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Divergent neural responses to narrative speech in disorders of consciousness

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Abstract

Objective: Clinical assessment of auditory attention in patients with disorders of consciousness is often limited by motor impairment. Here, we employ intersubject correlations among electroencephalography responses to naturalistic speech in order to assay auditory attention among patients and healthy controls. **Methods**: Electroencephalographic data were recorded from 20 subjects with disorders of consciousness and 14 healthy controls during of two narrative audio stimuli, presented both forwards and time-reversed. Intersubject correlation of evoked electroencephalography signals were calculated, comparing responses of both groups to those of the healthy control subjects. This analysis was performed blinded and subsequently compared to the diagnostic status of each patient based on the Coma Recovery Scale-Revised. **Results**: Subjects with disorders of consciousness exhibit significantly lower intersubject correlation than healthy controls during narrative speech. Additionally, while healthy subjects had higher intersubject correlation values in forwards versus backwards presentation, neural responses did not vary significantly with the direction of playback in subjects with disorders of consciousness. Increased intersubject correlation values in the backward speech condition were noted with improving disorder of consciousness diagnosis, both in cross-sectional analysis and in a subset of patients with longitudinal data. **Interpretation**: Intersubject correlation of neural responses to narrative speech audition differentiates healthy controls from patients and appears to index clinical diagnoses in disorders of consciousness.

Introduction

Patients with chronic disorders of consciousness (DOC) have varied outcomes that are difficult to prognosticate.[1,2] Accurate assessment of higher level cognitive abilities such as auditory attention is essential for accurate diagnosis and may determine candidacy for assistive communication devices. However, many patients have impaired channels of motor communication, resulting in a mismatch between the clinical assessment of auditory comprehension and neuroimaging evidence.[3,4] Thus, quantifying auditory attention in this population is an urgent research priority.

Metabolic studies have demonstrated a difference in cortical auditory processing between vegetative state (VS) patients that lack the ability to interact with their environment and minimally conscious patients, who demonstrate behavioral interactions.[5–8] Attempts to discriminate auditory attention and processing in these MCS patients with electroencephalography (EEG) have focused on event-related potential paradigms utilizing single words and repeated sound sequences.[9–13] While such EEG measures appear to index cognitive processes, it is not clear that ERPs capture the type of auditory attention required to comprehend speech in everyday environments. Importantly, previous attempts to probe semantic verbal processing in DOC patients using EEG with short speech segments (mostly the N400 ERP component)[14,15] have generally failed to make diagnostic predictions for individual patients.[16] In contrast, EEG responses to longer

speech segments have shown promise in quantifying consciousness in acute traumatic brain injury.[17]

Here, we measure attention to a narrative speech stimulus in MCS patients using continuous, time-domain EEG measurements. In healthy populations, attention to speech results in entrainment of the subject's evoked activity not only to low-level features of the stimulus itself, but also the cortical activity of other subjects experiencing the same stimulus.[18–21] This effect has been observed in visual as well as auditory contexts for EEG,[19,20,22] functional magnetic resonance imaging,[23,24] and magnetoencephalography.[25,26] Moreover, intersubject correlation (ISC) of EEG evoked responses has been shown to discriminate attention better than conventional EEG measures[19] and is able to predict selective auditory attention during auditory stream segregation.[27,28] Through the use of narrative speech, our approach has the potential to capture sustained auditory attention, a prerequisite for comprehension of everyday speech.

In this single-blinded study, we employ ISC of EEG to assess sustained auditory processing of narrative speech. A total of 20 patients with DOC and 14 healthy controls were presented two narratives in both, a forwards and backwards (time-reversed) condition. We predicted that patients will have lower ISC of the EEG evoked activity as compared to healthy control subjects. ISC for healthy group and patients were extracted from time-locked EEG without knowledge of individual patient diagnoses. Individual subjects' ISC scores for forward and backward speech presentations were compared with healthy controls and among clinical diagnoses. Finally, we discuss the relevance of our findings in the search for biomarkers of auditory attention among DOC.

Methods

Subject recruitment

Healthy control and DOC subjects included were drawn from a convenience sample available from a multiday, inpatient hospital admission research study approved by the Weill Cornell Medical College Institutional Review Board. The study collects video EEG, multimodal neuroimaging data, and clinical outcome measures in the context of chronic DOC resulting from severe acquired brain injury. Healthy control subjects provided written consent, while consent was obtained from the legally authorized representatives of the DOC subjects.

Clinical outcome measures and blinding

Clinical assessments were made by serial administrations of the Coma Recovery Scale-Revised (CRS-R)[29] by neurologists during inpatient research admissions. Subscale scores from each patient's highest CRS-R and command following data from functional neuroimaging were assessed by an expert neurologist (senior author NS) to codify clinical diagnoses of VS, MCS−/+, or eMCS according to the following criteria: patients may remain wakeful but unresponsive to the external world in the persistent VS.[30] Others in the MCS may have inconsistent responses to their surroundings.[31] This category is subdivided into plus/minus, with MCS- designating individuals with exclusively low-level, reflexive behavior such as withdrawing from pain or turning toward sound. In contrast, the presence of higher level cognitive functions like inconsistent command following, yes/no questions, or intelligible vocalizations earns a designation of MCS plus (MCS+).[32] Patients emerged from the minimally conscious state (eMCS) can interact with their surroundings through functional object use or communicate reliably.

Clinical diagnostic measures such as the CRS-R are unable to assess higher level cognitive functions that characterize MCS+ and eMCS in patients with prominent motor output impairment. Such individuals fail to respond verbally or behaviorally to an examiner, but nonetheless demonstrate normal command following in functional neuroimaging paradigms. These individuals are said to be in a state of cognitive motor dissociation (CMD).[4] In our study, patients P5,[33] P13 at visit 1, P14, and P20 received CRS-R scores consistent with VS or MCS–, but demonstrated command following through functional neuroimaging. These neuroimaging findings were considered evidence of inconsistent command following, which meets criteria for MCS+. They were, consequently, coded as MCS+ for subgroup analyses.

Authors II, AP, and LP were blinded to these clinical diagnoses, with an agreement to unblind clinical diagnoses after ISC scores were generated for all individuals across all visits. Health status (healthy control vs. DOC patient) was not blinded in order to facilitate development of the ISC metric, which compares patients to healthy controls.

Stimulus presentation

A female narration of Lewis Carroll's *Alice in Wonderland* audio file (148 sec) was converted to 44,100 kHz WAV file for the *Alice* stimulus. It was subsequently reversed in time using Audacity (audacity.sourceforge.net) to create the backward *Alice* stimulus. The backward stimuli are identical to the forward, but simply with the direction of playback reversed. Forwards and backwards audio for a live performance of a stand-up comedy with music interlude, *Pieman* (Jim O'Grady; length 7 min), were obtained from Uri Hasson.[34]

With either stimulus, subjects were instructed to listen carefully to the story that they were to hear through their headphones. Both forward and backward audio files were then played with Presentation software (Neurobehavioral Systems, Inc), with mono audio presented binaurally through Etymotic Research ER3A earphones. Audio start and stop points were time-locked into the video EEG record using photic stimulation markers in the Natus Neuroworks software and paradigm audio was also recorded along with the video. One iteration each of forward and backward audio were interleaved with 30 sec of rest *(Alice;* Forwards-Rest-Backwards*)* or 60 sec of rest *(Pieman;* Backwards-Rest-Forwards*)*.

DOC subjects participated in a 2- to 3-day overnight study while HC subjects participated in a 24-h study. During each subject's study, the *Alice* paradigm was repeated 2–6 times in an effort to ensure at least one block of stimulus presentation with limited artifact. Of the healthy controls, 10 repeated the same paradigms at a 6-month revisit. Additionally, four patients had a second visit 1–3 years after their initial visit, three with *Alice* data. *Pieman* data were presented once per subject visit and not repeated upon subject revisit. All stimuli were presented while subjects were in an eyes-open, wakeful state.

Data collection

The EEG data were recorded using 37 electrodes (Nihon Kohden (Japan) silver-collodion disk electrodes, 10 mm) placed via an enhanced 10–20 arrangement, using the Natus XLTEK (Oakville, Canada) system. EEG was recorded with synchronized video. The typical interelectrode spacing was 3–4 cm and impedances were maintained $\leq$5 kΩ. Bipolar referencing was used, with a FCz reference and AFz ground electrode. Bilateral electrooculography (two leads) and electrocardiography were also recorded. Signals were amplified and digitized at 250 Hz using an antialiasing high-pass filter with a corner frequency at 0.4 times the digitization rate.

Data extraction and export

Video EEG data were reviewed in Natus Neuroworks software. *Alice* and *Pieman* trials in which subjects remained in an eyes-closed state for over 10 consecutive seconds or exhibited sustained vocalization and movement were not considered for further analysis. The remaining paradigms were exported to ASCII text files and imported to MATLAB (8.3). Forward and backward conditions were exported using in-house scripts for subsequent analysis.

In the *Alice* stimulus set, data from 14 healthy controls – 10 with two visits at a 6 month latency – were submitted for analysis for a total of 48 datasets. Data from 16 patient subjects (three longitudinal) totaled 55 datasets. Of these subjects, In the *Pieman* stimulus set, data from 12 healthy controls from single visits (one longitudinal) were submitted, yielding a total of 13 healthy control datasets. Data from 20 patient subjects (four with longitudinal data) were submitted for analysis, for a total of 22 datasets. Identifiers for patients versus controls were coded before submission to author II for single-blinded analysis.

Upon visual inspection, and prior to processing, some data had to be discarded due to limited quality, excessive movement artifacts, or a large number of missing electrodes (five more channels). For the *Alice* stimulus, we are left with 13 healthy controls (two of whom were only presented the *Alice* stimulus) for a total of 43 repeats and 11 DOC patients (one of whom was only presented the *Alice* stimulus) for a total of 38 repeats, and a grand total of 81 repeats for Alice. For the *Pieman* stimulus, we analyzed 12 healthy controls (one unique to *Pieman*) with a total of 13 repeats, as well as 19 DOC patients (nine unique to *Pieman*) with 22 repeats, and a grand total of 35 repeats.

Preprocessing

Data analysis follows Ki et al., 2016. Briefly, for each stimulus, raw EEG data was epoched across repetitions and filtered to remove drift and power-line noise (0.5 Hz 5th order high-pass and a 60 Hz 10th order band-stop Butterworth filter, respectively; extra padding of 2 sec in each epoch was removed after filtering). Eye movement artifacts were removed by regressing out activity from two EOG electrodes and Fp1 from all EEG electrodes.[35]

Our procedure for removing outliers precisely follows the Ki et al., 2016[19] rPCA method: "we processed the EEG data with robust principal component analysis (rPCA),[36] which identifies individual outlier samples in the data and substitutes them implicitly with an interpolation from other sensors, leveraging the spatial correlation between sensors among non-outlier samples. We used the inexact augmented Lagrange multiplier method for computing rPCA[37] and applied the method on the combined set of subjects."[16] This was done because the rPCA method allows for the substitution of outlier samples with interpolated data, ensuring the temporal continuity of the signal, which is essential to our analysis.

Intersubject correlation analysis

Our previous work suggests that attention to ongoing narrative speech can be reliably measured by correlating the evoked EEG of an individual subject to that of an

attentive group, with more attentive subject exhibiting higher ISC.[19] ISC is best measured, not on individual electrodes, but on the components of EEG that maximally correlate across subjects[18] (we used code published in Cohen 2016 for these computations[22]). Here, correlated components were optimized for maximal ISC on data available for the *Alice* stimulus. To not bias the components in favor of one group during this optimization, we include data from both DOC patients and healthy controls in both the forward and backward conditions. This gives us components with spatial distribution (Fig. 1A) resembling results from previous work on auditory stimuli.[19,22] These spatial distributions appear to emerge regardless of the auditory stimulus used, however, spatial distributions for the *Pieman* data did not replicate previous results. This indicated to us that these data were not sufficient for component extraction given the smaller and noisier sample compared to previous work. However, using the components extracted from *Alice*, we could compute ISC for both *Alice* (Fig. 1B) and *Pieman* stimuli (Fig. 1C).

Once the components are defined, we then measure how similar the responses of a given subjects are to that of the healthy controls. Thus, we calculate ISC for each subject by correlating component activity to that of the healthy control group, averaging over all possible pairings that involve a given subject. With this, we test of the null hypothesis that there is no difference between a given subject and the healthy group as a whole. As in previous work, we use the sum of the ISC values computed in the first three strongest components. ISC was computed for each recording, and then averaged across all available repetitions for a given subject, to prevent violating the independence assumption of the statistical tests. For Figure 1, this was further averaged across subsequent visits, where available. All signal processing was performed offline using MATLAB software (MathWorks, Natick, MA). For more detail on preprocessing and ISC computation, see the code that we provide at www.parralab.org/isc/

Results

EEG intersubject correlation during auditory narratives is reduced in DOC patients as compared to healthy controls

Fourteen healthy controls (39 ± 11 years of age, eight men) and 20 DOC patients (31 ± 13 years of age, four women) were included in the analysis. Video EEG were recorded while subjects were presented audio narratives through headphones. In the first experiment, subjects heard a short segment from a professionally narrated audiobook of *Alice in Wonderland* (148 sec). This was presented to 13 healthy controls (two unique to the *Alice* stimulus) and 11 DOC patients (one unique to the *Alice* stimulus). The sound was also played back time-reversed, resulting in a forward and backward playback, which was repeated several times for each subject ($N = 3.3 \pm 1.4$ for controls and $N = 3.5 \pm 1.8$ for patients). Some subjects participated in two visits on separate days, resulting in a total of 81 recordings included in subsequent analysis (see Stimulus Presentation).

We extracted components of the EEG that were maximally correlated between subjects during presentation of the *Alice* stimulus following established procedures[18,22] (see Intersubject correlation analysis). Figure 1A shows the three correlated components that capture most of the (ISC) in these data. These are consistent with previous findings for auditory narratives.[19,22] We measured ISC in these three components, correlating both patients and healthy participants to the healthy participants. Thus, ISC measured for each subject, how similar evoked responses are to those of a healthy normative group. ISC values are shown in Figure 1 for each subject. As expected, patients have lower ISC compared to the control group in particular for the *Alice* stimulus (Fig. 1B). Furthermore, backward playback reduced ISC, at least in healthy participants.

To test for statistical significance of these effects, we performed a two-way ANOVA with fixed factors of playback conditions (forward/backward) and health status (control/patient). To control for the evident variability of ISC across subjects, we included subject identity as a random effect. We found a strong effect for health status ($F(1, 114) = 32.76$, $P = 5.4 \times 10^{-6}$) and a strong interaction between playback condition and health status ($F(1, 114) = 18.23$, $P = 1.3 \times 10^{-4}$). The random effect of subject was highly significant ($F(22, 114) = 4.05$, $P = 8.8 \times 10^{-4}$) indicating that ISC is quite variable across subjects. Follow-up comparison shows that ISC drops for backward playback in healthy controls ($t(12) = 5.97$, $P = 6.5 \times 10^{-5}$). ISC is also lower for patients as compared to controls in the forward playback condition ($t(22) = 7.59$, $P = 1.4 \times 10^{-7}$).

A more limited dataset was also available for an audio narrative involving a live recording of stand-up comedy (*Pieman*, Jim O'Grady),[34] in forward and backward playback (12 healthy controls and 19 DOC patients). Unlike the *Alice* stimulus, only one recording was available per subject in healthy controls and patient datasets (resulting is a total of 35 recordings). ISC was computed for this data set using the same components extracted with the *Alice* stimulus (Fig. 1C). As with the *Alice* datasets, a two-way ANOVA was performed to test for differences in ISC with fixed factors of health status and playback condition, and subjects as random factor. We find again a contrast

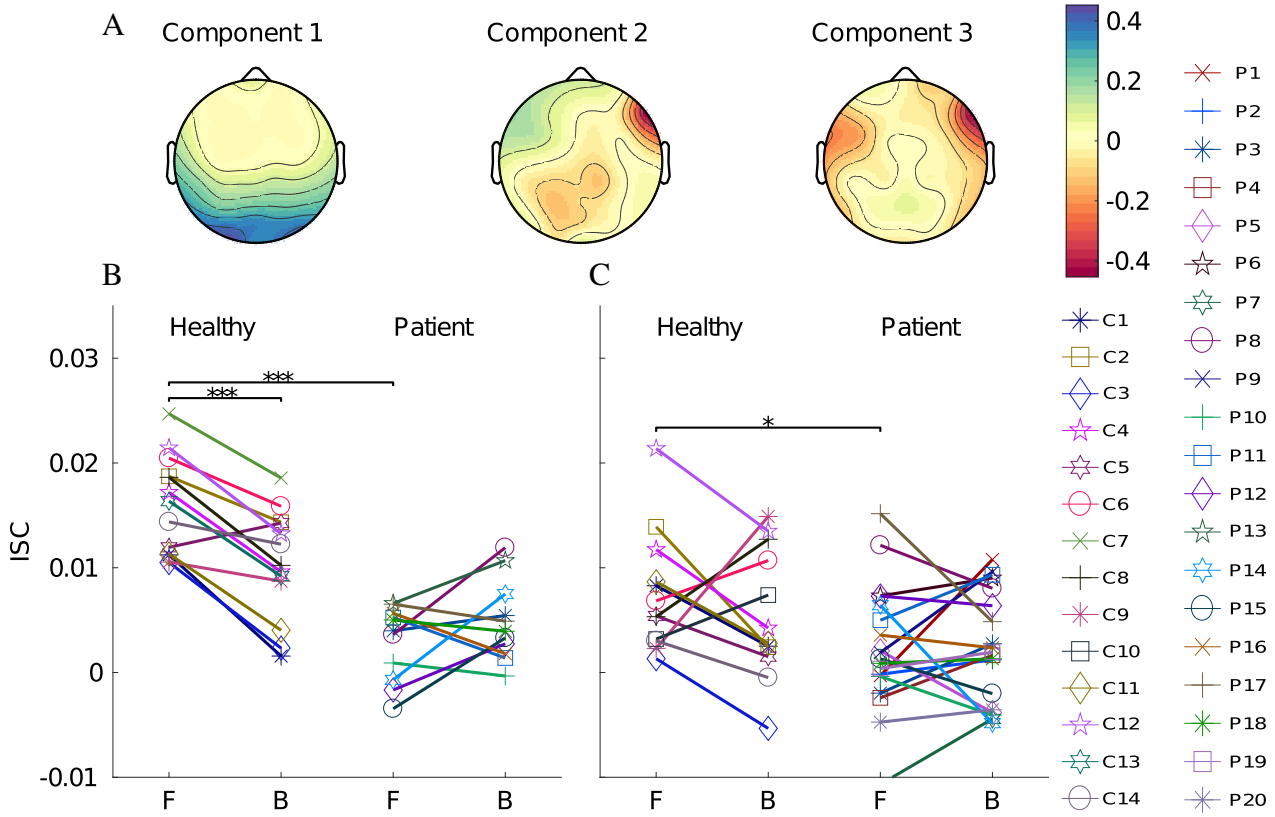

Figure 1. Intersubject correlation of EEG responses evoked by auditory narratives in disorders of consciousness (DOC) patients and healthy controls. (A) Spatial distribution of components of correlated activity between subjects. Color indicates sign and strength of contribution of each electrode to the component (units are arbitrary; see Haufe et al. [39]). These three components capture the strongest ISC and were computed here over all conditions in both patients and healthy controls using Alice – a segment of *Alice in Wonderland* narrated by a female speaker (148-sec long). (B) ISC of healthy controls (N = 13) and patients (N = 11) during the *Alice* stimulus. ISC is measured by correlating component activity of each subject to the cohort of healthy controls and summing over the first three components. It is measured separately for forward (F) and backward (B) conditions and averaged over repeated renditions and visits. (C) Same as in panel (B) but for *Pieman* – a 6-min live recording of a stand-up comedy performance for healthy controls (N = 12) and patients (N = 19). Significant post-hoc pairwise comparison are shown as black horizontal lines (***P < 0.001, ** P < 0.01, * P < 0.05, uncorrected).

between patients and healthy participants ($F(1, 8) = 5.52$, $P = 0.0255$), driven by a contrast in the forward condition, ($t(29) = 2.489$, $P = 0.019$) but this time no effect from the playback condition ($F(1, 8) = 0.62$, $P = 0.44$) and no interaction between playback condition and health status ($F(1, 8) = 0.9$, $P = 0.35$). A three-way ANOVA with stimulus as additional factor (*Alice* vs. *Pieman*) confirms that the *Pieman* story elicited overall lower ISC values ($F(1, 142) = 9.24$, $P = 0.006$).

ISC during backward playback of speech correlates with diagnostic status of DOC patients

The previous analysis was done blinded to the clinical diagnosis of the patients. Patients had suffered a variety of etiologies and carried one of four diagnoses: VS, MCS−, MCS+, and eMCS (see MCS). After unblinding, these diagnoses were coded as a categorical variable for statistical analysis. We performed three planned comparisons between this categorical diagnosis and ISC, namely, forward and backward conditions as well as their difference as a possible control for the evident variability in ISC across subjects.

Figure 2 shows the comparison of forward and backward presentation ISC values using the *Alice* data across these diagnosis groups MCS–, MCS+, and eMCS. Here, we separated visits 1 and 2 as the diagnostic criteria also changed for the patients where data from two visits were available. The single patient in VS (P7) did not have an *Alice* recording, so this diagnosis group was not presented. A one-way ANOVA with diagnostic state as factor shows a significant effect for ISC backward presentation ($F(2, 11) = 9.46$, $P = 0.0041$) which remains significant after correction for the three planned comparisons

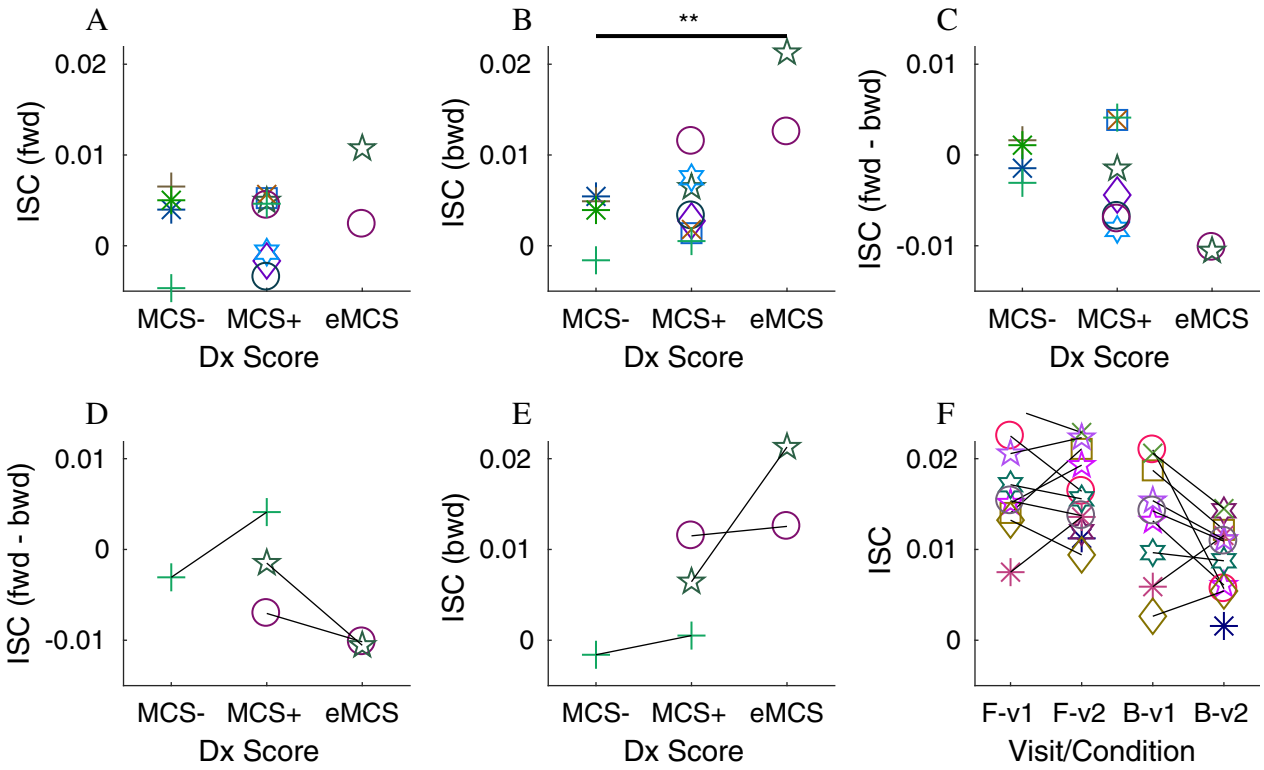

Figure 2. Comparison of ISC with clinical diagnosis in disorders of consciousness (DOC) patients. (A) ISC for the *Alice* stimulus during forward playback and (B) backward playback for $N = 11$ patients. Black line represents significant influence of diagnosis on ISC score ($P < 0.01$) (C) difference in ISC between forward and backward playback. Here, visit 1 and 2 are separated as diagnosis also changes across visits. (D) Change in ISC difference over two visits for the three patients for which this data was available. (E) As in panel (D) but for backward playback. (F) For reference, we show here the variability of ISC measures across visits in healthy controls. No data for the *Alice* condition, was available from vegetative state (VS) patients in this sample. Subject symbols and colors are consistent with Figure 1.

($P = 0.012$). Figure 2(B) suggest that this effect results from an increase of ISC for backward speech with improving diagnosis across patients.

For three patients, two time points of recordings for the *Alice* stimulus were available separated by 12 months (P8), 36 months (P10), and 17 months (P13). During this time, diagnostic score improved on all three subjects (Table 1). For all three patients, ISC to the backward speech increased along with the clinical diagnosis (Fig. 2E), although the change appears meaningful for only one of them, considering the normal fluctuations seen in healthy controls across visits (Fig. 2F). For this patient, brain metabolism as measured with positron emission tomography (PET) markedly increase from visit 1 to visit 2 (Fig. S1). The clinical history of this patient is described in detail in the Appendix S1.

Discussion

To our knowledge, this is the first study to assay EEG responses to naturalistic speech in patients with chronic DOC. By correlating EEG responses to those of healthy controls during auditory narratives, we demonstrate that healthy controls have more similar within-group responses than do patients. The contrast between forward and backward speech observed in healthy controls is absent in patients, although the strength of response to backward speech appears to be linked to diagnostic score.

The topography of the three most salient ISC components and higher forward versus backward ISC scores in our healthy controls (Fig. 1) closely replicate prior studies with narrative speech.[19,22] In healthy populations, we interpret ISC as a measure of the reliability of auditory evoked responses, which are modulated by attention. As ISC scores in narrative speech is modulated by attention,[19] the DOC patients' lower ISC scores could be interpreted as evidence of impairment of normal auditory attention. Given the extent of damage in these patients, it is also possible that more basic auditory perception is impaired and thus neural responses are weaker and less reliable. Additionally, the heterogeneous injury patterns of DOC patients might independently contribute to this

Table 1. Patient Demographics and diagnoses: Demographics of all 20 disorders of consciousness (DOC) subjects included in this study.

							CRS-R subscores							
Code	Age at study	Age at injury	Sex	Race	Injury type	Total CRS-R Score	Auditory (0–4)	Visual (0–5)	Motor (0–6)	Oro-motor (0–3)	Communication (0–2)	Arousal (0–3)	CMD criteria met	Diagnosis
P1	45	35	F	W (NH)	Encephalitis	19	4	4	6[1]	2	1	2		eMCS
P2	30	23	M	W (NH)	TBI	23	4	5	6[1]	3	2[1]	3		eMCS
P3	24	16	M	W (NH)	TBI	9	2	2	3	0	0	2		MCS–
P4	57	53	M	W (NH)	TBI	21	4	5	5	3	1	3		MCS+
P5	20	17	F	W (NH)	HAI (CA)	6	1	0	1	2	0	2	Yes (EEG) [2]	MCS+
P6	40	37	M	W (NH)	HAI	15	4	3	2	3	1	2		MCS+
P7	23	20	M	Asian	TBI	6	2	0	1	1	0	2		VS
P8-v1	27	22	M	W (NH)	TBI	17	4	3	6[1]	1	1	2		eMCS
P8-v2	28	22	M	W (NH)	TBI	14	4	2	5	1	0	2		MCS+
P9	36	19	M	W (NH)	TBI	19	4	4	6[1]	2	1	2		eMCS
P10-v1	23	12	F	W (NH)	TBI	12	2	3	3	2	0	2		MCS–
P10-v2	26	12	F	W (NH)	TBI	13	4	3	2	2	0	2		MCS+
P11	21	17	M	W (NH)	HAI	16	4	2	4	3	1	2		MCS+
P12	25	20	M	W (NH)	TBI	17	4	4	4	3	0	2		MCS+
P13-v1	19	18	F	Black	TBI	10	3	3	2	0	0	2	Yes (fMRI)	MCS+
P13-v2	20	18	F	Black	TBI	23	4	5	6[1]	3	2[1]	3		eMCS
P14	26	23	M	Black	TBI	11	2	3	3	1	0	2	Yes (fMRI)	MCS+
P15	57	54	M	W (NH)	SAH	19	4	5	5	2	1	2		MCS+
P16	22	21	M	W (NH)	TBI	17	4	4	4	2	1	2		MCS+
P17	26	25	M	W (NH)	TBI	6	1	3	1	0	0	1		MCS–
P18	21	19	M	W (NH)	TBI	10	1	3	3	1	0	2		MCS–
P19	56	55	M	W (NH)	HAI (CA)	21	4	5	5	3	1	3		MCS+
P20	23	19	M	W (NH)	TBI	5	4	0	0	0	1	0	Yes (fMRI)	MCS+

Age at time of study as well as age of acquired brain injury are reported in years. Documentation of the Coma Recovery Scale-Revised (CRS-R) and its subscales are as previously reported (Section 2.2).

VS, vegetative state; MCS, minimally conscious state; eMCS, emerged from minimally conscious state; CMD, cognitive motor dissociation; W, white/Caucasian, NH, non-Hispanic, TBI, traumatic brain injury; HAI, hypoxic/anoxic injury; CA, cardiac arrest; SAH, subarachnoid hemorrhage.

[1]Denotes emergence from MCS.

[2]Full case report in Forgacs et al., 2016.[33]

effect, as ISC was computed here by correlating EEG of patients with that of healthy controls.

In addition to having lower ISC values than healthy controls, the contrast between forward and backward ISC scores was absent in this group of DOC patients (Fig. 1B–C). Interestingly, the absolute value of the backward ISC scores correlated positively with clinical diagnosis (Fig. 2B). This finding contrasts with a prior functional magnetic resonance imaging (fMRI) study with naturalistic speech, where time-reversed stories elicited stronger blood-oxygen level-dependent (BOLD) responses in controls than forwards presentation, and two MCS patients lacked BOLD responses entirely to backwards stimuli.[8] These divergent group findings in controls could reflect methodology; EEG recordings have much higher temporal resolution than BOLD signals, directly reflect neuronal activity, and robustly encode lower level auditory features. Perhaps, ISC might reflect the novelty and perceptual salience of backwards stimuli in patients, but are less attended by healthy individuals who quickly recognize the stimulus as nonspeech, and therefore lose interest. Regardless, as the strength of backwards ISC response correlates positively with clinical diagnosis and reliable auditory attention is required for MCS+ and eMCS diagnoses, ISC values appear to index a clinically important element of auditory processing.

Our study has several limitations. Primarily, the sample size of 20 DOC patients, with only 12 that could be compared to the clinical diagnosis and only a single case of VS in our convenience sample. This precludes validation of this measure as a diagnostic tool, despite significant differences in backward ISC across diagnoses. The more

variable ISC values in the *Pieman* dataset, despite longer stimulus length, are primarily attributed to the single recording available for each subject. The higher ISC scores for *Alice*, may be the result of the more clearly articulated studio recording as compared to the live recording of the *Pieman* stimulus. Lastly, these paradigms were presented as part of a rigorous testing schedule throughout overnight visits; such a schedule would be expected to reduce ISC values, as ISC scores decrease after repeated trials in healthy individuals.[19] Future studies would benefit from more stimulus repetitions during outpatient testing to minimize fatigue and improve the reference dataset among healthy control participants.

While our data establish ISC of neural activity during audition as a possible biomarker for auditory processing in DOC, interpretative caution is required. For example, Patient 13 demonstrated remarkable clinical improvement, which correlated with an increase in ISC values in the second visit (Fig. 2D; discussed in supplement). While these findings are encouraging and mirror her recovery of communication, we argue against inferring the quality of narrative capacity or subjective conscious experience of this or any individual patient,[38] as neither EEG nor BOLD signals can be causally linked to higher cognitive functions. Instead, we focus on the diagnostic and prognostic promise of neurophysiological measures like EEG responses to narrative speech.

In summary, we present the first evidence that EEG evoked responses to narrative speech in DOC patients may reflect clinically important elements of auditory processing. Further research is needed to untangle the cognitive processes required for higher level attention and cognition from the cortical markers of more basic auditory processing. That said, these data demonstrate the potential of correlating neural activity in response to naturalistic speech to that of healthy controls as an index of auditory processing that might be developed into a diagnostic tool in the search for covert cognition in these patients.

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Author contributions

BF and LP designed the study. BF and MC collected patient data with subjects recruited by NS. BF reviewed and exporting video EEG data. AP developed analysis codes and conducted the pilot data analysis. II conducted advanced preprocessing as well as primary and secondary analyses, under the direction of LP. BF, II, and LP wrote the manuscript with contributions from MC and NS.

Conflicts of interest

The authors declare no financial conflicts of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Interval increases in metabolic activity mirror clinical improvement in subject P13
Appendix S1. Patient 13 clinical history

