showed baseline patterns associated with conscious awareness (e.g., feedback-dominant connectivity). It is the *inability* for 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 Data 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 Supplemental Discussion).

Though the Adaptive Reconfiguration Index showed promising preliminary results as prognostic tool for consciousness recovery, it showed no association to 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 Come Recovery Scale-Revised assessment (29), such as pain, reflexive motor activity, fatigue and psychoactive medication, which are known to affect 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 accuracies. 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 minimally conscious state (2), and expert assessment of PET images was 82% accurate in distinguishing these same categories (4). The Perturbational Complexity Index was also shown to detect minimally conscious

state with a sensitivity of 94%, and to identify unresponsive wakefulness syndrome patients 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 the propofol perturbation may therefore indirectly reflect the brain's preserved ability for self-organization (30). When the brain has operated in a come 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 following a brain injury, and that speed of cognitive recovery is faster in the first few months to years following a severe brain injury (34,35). Though 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 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, its potential clinical application and translational potential, and to highlight to potential for the Adaptive Reconfiguration Index to aid in the 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 the prognostic accuracy of the Adaptive Reconfiguration Index to the prognosis made by the treating team. A second limitation to 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 if they were in fact anesthetized by the propofol received. However, given that a brain injury and/or an American Society of Anesthesiologists status ≥3 is known to make patients more vulnerable to the effects of anesthesia, this target effect site concentration was recommended by our team of neuroanesthesiologists, as 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 in patients who were breathing spontaneously. Another study limitation is our follow-up assessment of consciousness recovery, carried out 90 days following 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, as 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. Though the attending physician's suspicion could not be confirmed prior to the 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 Data 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 anesthetic-induced reconfiguration of alpha network hubs and directed functional connectivity, the Adaptive Reconfiguration Index discriminated with 100% accuracy patients who recovered within three months following the study. This accessible method of predicting consciousness recovery could have significant implications for clinical management and decision-making.

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Figure Legends

Figure 1. Study protocol and analytic approach.
Patients underwent propofol anesthesia with a target effect-site concentration of 2.0 μg/mL, with concomitant high-density EEG (hd-EEG) recording. Five-minute epochs of hd-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 the predicted effect site concentration decreased below 0.5 μg/mL. Whole-brain alpha 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) The Hub_R and $dPLI_R$ were standardized, yielding the Hub_{RS} and $dPLI_{RS}$, which (d) were then summed to yield the Adaptive Reconfiguration Index.

Figure 2. Four individual cases depicting the alpha network's response to propofol administration. .
For each case presented, topographic maps of the node degree of alpha EEG networks and matrices of functional connectivity are presented across *pre-anesthesia* (green), *anesthesia* (orange) and *post-anesthesia* (blue) epochs. For hubs, the colormap represents the Z-score of the normalized node degree for each electrode. For 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 colorbar bordering each matrix: frontal (orange), central (blue), parietal (yellow), occipital (green), and temporal (grey). The colormap 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 (Hub_{RS} and $dPLI_{RS}$) are depicted in the right-hand column of each panel (yellow), and the Adaptive Reconfiguration Index is indicated in the bottom right-hand corner of each case. A) Case 3, who was in an 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 was in an 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 was in a 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 48h of withdrawal of treatment, the attending physician indicated a suspicion of complete locked-in syndrome and potentially preserved awareness. Though 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.

Figure 3. Adaptive Reconfiguration Index value per patient.
Individual Adaptive Reconfiguration Index values are depicted by 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, while 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.

Figure 4. The Adaptive Reconfiguration Index was significantly higher in patients who later recovered consciousness.
(A) Hub reconfiguration (Hub_R), (B) dPLI reconfiguration ($dPLI_R$) and (C) Adaptive Reconfiguration Index values are depicted per group. Patients who later recovered full consciousness within 90 days of the study constitute the "Recovered" group (n = 3) (blue), while 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 and dPLI reconfiguration when these indices were taken separately, and had 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-value = 0.008) and the Adaptive Reconfiguration Index (one-tailed p-value = 0.008), and showed a trend toward significance for $dPLI_R$ (one-tailed p-value = 0.033).
*: $p < 0.05$; **: $p < 0.025$

Figure 5. The Adaptive Reconfiguration Index predicts 90-day recovery of consciousness.
The standardized reconfiguration of hubs (Hub_{RS}) (y-axis) and the standardized reconfiguration of the dPLI ($dPLI_{RS}$) (x-axis) are plotted per participant in a two-dimensional feature space, yielding the ARI. ARI 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.

Figure 6. The Adaptive Reconfiguration Index cannot predict current level of consciousness.
The standardized reconfiguration of hubs (Hub_{RS}) (y-axis) and the standardized reconfiguration of the dPLI ($dPLI_{RS}$) (x-axis) are plotted per participant in a two-dimensional feature space, yielding the ARI. ARI value per participant is depicted with X's ("No signs of consciousness") and circles ("Some signs of consciousness") according to diagnosed level of consciousness at the time of the study, as per 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.

Figure 7. The Adaptive Reconfiguration Index calculated on 18 EEG channels predicts recovery of consciousness within 90 days.

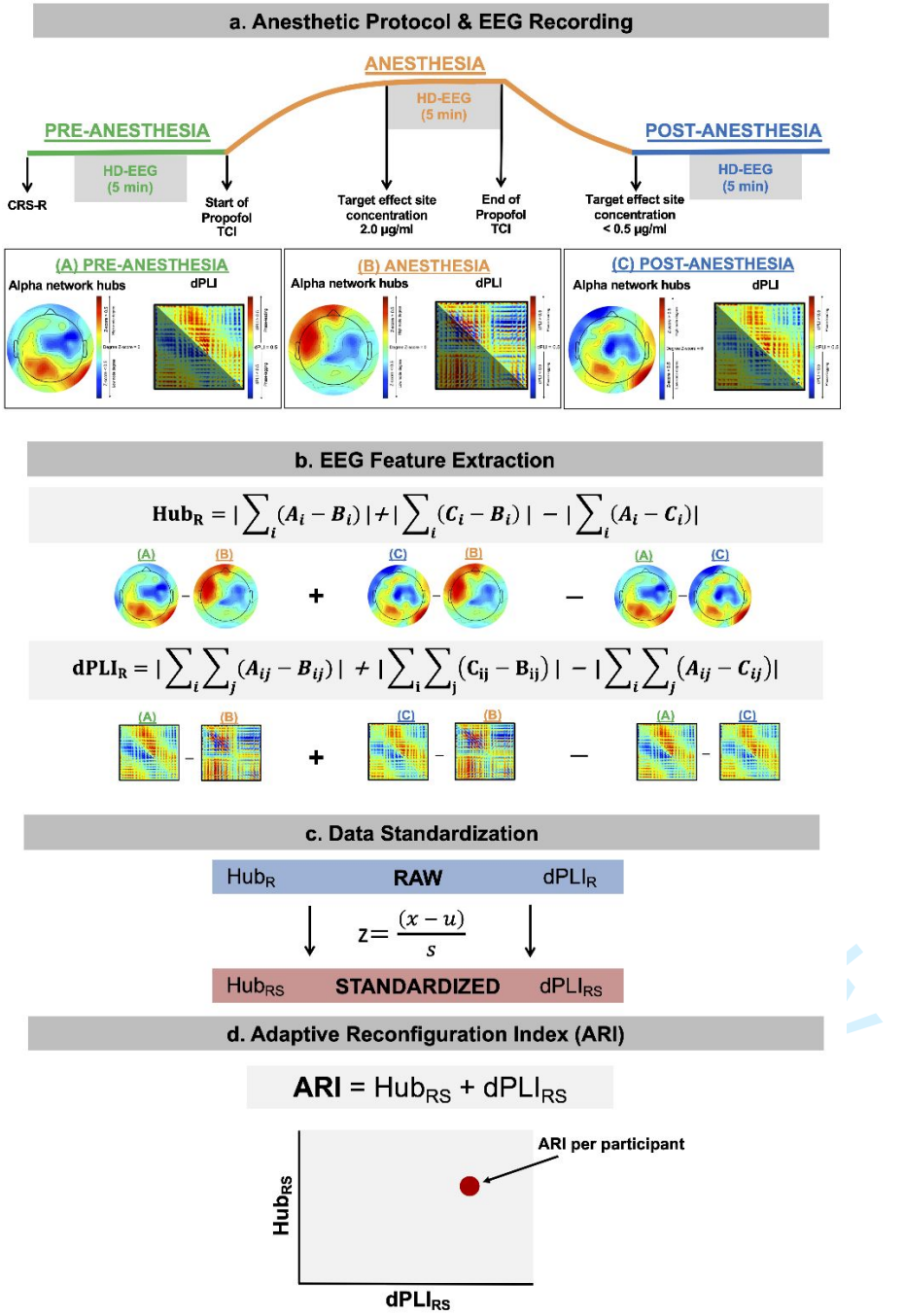
(A) Hub reconfiguration (Hub_R), (B) dPLI reconfiguration ($dPLI_R$) and (C) Adaptive Reconfiguration Index values calculated on 18-channel EEG are depicted for patients who later recovered full consciousness within 90 days of the study (i.e., "Recovered") (blue) and those who did not recover full consciousness 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-value = 0.008) and the Adaptive Reconfiguration Index (one-tailed p-value = 0.008), and showed a trend toward significance for $dPLI_R$ (one-tailed p-value = 0.033). In panel (D), The standardized reconfiguration of hubs (Hub_{RS}) (y-axis) and the standardized reconfiguration of the dPLI ($dPLI_{RS}$) (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 90 days following the study. The logistic regression decision boundary (dashed line) accurately separated both groups according to their 90-day outcome.
*: $p < 0.05$; **: $p < 0.025$

Table 1. Demographic and clinical characteristics of the 12 patients who underwent anesthetic perturbation

ID	Age	Sex	Brain injury	Time since injury	Phase post-injury	CRS-R at study	Diagnosis at study	Recovery of consciousness 90 days post-study
1	42	F	Stroke	21 days	Acute	3	UWS	YES
2	29	M	TBI	58 days	Acute	4	UWS	YES
3	50	F	Stroke	25 days	Acute	4	UWS	YES
4	40	M	Stroke	6 days	Acute	0	Coma	Suspected LIS prior to WOT*
5	74	F	Anoxic	10 days	Acute	0	Coma	NDD*
6	75	F	Stroke	10 days	Acute	5	UWS	NO
7	18	F	TBI	21 days	Acute	5	UWS	NO
8	24	M	Anoxic	8 years	Chronic	5	UWS	NO
9	53	F	Anoxic	9 months	Chronic	5	UWS	NO
10	28	F	Anoxic	1 year	Chronic	6	UWS	NO
11	28	M	TBI	11 years	Chronic	10	MCS	NO
12	36	F	TBI	2 years	Chronic	11	MCS	NO

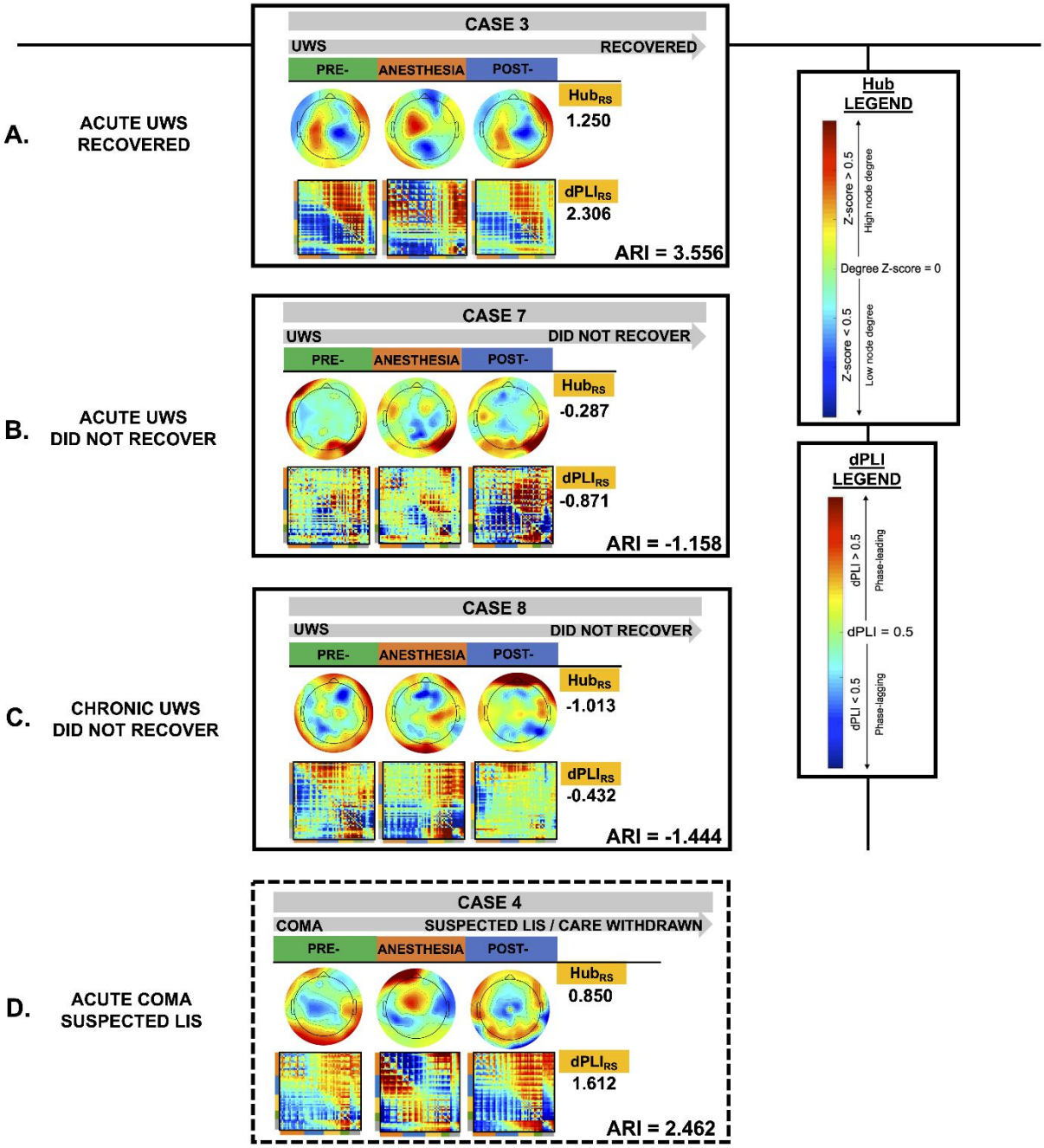
* Withdrawal of treatment or support took place prior to the 90-day follow-up.
CRS-R: Coma Recovery Scale-Revised; DOC: disorder of consciousness; EEG: electroencephalography; LIS: locked-in syndrome; MCS minimally conscious state; NDD: neurological determination of death; TBI traumatic brain injury;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

Figure 1. Study protocol and analytic approach.



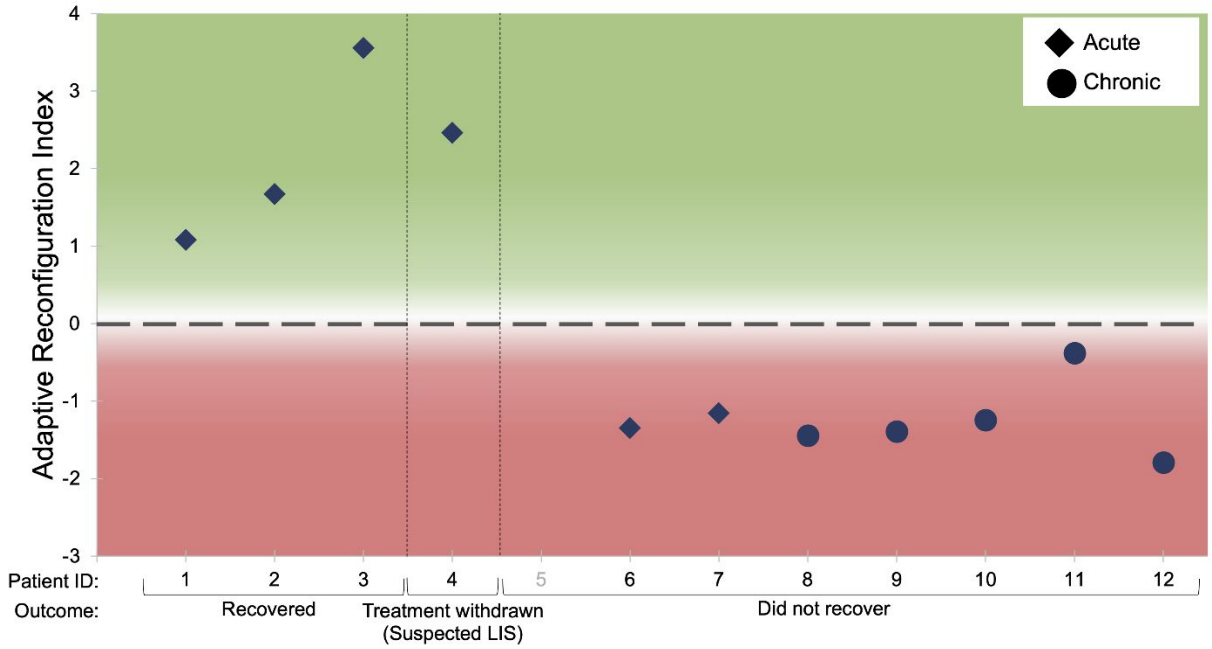
ARI: adaptive reconfiguration index. EEG: electroencephalography; dPLI: directed phase lag index; $dPLI_R$: reconfiguration of the directed phase lag index; $dPLI_{RS}$: standardized reconfiguration of the directed phase lag index; HD-EEG: high density electroencephalography; HUB_R: hub reconfiguration; HUB_{RS}: standardized hub reconfiguration; TCI: target-controlled infusion.

Figure 2. Four individual cases depicting the alpha network's response to propofol administration.



dPLI: directed phase lag index; $dPLI_{RS}$: standardized reconfiguration of the directed phase lag index; HUB_{RS}: standardized hub reconfiguration; LIS: locked-in syndrome; UWS: unresponsive wakefulness syndrome

Figure 3. Adaptive Reconfiguration Index values per patient



LIS: locked-in syndrome

Figure 4. The Adaptive Reconfiguration Index was significantly higher in patients who later recovered consciousness.

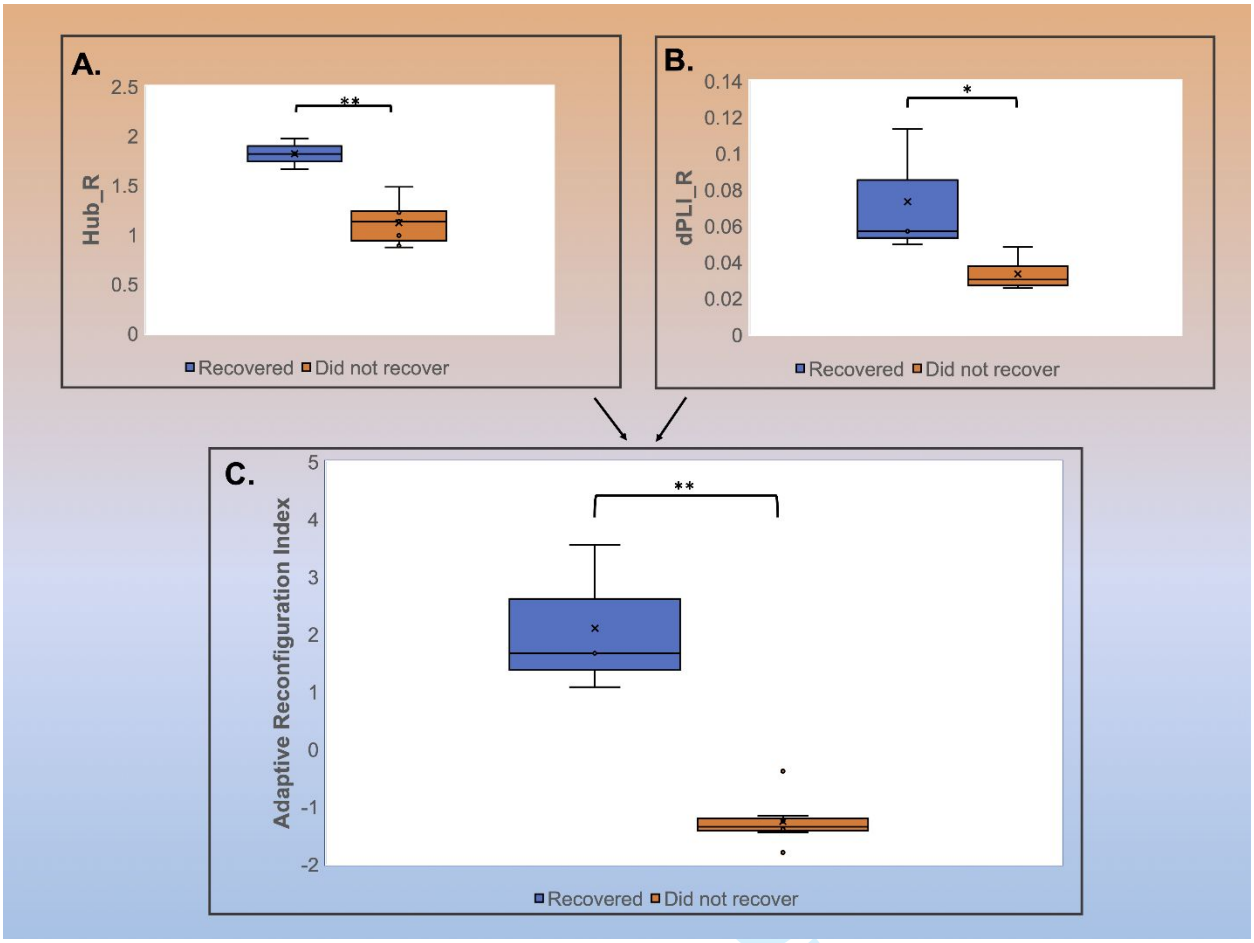
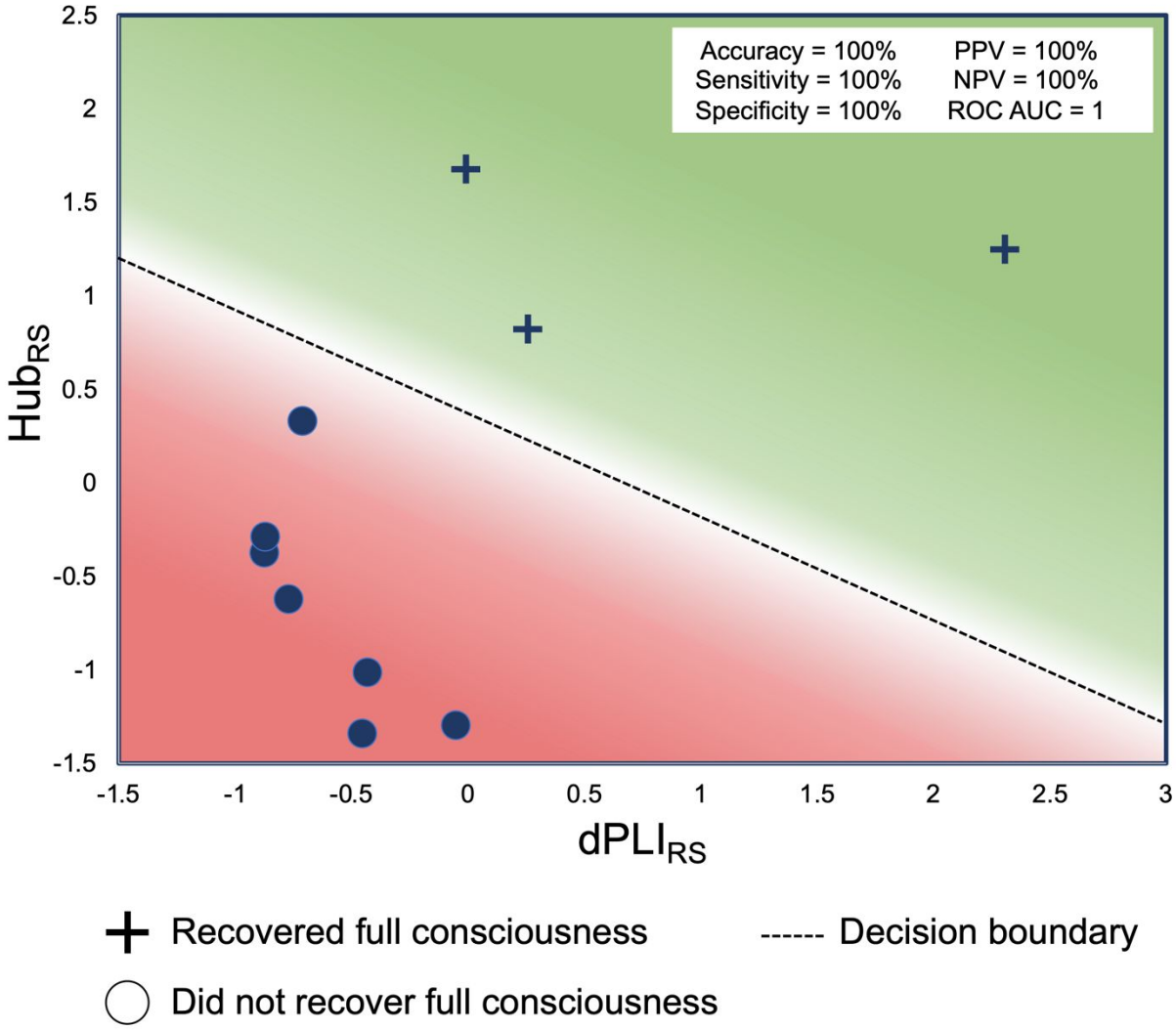


Figure 5. The Adaptive Reconfiguration Index predicts 90-day recovery of consciousness.



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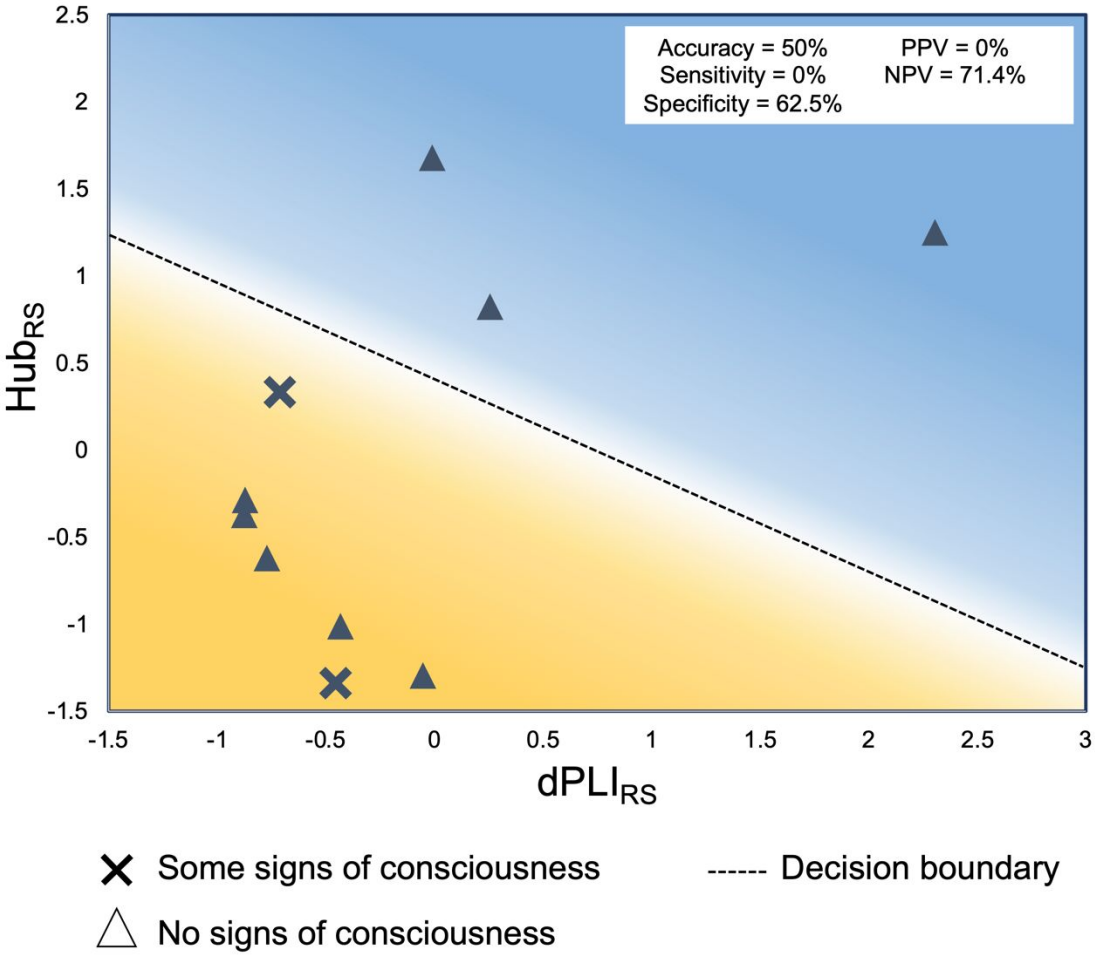

Figure 7. The Adaptive Reconfiguration Index calculated on 18 EEG channels predicts recovery of consciousness within 90 days.