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Covert Speech Comprehension Predicts Recovery From Acute Unresponsive States

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Objective: Patients with traumatic brain injury who fail to obey commands after sedation-washout pose one of the most significant challenges for neurological prognostication. Reducing prognostic uncertainty will lead to more appropriate care decisions and ensure provision of limited rehabilitation resources to those most likely to benefit. Bedside markers of covert residual cognition, including speech comprehension, may reduce this uncertainty.
Methods: We recruited 28 patients with acute traumatic brain injury who were 2 to 7 days sedation-free and failed to obey commands. Patients heard streams of isochronous monosyllabic words that built meaningful phrases and sentences while their brain activity via electroencephalography (EEG) was recorded. In healthy individuals, EEG activity only synchronizes with the rhythm of phrases and sentences when listeners consciously comprehend the speech. This approach therefore provides a measure of residual speech comprehension in unresponsive patients.
Results: Seventeen and 16 patients were available for assessment with the Glasgow Outcome Scale Extended (GOSE) at 3 months and 6 months, respectively. Outcome significantly correlated with the strength of patients' acute cortical tracking of phrases and sentences ($r > 0.6$, $p < 0.007$), quantified by inter-trial phase coherence. Linear regressions revealed that the strength of this comprehension response (beta = 0.603, $p = 0.006$) significantly improved the accuracy of prognoses relative to clinical characteristics alone (eg, Glasgow Coma Scale [GCS], computed tomography [CT] grade).
Interpretation: A simple, passive, auditory EEG protocol improves prognostic accuracy in a critical period of clinical decision making. Unlike other approaches to probing covert cognition for prognostication, this approach is entirely passive and therefore less susceptible to cognitive deficits, increasing the number of patients who may benefit.

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Accurate early prognostication is vital for efficient stratification of patients after traumatic brain injury (TBI). On average, across the spectrum of severe TBI, adequate prognostic accuracy is often achievable from patient behavior and computed tomography (CT) characteristics at admission.[1] However, the subset of patients who continue to fail to obey commands after washout of sedation pose one of the most significant challenges for neurological prognostication. In these cases, clinicians and families must decide whether to "wait and see" or to consider treatment withdrawal. Indeed, a lack of command-following in the early period post-sedation is associated with poor outcome, including Vegetative State / Unresponsive Wakefulness Syndrome (VS/UWS),[2] thus placing a "window of opportunity" for cessation of life-sustaining therapy at a time of considerable prognostic uncertainty.[3]

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Recent research has demonstrated that a significant proportion of unresponsive patients retain a level of cognition and even consciousness that is not evident from their external behavior - the so-called "cognitive-motor" dissociation.[4] This covert consciousness is typically probed with paradigms that require the patient to follow repeated commands to imagine that they are moving (eg, Refs. 5–7). Indeed, there is evidence that a minority of patients in acute unresponsive states can appropriately modulate their electroencephalography (EEG)-detected brain activity in response to these commands, and that these patients have a higher probability of good outcome.[8]

However, two key aspects of the covert command-following approach limit its clinical utility. First, the cognitive demands of this approach are restrictively high and, thus, whereas successful demonstration of covert command-following is a widely accepted clinical marker of awareness and useful for prognosis, its sensitivity is compromised by precluding many patients with cognitive deficits from demonstrating the extent of their abilities.[7,9] Second, relatively confident prognostication is possible for many patients by means of more easily acquired and easily interpreted clinical characteristics, such as the Glasgow Coma Scale (GCS) score at admission,[10] thus questioning the added benefit of measures of covert command-following as a whole. What is needed, therefore, is an approach to identifying covert cognition that has minimal "passive" cognitive demands, and therefore higher sensitivity, and that is beneficial in cases of highest clinical uncertainty, such as those who fail to regain behavioral command-following after sedation washout.

An EEG measure of speech comprehension is one such passive approach to identifying covert cognition that has recently shown prognostic value in chronic disorders of consciousness[11] (see also Coleman et al[12] for similar outcomes in a functional magnetic resonance imaging [fMRI] study). Using a similar approach, we investigated the level of covert speech comprehension evident in the EEG of a group of sedation-free yet unresponsive patients with acute TBI in the intensive care unit. Our aim was to ascertain the value of markers of covert speech comprehension for improving prognostic accuracy at 3 months and 6 months postinjury, thus reducing uncertainty in this critical period of decision making.

Methods

Participants

We screened all 139 patients with severe TBI admissions to the intensive care unit of the Queen Elizabeth Hospital, Birmingham (England), between April 2018 and October 2019. Inclusion criteria of this study required patients to have a GCS motor score below 6 (ie, not obeying commands), to be aged over 18 years, and to be receiving care as a result of a TBI. Exclusion criteria were: patients moribund, those with a history of moderate or severe TBI or neurological disorder, those who were not an English-speaker, those with CT evidence of brainstem-only lesion (ie, suspected locked-in syndrome), those with CT evidence of focal left lateral temporal lobe lesions (ie, suspected specific language deficits), and those with known hearing impairments. Of the 139 screened patients, 28 patients were consented onto the study, and 21 patients met all inclusion/exclusion criteria at the time of EEG, between 48 hours and 7 days after sedation hold. After excluding data from 2 patients due to artifacts/technical issues, 17 patients (or their consultees) were available for outcome assessment at 3 months (median = 3 months + 4.5 days, range = 3 months to 2 days to 3 months + 30 days) post-EEG, and 16 patients (or their consultees) were available for outcome assessment at 6 months (median = 6 months + 4 days, range = 6 months to 3 days to 6 months + 48 days) post-EEG (for patients' characteristics, see Table 1). We assessed outcome with the extended version of the Glasgow Outcome Scale[13] via telephone conversation with patients or their consultees. All outcome assessors were blind to the EEG results of the respective patients. Note that none of the patients had achieved command following on their GCS at any point between sedation hold and the EEG, giving us confidence that the lack of command following evident in the GCS immediately prior to the EEG does not reflect a transient fluctuation, but a sustained lack of behavior. Full details of each patient are available in the on-line data repository that accompanies this paper (https://osf.io/wu2vy/).

This study was approved by the West Midlands Coventry and Warwickshire Research Ethics Committee, the Health Research Authority, and was sponsored by the University of Birmingham, England. Personal or Nominated Consultees of each patient were identified by the clinical team and approached to provide written consent. Consultees also consented to be contacted for outcome interviews. Patients who regained capacity during the follow-up period also re-consented. The study was coordinated by the Surgical Reconstruction and Microbiology Research Centre, University Hospitals Birmingham. The first and the last author analyzed the data. All data, stimuli, and analysis scripts are shared via the sharing platform OSF (https://osf.io/wu2vy/).

Results of this study are reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for reporting

TABLE 1. Patients' Characteristics

Patient	Sex	Age [yr]	GCS EEG (E/V/M)	Days after injury	CT grade	3-month outcome	6-month outcome
1	M	72	1/1T/3	5	2	Death (1)	Death (1)
2	F	86	1/1T/4	5	2	Death (1)	Death (1)
3	M	26	1/1/4	17	5	Vegetative state (2)	Vegetative state (2)
4	M	40	1/1T/3	12	5	Lower severe disability (3)	Lower severe disability (3)
5	M	59	3/1/1	13	5	Lower severe disability (3)	Lower severe disability (3)
6	F	44	1/1T/4	10	5	Lower severe disability (3)	Lower severe disability (3)
7	M	82	1/1T/1	3	5	Vegetative state (2)	Lower severe disability (3)
8	M	64	1/1T/3	9	5	Death (1)	Death (1)
9	M	70	1/1/4	5	5	Lower severe disability (3)	Vegetative state (2)
10	M	70	4/1/5	10	6	Upper moderate disability (6)	Lower good recovery (7)
11	M	27	2/1/4	19	2	Lower severe disability (3)	Lower severe disability (3)
12	M	77	1/1T/4	12	2	Lower severe disability (3)	Lower severe disability (3)
13	M	54	1/1T/4	10	2	Upper moderate disability (6)	Upper moderate disability (6)
14	M	59	1/1T/4	9	3	Lower severe disability (3)	—
15	F	59	4/1T/3	14	5	Lower severe disability (3)	Lower severe disability (3)
16	M	61	4/1T/3	15	2	Upper severe disability (4)	Upper moderate disability (6)
17	M	32	4/1T/5	17	2	Upper severe disability (4)	Lower moderate disability (5)

For each patient, gender, age, GCS score (eye response [E]: 1 = no response to 4 = spontaneous; verbal response [V]: 1 T = no response, intubated, 1 = no response to 5 = orientated; motor response [M]: 1 = no response to 6 = obeying), days after injury, CT Marshall Grade (grade I = no visible intracranial pathology to grade VI = high or mixed-density lesion, not surgical), 3-month and 6-month follow-up outcome measured via GOSE (1 = death to 8 = upper good recovery).
CT = computed tomography; EEG = electroencephalography; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended.

observational studies[14] and the according protocol will be provided upon request.

Stimuli
We constructed a total of 288 mono-syllabic English words using the male voice of the Apple synthesizer (Macintalk, voice Alex; Apple MacBook Pro Third generation), segmented using Audacity software version 2.1. Importantly, words were isochronous, of 320 ms in length, which resulted in a presentation frequency of 3.125 Hz for the word rate, 1.56 Hz for the phrase rate, and 0.78 Hz for the sentence rate. The words included 144 nouns, 72 adjectives, and 72 verbs (details can be obtained upon request and will be shared via the platform OSF upon publication). A total of 72 four-word sentences were constructed, conforming to the syntactic structure: adjective - noun - verb - noun and a trial consisted of 12 of these 4-word sentences, resulting in a total of 864 meaningful 4-word sentences. Each sentence was played a minimum of 8 times and a maximum of 9 times per patient throughout the experiment. The order with which they were presented was randomly chosen on a trial-by-trial basis, avoiding occurrence of the same 4-word sentence more than once per trial. All stimuli were presented via the MATLAB toolbox Psychtoolbox.[15] Individual trials were separated by a jittered delay of 1.2 to 2.2 seconds, randomly chosen from a uniform distribution.

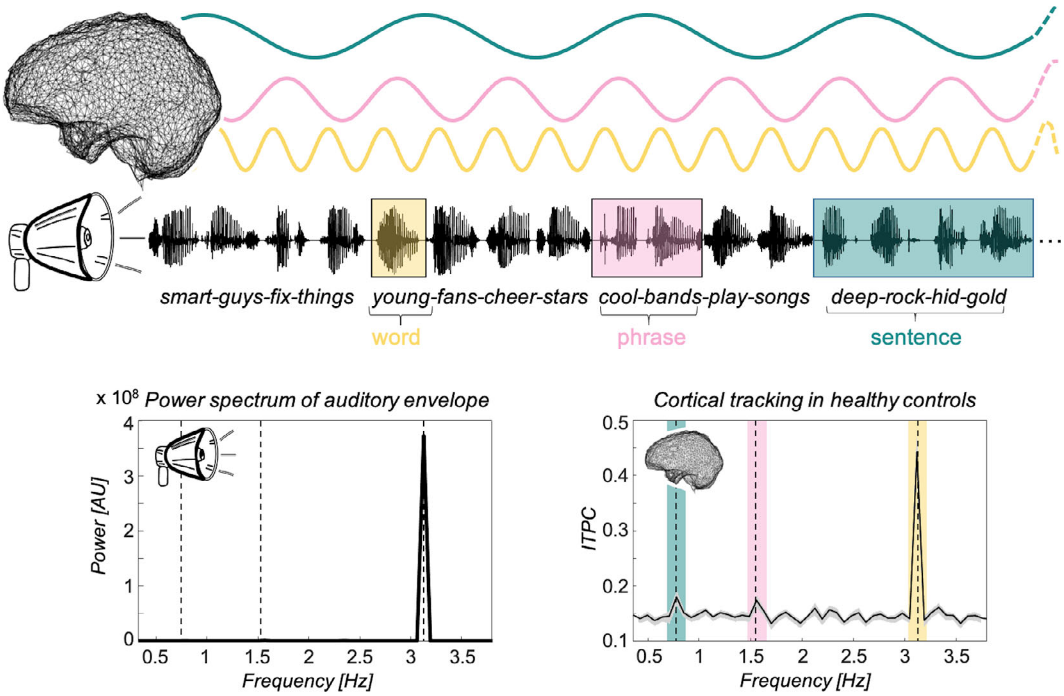

FIGURE 1: Experimental paradigm and EEG data analysis. (A) Patients heard 72 trials, composed of 24-word sequences (here shown for an example of 4 sentences), which were played continuously, without any acoustic gaps. Individual words (eg, "young") were played at a frequency of 3.125 Hz, phrases (eg, "cool bands") at 1.56 Hz, and sentences (eg, "deep rock hid gold") at 0.78 Hz. Brain activity was recorded via EEG and analyzed for cortical tracking, quantified by inter-trial phase coherence (ITPC). (B) This panel shows the power spectrum of the auditory envelope, containing only one peak at the word rate (3.125 Hz). (C) This panel shows average cortical tracking over 20 healthy, comprehending participants (these data are taken from our recent study, testing the same paradigm in healthy participants, for details see Sokoliuk et al. [2020] bioRxiv), with significant peaks at target frequencies (words, phrases, and sentences) marked accordingly. EEG, electroencephalography. [Color figure can be viewed at www.annalsofneurology.org]

Prior to the experiment, patients were instructed to passively listen to the auditory stimuli. Patients were naïve to the sentence structure of the stimulus material and were presented with 72 trials.

We placed two equally spaced breaks within the approximately 18-minute stimulation to allow access for nursing staff or family if required.

Study Procedures

Patients heard a series of isochronous mono-syllabic words presented at a rate of 3.125 Hz via earphones (Etymotic ER-1). Every 4 words of this stream formed a meaningful sentence composed of 2 two-word phrases (eg, sharp-knife-cuts-meat). Therefore, a meaningful phrase (eg, sharp-knife) occurred within the stream at a rate of 1.56 Hz, and a meaningful sentence at a rate of 0.78 Hz. Importantly, the physical properties of the stimulus (ie, its envelope) varied only at the rate of the words (3.125 Hz). There was no acoustic information within the stimulus at the rate of the phrases or sentences (see Fig 1B). Therefore, oscillations within the EEG signal that occur at the rate of the phrases and sentences are necessarily generated in a top-down manner by a comprehending listener. Indeed, phrase/sentence rate oscillations in the EEG are only evident in participants who are awake and who comprehend the speech stimulus.[16,17]

EEG Acquisition

A clinical electrophysiologist recorded the EEG data at 256 Hz or 512 Hz with a 19-electrode clinically certified EEG system, using a XlTek Brain Monitor EEG amplifier (Natus Medical Incorporated, Pleasanton, CA) with a 10/20 montage and additional right and left mastoid electrodes. The ground and reference electrodes were placed across the vertex. Data quality was monitored during acquisition and in subsequent offline artifact correction. Of those 13 patients with eventual tracheostomy placement, EEG acquisition occurred prior to placement of tracheostomy in 6 patients, and of those 5 patients with eventual placement of percutaneous endoscopic gastronomy (PEG) tube, EEG acquisition occurred prior to placement in all patients.

EEG Analysis

Pre-Processing. EEG data pre-processing was performed using custom-written Matlab scripts (all analysis scripts can be obtained upon request and will be shared via the platform OSF upon publication) and functions of the Matlab toolbox FieldTrip[18] as well as eeglab.[19]

EEG data was filtered between 0.01 and 100 Hz, using a Hamming windowed sinc FIR filter. Additionally, a notch filter was applied at 48 to 52 Hz and 98 to 102 Hz, using a Hamming windowed sinc FIR filter to reduce line noise. Subsequently, the data was epoched into trials starting 1 second before stimulus onset and lasting for the whole length of each auditory stream. This way, trials of 16.36 seconds were created. Then, data were visually inspected for artifacts as well as noisy channels, which were removed from the data before an ICA was computed,[20] to remove blinks and horizontal eye movements from the data. Finally, noisy channels were interpolated by using data of their neighbors, which were identified via the triangulation method, as implemented in FieldTrip,[18] before the data were re-referenced to average.

Subsequently, data were downsampled to 256 Hz to assure the same sampling rate for all recordings and a low-pass filter at 25 Hz (butterworth) was applied to the data given the low cutoff of the frequencies of interest (<4 Hz). In preparation for the next analysis step, all trials were further cut to discard the first 2.28 seconds (resulting in 11 of the 12 four-word sequences per trial), which correspond to the 1 second pre-stimulus period and the first 4-word sequence, to avoid including the transient EEG response to the onset of the auditory stimulus, and to match the approach of previous studies.[17,21]

Inter-Trial Phase Coherence. Inter-trial phase coherence (ITPC) was used as a measure to quantify the extent to which patients' EEG oscillated in synchrony with the words/phrases/sentences. This was achieved by first computing the Discrete Fourier Transform (DFT) of the data, for each trial and electrode separately, to transform the signal into the frequency domain with 0.07 Hz resolution (ie, 1/[15.36 seconds to 1.28 seconds]). Equation (1) shows how ITPC was calculated for each frequency (f) over all trials (k), where K is the number of all trials, and θ the respective phase angle of the complex-valued Fourier coefficients (cf. Refs. 17, 21). This resulted in 7,041 ITPC values for each of the 19 electrodes for every patient. For all analyses, we subsequently averaged ITPC values across all electrodes.

Inter-trial phase coherence

$$\mathrm{ITPC}(f) = \left(\sum\nolimits_k \cos(\theta_k)\right)2/K + \left(\sum\nolimits_k \sin(\theta_k)\right)2/K \tag{1}$$

Glasgow Outcome Scale Extended Outcome Data Acquisition

We conducted phone-call follow-ups at 3 months and 6 months to assess the patients' outcome via the Glasgow Outcome Scale Extended (GOSE).[13] GOSE scores could reach a minimum of 1 and a maximum of 8 (1 = death; 2 = vegetative state; 3 = lower severe disability; 4 = upper severe disability; 5 = lower moderate disability; 6 = upper moderate disability; 7 = lower good recovery; and 8 = upper good recovery). These interviews were either conducted with the patients' consultee or, if patients had capacity, with the patients themselves (all GOSE outcome data will be shared via the platform OSF upon publication).

Statistical Analysis

As our aim was to detect signatures for linguistic processing, we averaged the ITPC values for phrases and sentences into one "comprehension" rate. This has the added advantage of increasing sensitivity in our measure because ITPC values for rates at higher-level linguistic structures are known to be small in healthy participants.[21] Yet, results remain qualitatively similar if using phrase and sentence ITPC separately (phrases: rho [3 months] = 0.627; rho [6 months] = 0.811; sentences: rho [3 months] = 0.437; rho [6 months] = 0.375).

At each rate of interest (words and phrases/sentences), we calculated the Spearman correlation between ITPC and GOSE at 3 months and 6 months separately. To ensure the specificity of these correlations to the frequencies of interest, we used a bootstrap test. Therefore, the actual correlation coefficients (rho) obtained from the Spearman correlations were individually compared to a distribution of 1,000 surrogate correlation coefficients. These were obtained by correlating the ITPC value of a randomly chosen "chance frequency" (ie, a frequency that is non-harmonic to word, phrase, or sentence rate) for the word rate, and the average ITPC over a chance frequency and its first harmonic, for phrase + sentence rate, with the GOSE outcome after 3 months and 6 months. Obtained p values were further controlled for multiple comparisons by applying false discovery rate (FDR) detection.[22,23]

Linear Regression Modeling

To test the prognostic value of ITPC beyond clinical characteristics, we computed separate backward multiple linear regressions using the software JASP (version 0.12.2.0[24]). The linear regressions were computed for each follow-up time point with GOSE as the dependent variable, and the following predictors: (1) standard clinical prognostic parameters, taken from clinical notes: age, GCS score at time of EEG recording (ie, the most recent GCS prior to the EEG recording [median 1.5 hours prior, range < 15 minutes to 4.75 hours]), number of days between the injury and the EEG recording, CT Marshall grade, and (2) EEG-specific parameters computed by the research team: ITPC at the word rate, and ITPC at the phrase/sentence rate. The regression analysis was performed using the backward method, which entails initial simultaneous entering of all predictors and stepwise removal of those predictors, which are less informative ($p > 0.1$) until significant ($p < 0.05$) predictor/s for the best fitting model is/are found.

Prior to regression, we normalized GOSE scores using a rank-based inverse Gaussian method to achieve a normal distribution of the dependent variable.[25]

Results

Correlation between ITPC and Outcome

The extent to which patients' EEG oscillated in synchrony with the individual words of the auditory stimulus did not significantly correlate with outcome at either 3 or 6 months (GOSE 3 months: rho = 0.341, 95% confidence interval [CI] = −0.17 to 0.710, p = 0.181; GOSE 6 months: rho = 0.401, 95% CI = −0.100 to 0.767, p = 0.124; Fig 2A, B). However, crucially, cortical tracking of higher-level linguistic structures correlated significantly with outcome at both 3 and 6 months (GOSE 3 months: rho = 0.638, 95% CI = 0.298 to 0.853, p = 0.006; GOSE 6 months: rho = 0.751, 95% CI = 0.474 to 0.927, p = 0.001; Fig 2C, D). A bootstrap approach revealed that this correlation between the 3 and 6-month outcome and higher-level cortical tracking is stronger than any correlation at 1,000 randomly selected non-target rates (ie, $p < 0.001$), thus demonstrating the specificity of the prognostic value of higher-level cortical tracking.

Linear Regression Modeling

At 3 months postinjury, the variance of outcome was best explained by a model containing GCS score at the time of EEG (p = 0.03, beta = 0.453, regression coefficient = 0.212, 95% CI = 0.024 to 0.4) and the magnitude of higher-level (ie, phrases and sentences) cortical tracking (p = 0.027, beta = 0.463, regression coefficient = 16.243, 95% CI = 2.136 to 30.349; statistics of the winning model; ie, the model with the largest F statistic: F (2,14) = 10.386; p = 0.002; adjusted R^2 = 54%). This combination of predictors explained 17.5% more variance of outcome than a model containing only GCS score at the time of the EEG (Table 2).

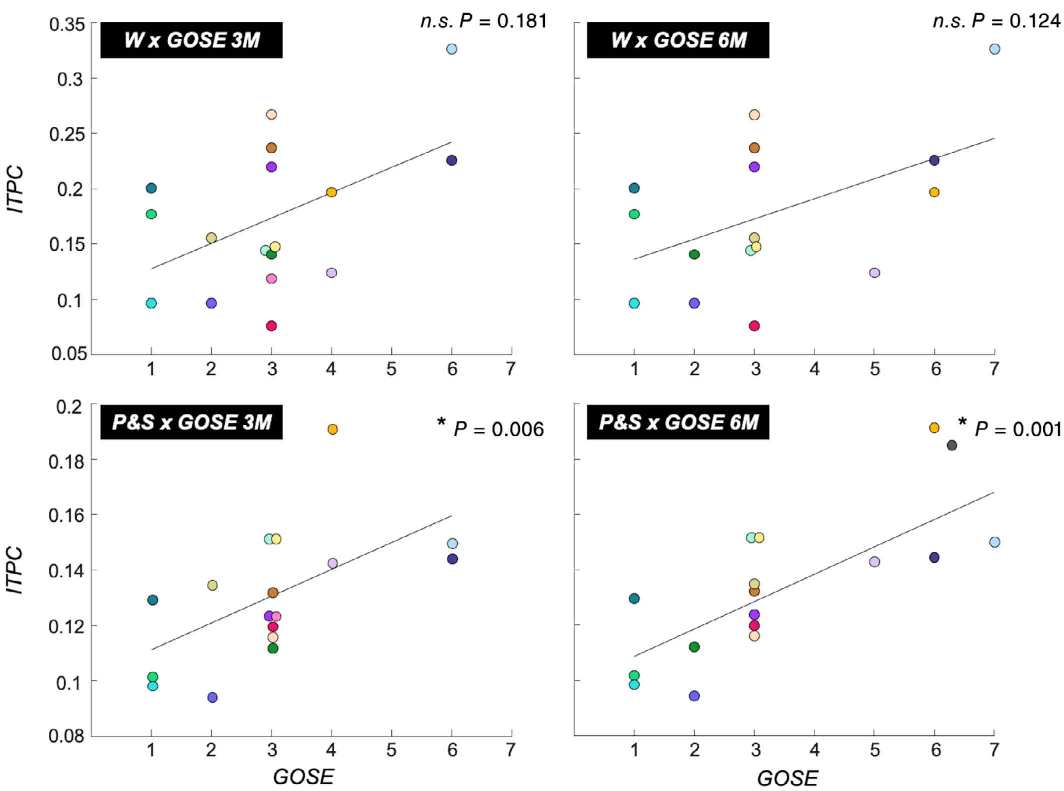

FIGURE 2: Correlation between cortical tracking and GOSE outcome. (A) Cortical tracking of words did not show significant correlations with the outcome at three and (B) 6 months following EEG. (C) Strong correlations were observed between cortical tracking of phrases and sentences and outcome at 3 months and (D) 6 months. The p values represent FDR-corrected p values; filled circles represent individual patients (same shade for each patient across the 4 panels). Abbreviation "W" in panels (A) and (B) describes "words" and "P&S" in panels (C) and (D) describes "phrases and sentences." EEG, electroencephalography; FDR, false discovery rate; GOSE, Glasgow Outcome Scale Extended; ITPC, inter-trial phase coherence; n.s., not significant. [Color figure can be viewed at www.annalsofneurology.org]

TABLE 2. Linear Regression Modeling — 3 Months' GOSE Outcome

3 months	Coefficients					Model Summary	ANOVA	
Model		Beta (standardized)	Beta (unstandardized)	*t*	*p*	Adjusted R^2	F	*p*
1	Age	−0.139	−0.006	−0.408	0.692	0.419	2.924	0.065
	GCS at EEG	0.385	0.180	1.475	0.171			
	Days after injury	−0.012	−0.002	−0.031	0.976			
	CT grade	0.075	0.040	0.329	0.749			
	ITPC words	0.151	1.893	0.614	0.553			
	ITPC phrases + sentences	0.449	15.764	1.910	0.085			
2	Age	−0.131	−0.006	−0.647	0.531	0.472	3.859	0.029
	GCS at EEG	0.382	0.179	1.722	0.113			
	CT grade	0.076	0.041	0.354	0.730			
	ITPC words	0.151	1.899	0.646	0.531			
	ITPC phrases + sentences	0.449	15.744	2.007	0.070			
3	Age	−0.145	−0.007	−0.761	0.461	0.510	5.169	0.012
	GCS at EEG	0.367	0.172	1.750	0.106			
	ITPC words	0.189	2.379	0.949	0.362			
	ITPC phrases + sentences	0.419	14.696	2.101	0.057			
4	GCS at EEG	0.420	0.197	2.157	0.050	0.526	6.923	0.005
	ITPC words	0.145	1.822	0.772	0.454			
	ITPC phrases + sentences	0.427	14.982	2.181	0.048			
5	GCS at EEG	0.453	0.212	2.416	0.030	0.540	10.386	0.002
	ITPC phrases + sentences	0.463	16.243	2.470	0.027			

This table shows the results of the linear regression. Five models have been created, with the first model (1) including all predictors, which were narrowed down, using backward linear regression, until the winning model (5; ie, largest F statistic) shown at the bottom of the table. Details about the coefficients (standardized and unstandardized Beta, *t*, and *p* values [columns 3–6]), the model summary (Adjusted R^2 [column 7]) and the ANOVA (F and *p* values [columns 8 and 9]) are shown.
ANOVA = analysis of variance; CT = computed tomography; EEG = electroencephalography; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended; ITPC, inter-trial phase coherence.

At 6 months, the adjusted variance of outcome was again best explained by a model containing GCS score at the time of EEG (p = 0.095, beta = 0.330, regression coefficient = 0.152, 95% CI = −0.030 to 0.333) and the magnitude of higher-level cortical tracking (p = 0.006, beta = 0.603, regression coefficient = 20.756, 95% CI = 7.105 to 34.408; statistics of the winning model; ie, the model with the largest F statistic: F (2,13) = 11.601; p = 0.001; adjusted R^2 = 58.6%). Furthermore, a model containing these 2 covariates explained 29.8% more variance of outcome than a model containing only the GCS score at the time of the EEG (Table 3).

TABLE 3. Linear Regression Modeling—6 Months GOSE Outcome

6 months	Coefficients					Model summary	ANOVA	
Model		Beta (standardized)	Beta (unstandardized)	t	p	Adjusted R^2	F	p
1	Age	0.078	0.004	0.246	0.811	0.532	3.847	0.035
	GCS at EEG	0.200	0.092	0.823	0.432			
	Days after injury	0.231	0.041	0.643	0.536			
	CT grade	0.183	0.097	0.875	0.455			
	ITCP words	0.176	2.219	0.781	0.405			
	ITPC phrases + sentences	0.600	20.663	2.761	0.022			
2	GCS at EEG	0.211	0.097	0.922	0.378	0.576	5.082	0.014
	Days after injury	0.161	0.029	0.764	0.463			
	CT grade	0.170	0.090	0.882	0.398			
	ITCP words	0.184	2.321	0.867	0.406			
	ITPC phrases + sentences	0.599	20.633	2.897	0.016			
3	GCS at EEG	0.305	0.140	1.626	0.132	0.592	6.451	0.006
	CT grade	0.178	0.094	0.942	0.366			
	ITPC words	0.130	1.642	0.663	0.521			
	ITPC phrases + sentences	0.622	21.409	3.096	0.010			
4	GCS at EEG	0.336	0.154	1.891	0.083	0.611	8.868	0.002
	CT grade	0.230	0.121	1.365	0.197			
	ITPC phrases + sentences	0.668	22.995	3.630	0.003			
5	GCS at EEG	0.330	0.152	1.801	0.095	0.586	11.601	0.001
	ITPC phrases + sentences	0.603	20.756	3.285	0.006			

This table shows the results of the linear regression. Five models have been created, with the first model (1) including all predictors, which were narrowed down, using backward linear regression, until the winning model (5; ie, largest F statistic) shown at the bottom of the table. Details about the coefficients (standardized and unstandardized Beta, t, and p values [columns 3–6]), the model summary (Adjusted R^2 [column 7]), and the ANOVA (F and p values [columns 8 and 9]) are shown.

ANOVA = analysis of variance; CT = computed tomography; EEG = electroencephalography; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended; ITPC, inter-trial phase coherence.

Discussion

With a simple, passive, bedside EEG paradigm, we have shown that post-traumatic patients who remain in an unresponsive state despite being sedation-free may nevertheless comprehend speech. Furthermore, the strength of each patient's evidence for speech comprehension augmented the accuracy of prognoses at 3 and 6 months, relative to prognoses made on the basis of clinical characteristics alone. This approach, therefore, may significantly reduce prognostic uncertainty in a critical phase of medical decision making, thus ensuring more appropriate decisions regarding continuation of life-sustaining therapy and more appropriate distribution of limited rehabilitation resources to those most likely to benefit.

Our results are consistent with previous studies that have demonstrated covert cognition and even consciousness in patients who are unresponsive as a result of a severe brain injury (eg, see Refs. 5, 7, 26, 27). For example, Claassen et al (2019)[8] elegantly demonstrated that 15% of acute patients across etiologies exhibited appropriate modulations of their EEG in response to verbal commands to move, despite those patients being unable to follow this command with their overt behavior. Furthermore, those patients who exhibited such "cognitive-motor dissociation" were more likely to achieve a good outcome at 12 months (GOSE > = 4), although it is unclear to what extent the presence of cognitive-motor dissociation in that study augmented the accuracy of outcome predictions made on the basis of clinical characteristics. Although EEG evidence for covert command-following is both striking and consistent with a considerable level of preserved consciousness and cognition,[5,6] such command-following approaches also run the risk of considerable false negative results due to their high cognitive demands. Indeed, as previously argued,[5] successfully completing an assessment of covert command-following involves, among other faculties, sustained attention, response selection, working memory, and language comprehension. Consequently, it is likely that the residual capacities of some patients are missed due to cognitive deficits that impair their ability to successfully produce appropriate modulations of their EEG. Our approach therefore complements the work of Claassen et al (2019),[8] and others, by providing a means to identify covert cognition and consciousness by focusing on one domain of cognition and without relying on successful command-following, thus increasing the number of patients who may benefit.

Does EEG tracking of high-level linguistic structures in the acute phase postinjury, therefore, indicate that these patients are conscious of what they hear? In the absence of a hypothetical consciousness meter, it is impossible to directly infer another's conscious state. Nevertheless, tracking of high-level linguistic structures vanishes in sleep[17] and is not evident when listening to speech in a language that one does not understand, even if that speech stimulus contains high-level linguistic structures.[16] Cortical tracking of meaningful structure within speech therefore appears to require (or reflect) conscious comprehension on the part of the listener. However, this necessarily requires a reverse inference from a passive neural response. Indeed, there is significant debate regarding the specific linguistic paradigms and neural markers that reflect a conscious experience of comprehension, and whether a passive paradigm is ever sufficient for this conclusion.[28,29] Indeed, previous efforts to investigate speech comprehension in unresponsive patients using the classic semantic N400 event-related potential have met with challenges of low sensitivity and confounding influences of attention[30–32] (cf. Ref. 33; although see Ref. 34). Future investigations of the correlation between the comprehension tracking response and other measures of covert command-following will speak to this conclusion (see eg, Ref. 35). Nevertheless, whether a reflection of unconscious processes or of a conscious comprehension experience, the prognostic value of our approach emphasizes its potential clinical utility.

Could the prognostic value of EEG reported here reflect nonspecific electrophysiological features that are unrelated to the speech itself? The speech stimulus is designed specifically to induce oscillations in the EEG of a conscious comprehender at the rates of meaningful structure (ie, phrases and sentences). Therefore, any prognostic value that stems from speech comprehension should be specific to the rates of those meaningful structures. Indeed, this is what we observe in our data. Using a Bootstrap approach (see Methods section), we quantified the prognostic value of ITPC values at 1,000 non-target rates and found that none of these non-target rates were more strongly correlated with outcome than the high-level linguistic rates. Our data therefore provide strong evidence of a specific relationship between cortical tracking of linguistic structure and outcome up to 6 months postinjury.

The prognostic value of our approach in the acute period postinjury is also consistent with recent evidence that linked higher-level cortical tracking, combined with nonspecific EEG features, with better outcome in chronic disorders of consciousness.[11] Our results extend and complement that important observation by indicating the prognostic value of this paradigm in the acute period in which significant clinical decisions must be made regarding plans for rehabilitation or palliative care. Indeed, earlier identification of potential for recovery could reduce uncertainties faced by clinicians and families and accelerate access to appropriate therapies.[36]

A limitation of our study is the size of the sample, which is a direct result of our deliberately narrow inclusion criteria that ensured a group of patients who have the most to benefit from a reduction in prognostic uncertainty (ie, those who are not obeying commands after complete washout of sedation in the intensive care unit). Nevertheless, the strength of our effects in bootstrap analyses provide confidence in the prognostic value of our approach in more extensive cohorts - studies of which will subsequently allow for the identification of an ITPC outcome confidence value per patient. Indeed, a receiver operating characteristic (ROC) analysis of our sentence / phrase-level

ITPC data indicates 100% sensitivity and 80% specificity for a distinction between bad outcome (death, VS/UWS) and good outcome at 6 months (GOSE > = 3; threshold = 0.116; see Fig 2D). However, a more extensive sample in the future will allow for stronger claims regarding the robustness of single-subject classification procedures that will also speak, for example, to the scalp locations of the most informative data. A more fine-grained quantification of patient outcome, investigating for instance patients' capacity for language production, may also have been possible with in-person assessments rather than telephone interviews with the GOSE. Furthermore, multiple applications of this paradigm per patient could minimize potential confounding influences of patient arousal, for example, Classeen et al[8] and Wannez et al.[37]

A further limitation of this paradigm is the necessary exclusion of patients with language deficits subsequent to their injuries. Although this approach allows us to probe a high level of cognitive function, an assessment battery that combines other non-linguistic cognitive EEG approaches, such as the mismatch negativity,[38–41] will maximize clinical utility of EEG in the acute phase postinjury. Finally, due to our concerns regarding the appropriateness of diagnostic terms, such as VS/UWS/minimally conscious state (MCS) for our patients in this acute period, we did not acquire data from behavioral assessments for such differential diagnosis, such as the Coma Recovery Scale.[42] As the level of behavioral responsiveness in the acute period is linked to outcome,[43] such differential diagnostic data may have provided a more accurate description of each patient's level of awareness, and consequently greater prognostic power relative to our available measures. Nevertheless, it is reassuring to note that conducting the same analyses as above but with the GCS Motor Score in place of the total GCS score (ie, a more specific measure of behavioral responsiveness that can approximate the VS/MCS distinction) leads to the same conclusions regarding the added prognostic value of cortical tracking of speech (see Supplementary Information folder under the provided OSF link for full details). Finally, whereas our data were collected prior to goals of care decisions for some patients (eg, prior to tracheostomy placement for 6/13 patients; see Methods section), this was not the case for all. Consequently, the value of our approach for clinical decision making must be further uncovered via investigations at earlier time points postinjury.

In conclusion, cortical tracking of the meaning of speech, quantified via a simple, passive auditory bedside-EEG paradigm, increases the accuracy of prognoses at 3 months and 6 months for patients in acute post-traumatic unresponsive states relative to prognoses made solely on the basis of standard clinical characteristics. Given recent evidence of delayed recovery of consciousness and functional independence following severe brain injury,[2,44] this paradigm augments clinical prognostic practice and reduces uncertainty at a critical phase of decision making in the intensive care unit.

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Author Contributions

R.S., L.M., T.H., S.S., A.B., U.N., and D.C. contributed to the conception and design of the study. R.S., G.D., L.B., T.H., S.S., T.V., K.M.Y., and D.C. contributed to the acquisition and analysis of data. R.S. and D.C. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

The authors declare no conflict of interest.

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