Cortical response to the natural speech envelope correlates with neuroimaging evidence of cognition in severe brain injury

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Summary

Recent studies identify severely brain-injured patients with limited or no behavioral responses who successfully perform functional magnetic resonance imaging (fMRI) or electroencephalogram (EEG) mental imagery tasks [1-5]. Such tasks are cognitively demanding [1]; accordingly, recent studies support that fMRI command following in brain-injured patients associates with preserved cerebral metabolism and preserved sleep-wake EEG [5, 6]. We investigated the use of an EEG response that tracks the natural speech envelope (NSE) of spoken language [7-22] in healthy controls and brain-injured patients (vegetative state to emergence from minimally conscious state). As audition is typically preserved following brain-injury, auditory paradigms may be preferred in searching for covert cognitive function [23-25]. NSE measures are obtained by cross-correlating EEG with the natural speech envelope. We compared NSE latencies and amplitudes with and without consideration of fMRI assessments. NSE latencies showed significant and progressive delay across diagnostic categories. Patients who could carry out fMRI based mental imagery tasks showed no statistically significant difference in NSE latencies relative to healthy controls; this subgroup included patients without behavioral command following. The NSE may stratify patients with severe brain injuries and identify those patients demonstrating "cognitive motor dissociation (CMD)" [26] who show only covert evidence of command following utilizing neuroimaging or electrophysiological methods that demand high levels of cognitive function. Thus, the NSE is a passive measure that may provide a useful screening tool to improve detection of covert cognition with fMRI or other methods and improve stratification of patients

with disorders of consciousness in research studies.

Results

Neuronal Representation of the Natural Speech Envelope in Healthy Controls

The grand average NSE-EEG cross-correlation function for healthy controls is shown in Figure 1. The latency of the greatest correlation magnitudes occurred at approximately 90 msec and 200 msec; similar results were attained in previous studies investigating the neuronal tracking of the amplitude envelope of natural continuous speech [7-13, 15]. The neuronal response to the NSE was largest over the bilateral posterior temporal channels and the anterior left central channels.

Natural Speech Envelope Response in Relation to the Behavioral Diagnosis

We investigated the neuronal representation of the NSE across the patient groups and healthy controls. Example traces of the individual average NSE–EEG cross-correlation functions are displayed for five representative subjects in Figure 2. The latencies of the CL1 and CL2 components for each patient group and healthy controls as determined by the behavioral diagnosis are presented in Figure 3A (upper left and right panels). Latencies of CL1 and CL2 components of the NSE response showed a progressive increase that graded with the severity of the behavioral diagnosis; that is, the earliest NSE responses occurred in the healthy controls and the most delayed latency responses were observed in the MCS and VS patient groups. Augmenting the behavioral categories with evidence obtained for positive results of fMRI command following, a new group emerged

with NSE latencies that were not significantly different from healthy controls (Figure 3B, lower left and right panels).

We first performed statistical analysis on the individual averages of the NSE–EEG cross-correlations in patients grouped by behavioral diagnosis without assessment of fMRI command following (Figure 3A). A log transformation was applied prior to one-way analysis of variance of the CL2 component to meet the assumption of homogeneity of variance. As the homogeneity of variance was not met for the CL1 component, Welch's ANOVA and Games-Howell post hoc tests were implemented to test for significant differences of the NSE response components between the patient groups and the healthy controls.

One-way analysis of variance revealed a significant group effect on the CL1 and CL2 latencies across the behaviorally defined groups (CL1: $F(3,8.069)=29.44$; CL2: $F(3,27)=7.98$, $p<.001$ for both). Specifically, the latency of the CL1 and CL2 components was significantly delayed in the VS patients as compared to the healthy controls, EMCS, and MCS patients (VS to HC: CL1, $p<.01$; CL2, $p<.001$; VS to EMCS: CL1, $p<.01$; CL2, $p<.01$; VS to MCS: CL1, $p<.005$; CL2, $p<.05$). We did not find any other significant difference in the latency of the CL1 and CL2 components between any of the other groups. The one-way analysis of variance did not indicate a significant group effect for the amplitudes of the CL1 and CL2 components ($F=.812$, $p=.497$; $F=1.43$, $p= .255$, Table S2A).

Statistical analysis was then performed on the individual averages of the NSE–EEG cross-correlations with behavioral categorization reorganized by the removal of patients with positive evidence of fMRI command following as a separate group (Figure 3B). One-way analysis of variance revealed a significant group effect on the CL1 latency across the patient groups ($F(4, 29) = 36.79$, $p<0.001$). Specifically, the latency of the CL1 component was significantly delayed in the EMCS, MCS, and VS patients as compared to the healthy controls (EMCS: $p=.034$, MCS: $p<.001$, VS: $p<.001$). The latency of the CL1 component was significantly prolonged in the MCS and VS patients as compared to the fMRI CF+ patients (MCS: $p<.001$, VS: $p<.001$) and in the VS patients as compared to the EMCS ($p<.001$) and MCS patients ($p=.001$). One-way analysis of variance revealed a significant group effect on the CL2 latency ($F(4,26) = 18.66$, $p<.001$). Post hoc analysis verified that the CL2 component was significantly delayed in the MCS and VS patients as compared to the healthy controls (MCS: $p<.001$; VS: $p<.001$) and fMRI CF+ patients (MCS: $p=.001$; VS: $p<.001$), and in the VS patients as compared to the EMCS patients ($p=.001$). There was no statistically significant difference in the latencies of the CL1 and CL2 components between the healthy controls and fMRI CF+ patients. We did not find any other significant difference in the latency of the CL1 and CL2 components between any of the other groups. The one-way analysis of variance did not indicate a significant group effect on the amplitudes of the CL1 and CL2 components ($F=1.38$, $p=.266$; $F=1.46$, $p=.242$, Table S2B).

The Imaging Characteristics of fMRI CF+ Patients

Ten of the brain-injured subjects had statistically significant BOLD activation during the

active imagery task as compared to the resting state condition. Behavioral examinations with the CRS-R diagnosed seven of the fMRI CF+ patients in MCS and three as EMCS. However, only three of the fMRI CF+ patients demonstrated functional communication (Table S3). BOLD activation in the fMRI command following tasks and representative horizontal, coronal, and sagittal image slices of the ^{18}FDG-PET resting state metabolic activity as a qualitative clinical characterization of the patient brain function are displayed in Figure 4 for six representative fMRI CF+ patients.

Discussion

Here we find that patients with evidence of fMRI command following show no statistically significant difference in NSE latencies relative to healthy controls. Latencies of both the CL1 and CL2 components, however, showed significant delay for VS and MCS patients when compared with healthy controls and fMRI CF+ patients. The EMCS patient group demonstrated variability in their NSE responses, with CL1 latency delayed relative to healthy controls but no significant difference in CL2 latencies from those of fMRI CF+ and MCS patients. Importantly, at the group level NSE latency differences showed improved correlation with behavioral evaluations when fMRI CF+ patients were removed across categories. Comparison of NSE latencies with separation of groups based only on behavioral diagnosis revealed no significant differences between MCS, EMCS, and healthy subjects for the CL1 or CL2 latencies. This finding may help improve the integrity of future research studies (e.g. preservation of various sleep features across VS, MCS, and EMCS populations or similar inquires), as fMRI CF+ patients with preserved

speech processing may retain other unique aspects of preserved cerebral function.

The correspondence of CL1 and CL2 latencies in the fMRI CF+ group with those of healthy controls indicates that the NSE response measure may stratify the likelihood that patients harbor unidentified higher-level cognitive function. Additionally, the correspondence of the fMRI CF+ group's NSE latencies with those of healthy controls supports evidence from other studies that fMRI command following correlates with preserved cerebral function [6, 27]. As Owen et al. noted in their original reports, successful completion of fMRI mental imagery tasks is highly cognitively demanding; typically, for a full trial of a fMRI mental imagery command following paradigm, the subject is required to sustain attention to a specific cognitive effort for ~30 seconds at a time and to hold task instructions over 8 full repeats [1-3]. The preservation of NSE latencies likely correlates with a wide preservation of brain networks supporting sustained attention, working memory, and other task-related cognitive processes. Thus, the NSE may be utilized as a screening tool to better allocate the resource of MRI investigations in patients without behavioral command following.

Prior studies have used a range of stimuli to separate diagnostic categories within patients with disorder of consciousness. In a recent report, a subset of patients without behavioral or neuroimaging evidence of command following showed isolated preservation of brain function in neuroimaging paradigms or electrophysiological evidence of cortical processing of language stimuli and a more preserved corticothalamic functional architecture [28]. Event-related potential studies have found that the presence

of the P300 and the mismatch negativity (MMN) event-related potential components correlate with improved clinical outcomes in brain-injured patients [29-34]. In such studies, the subject's own name has been utilized as an emotionally salient and personally meaningful stimulus in the oddball paradigm [25, 35]. These findings emphasize the importance of employing salient and meaningful auditory stimuli to elicit robust neural responses. Signorino et al. found that emotional stimuli that consisted of the patient's name or short phrases spoken by the patient's familial members significantly increased the probability of eliciting the P300 response in brain-injured patients [36]. In another event-related potential study, Holeckova et al. found that speech with familiar speakers significantly enhanced the robustness of the neural response in healthy controls; these studies support the use of emotionally salient and meaningful speech stimuli in the clinical assessment of patients with disorders of consciousness [37]. Perrin et al. utilized the subject's own name in an auditory event-related potential paradigm that assessed the auditory response in brain-injured patients and healthy controls, and found that the auditory stimuli elicited a P300 response in MCS patients and in 3 of 5 VS patients [25]; This study and others found a progressive slowing of the latency of name-related event-related potentials separated MCS and VS patients from healthy controls and that such latency delays are associated with recovery of consciousness [25, 30, 35, 38-41]. Importantly, no significant differences appeared between locked-in patients as compared to healthy controls.

Graded correlations of bedside behavior with quantitative measurements that do not utilize sensory input have been demonstrated in severely brain-injured patients in a

study that combined transcranial magnetic stimulation (TMS) with high-density EEG. [42, 43]. A single nominal value termed as the perturbational complexity index (PCI) was extracted from the complex waveforms produced in the EEG by the TMS pulse. The authors found that the PCI distinguishes MCS patients from VS. Casarotto et al. further demonstrated that this measure shows a graded shift across the full range of DOC with a single nominal value as also seen here for the NSE. The relationship of PCI to fMRI+ CF is not yet known; while the naturalness and ease of obtaining the NSE measurement improves upon the complexity of the TMS measurement the PCI measure uniquely allows for an assessment independent of sensory input.

Across the group of 21 patients studied here, behavioral assessments using the CRS-R identified patient diagnostic categories as 3 VS, 12 MCS, and 6 EMCS; seven MCS patients and three EMCS patients demonstrated fMRI command following responses as assessed by the motor imagery paradigm. Recategorizing based on fMRI CF+ thus resulted in 10 fMRI CF+ patients, including 3 EMCS patients, and 7 MCS patients. One EMCS patient communicated with an external augmentative communication device; the other two spoke fluently. The seven fMRI CF+ MCS patients ranged in diagnosis from MCS-, showing no command following responses to MCS+, with clear demonstrations of command following on their best CRS-R evaluation, although some patients showed fluctuations across these categories on different examinations [44]. Of the total 10 fMRI CF+ patients included in this study, the original diagnoses in the medical record from their outside assessments included 5 VS, 2 MCS, and 3 EMCS patients.

Our findings support the inference that fMRI CF+ responses identify patients with more preserved cerebral function than typically present in VS and MCS patients. The results of prior studies suggest that motoric impairment masks cognitive function in fMRI CF+ patients. In the first cohort study of fMRI mental imagery in VS and MCS patients, Monti et al. only identified one MCS patient out of 31 with fMRI CF+ responses and this subject only showed visual tracking early on (1.3 months) following traumatic brain injury [2]. However, four out of 23 patients in the Monti et al. study initially diagnosed as in VS showed fMRI CF+ responses. Thus, all of the initial fMRI CF+ patients reported in this cohort had no motor responses that could provide a communication channel. Other studies show that even with an inconsistent communication channel, fMRI CF+ patients preserve greater degree of normal integrative brain physiology. Forgacs et al. identified four of 44 DOC patients with limited overt behavioral responsiveness with positive fMRI CF+ responses; all of these subjects demonstrated preserved wakeful and sleep EEG architecture, and retained a preserved glucose metabolism as measured by ^{18}FDG-PET [6].

Supplementary videos illustrate the three-dimensional brain anatomy and pattern of cerebral metabolism for five fMRI-CF+ subject shown in Figure 4 (Movie1: videos A-E). The full sequences of 3D structural MRI images reveal that the fMRI CF+ patients demonstrate a wide heterogeneity of injury patterns. Importantly, marked structural injuries to bilateral brainstem and thalamic regions as well as evidence of significant lesions within the dominant language hemisphere are observed. These observations

underscore the relative simplicity of the NSE measure in identifying the integrity of auditory processing. Despite these differences in patterns of structural injuries, the overall profile of cerebral metabolism in each fMRI CF+ patient subject reveals a relative preservation of cortical metabolism in both hemispheres (FDG-PET images are scaled from 0 to 9 in SUV units) which is consistent with prior reports [6]. Taken together with the present NSE findings, these results support the identification of fMRI CF+ as a marker for a distinct subpopulation of patients. Such patients with no or minimal behavioral responsiveness (consistent with coma, VS or MCS-) and covert evidence of command following (establishing by fMRI, electrophysiological, or other modalities) may be characterized using the term 'cognitive motor dissociation (CMD)' [26].

There are several limitations to the NSE method and its translation to clinical practice. In our study, we utilized personalized narratives that were recorded by the patient's family members; prior studies have demonstrated that personal and meaningful stimuli elicit more robust and reliable auditory responses in brain-injured patients [45]. However, acquiring personalized narratives imposes an additional time constraint relative to the use of standardized stimuli. Similarly, the use of a standard narrative for the healthy control subjects may influence the saliency and level of attention allocated in comparison to narratives provided by family members that are personally meaningful. Future adaptations of these methods could surmount this limitation by developing real-time methods to track the auditory speech envelopes present in the ambient environment. A further important limitation of studies in severely brain-injured patients is the effect of fluctuations in arousal, responsiveness, or motivation [5]. Adaptation of the present

methods to allow for on-line continuous computation of the NSE would allow for greater ease in identifying brain states with more preserved language processing and patient engagement.

Future studies are needed to validate the strict correlation of fMRI CF+ responses with normal latency NSE components, but the present data support the consistency of this relationship. The correlation of normal latency NSE response components with fMRI CF+ show the utility of this passive paradigm to potentially index higher-level cortical processing and grade the level of cerebral function. Moreover, an electroencephalographic approach is cost-effective, efficient, and may be adapted for continuous tracking of recovery over time. Once identified, patients with evidence of command following activity can be tested to determine whether they can modulate the NSE response with attention to speech stimuli to guide auditory brain-computer interfaces to restore communication and reveal the fullness of their consciousness [46].

STAR*METHODS

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Supplemental Information

Supplemental information is included in the online article and contains three supplemental tables.

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Declaration of Interest

Chananel Braiman, Chagit Braiman, and Nicholas Schiff have submitted a patent that relates to this work. The authors declare that there are no other conflicts of interest.

Author Contributions

C.B.: research design, EEG data collection, analysis and interpretation of the data, manuscript preparation and revision; C.S.R.: manuscript revision; M.M.C.: research design, EEG data collection, and manuscript revision; E.A.F. and H.U.V.: fMRI and PET data acquisition, analysis, interpretation; T.R.: manuscript preparation and revision; N.D.S.: research design, analysis and interpretation of the data, manuscript preparation and revision, and supervision of the study.

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Figure Captions:

Figure 1: Grand Average Natural Speech Envelope Response in Healthy Controls.
A. Plot of the grand average natural speech envelope (NSE) response in healthy controls in a right temporal (T6) channel. The CL1 and CL2 peaks of the NSE response and their significance in the cross-correlation functions are labeled above. Cross-correlation values that exceed the dashed lines are significant at *p≤.05 FDR-corrected for the control cross-correlation distribution. B. The scalp topography of the amplitude of the CL1 and CL2 NSE peaks. The warmer colors indicate positive correlation values and the cooler colors indicate negative correlation values.

Figure 2: Individual Natural Speech Envelope Responses.
Plots of representative individual natural speech envelope (NSE) responses for a healthy control, a patient with evidence of command following in the functional magnetic resonance imaging paradigm (fMRI CF+), a patient that emerged from the minimally conscious state (EMCS), a minimally conscious state patient (MCS), and a vegetative state patient (VS) across the single best EEG channels (T6, FC6, T4, T4, T6). The CL1 and CL2 peaks of the NSE response for the individual subjects and their significance in the cross-correlation functions are labeled above. Cross-correlation values that exceed the dashed lines are significant at *p≤.05 FDR-corrected for the control cross-correlation distribution.

Figure 3: Natural Speech Envelope Response Latency in Relation to Behavioral Diagnosis and Imaging Assisted Diagnosis.
A. The mean and the SEM of the latencies of the CL1 and CL2 components of the NSE responses for the groups of healthy controls (HC), emerged from minimally conscious state patients (EMCS), minimally conscious state patients (MCS), and vegetative state patients (VS) are depicted in the top panel. **B.** The mean and SEM of the latencies of the CL1 and CL2 components of the NSE responses for the healthy controls (HC) and brain-injured patients reorganized with imaging assisted diagnosis (positive command following in the functional magnetic resonance imaging paradigm, fMRI CF+) are depicted in the bottom panel. The asterisks denote the significance level of the latency differences of the CL1 and CL2 NSE response components across the patient and healthy control groups (* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, N.S. = not significant). (See also Table S1A, S1B, S2A and S2B).

Figure 4: Neuroimaging Profile of the Patients with functional Magnetic Resonance Imaging (fMRI) Evidence of Command Following (fMRI CF+).
Clinical qualitative characterization of patients with the18fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) measurements of the resting state metabolic activity in the fMRI command following patients are depicted in the left panel. The fMRI BOLD (blood oxygen-level-dependent) activation in the motor imagery task as compared to the resting state condition is depicted in the right panel (p<.005). (See also Table S3)
A: anterior; L: left; P: posterior; R: right

Movie1: Three-dimensional Brain Anatomy and Metabolism in the Patients with functional Magnetic Resonance Imaging (fMRI) Evidence of Command Following (fMRI CF+).

Three-dimensional review of brain anatomy and cerebral metabolism for fMRI CF+ subjects shown in Figure 4. Full sequences of 3D structural MRI images reveal a wide heterogeneity of injury patterns present across the fMRI CF+ patient population including examples of marked brainstem and thalamic injuries and evidence of damage to dominant language hemispheres. Despite such wide differences in structural injury patterns, the overall profile of cerebral metabolism in patient subjects shows a relative preservation of cortical metabolism in both hemispheres (FDG-PET images are scaled from 0 to 9 in SUV units). **A**. PS-1 **B**. PS-2 **C**. PS-3. **D**. PS-5 **E**. PS-6

STAR *METHODS

CONTACT FOR REAGENT AND RESOURCE SHARING

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact: (cb647@cornell.edu).

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Participants

The study participants included thirteen healthy controls with no history of neurological disorder or auditory impairment and twenty-one severely brain-injured patients. This subset of the data was described in detail by Curley and colleagues [5]. Behavioral assessments diagnosed six of the brain-injured patients as emerged from minimally conscious state (EMCS), twelve in a minimally conscious state (MCS), and three in vegetative state (VS). The healthy control and patient demographic information are summarized in Table S1A and Table S1B. Healthy controls and brain-injured patients were admitted to The Rockefeller University Hospital (RUH) for the duration of the study. Informed consent was obtained directly from the healthy controls and from patients' legally authorized representatives. The study was approved by RUH and the Weill Cornell Medicine Institutional Review Boards.

METHOD DETAILS

Behavioral Assessment

The JFK Coma Recovery Scale – Revised (CRS-R) was used to behaviorally evaluate the

DOC patients [47]. This clinical evaluation was conducted at the bedside several times during the patient visit. The CRS-R examines the patient's arousal, communication, auditory, visual, verbal, and motor functions. The behavioral assessment diagnosed the patients as emerged from minimally conscious state, (EMCS), minimally conscious state (MCS), or vegetative state (VS). Patients with evidence of command following in the fMRI paradigm were characterized as fMRI CF+. The CRS-R was administered typically 3 times and the best CRS-R total score was utilized for the study. The EMCS patients were diagnosed after 2 consecutive assessments consistent with emergence from MCS.

Task and Stimuli

The patients were presented with personally relevant narratives recorded from the patients' surrogates. The personally relevant narratives included recollections and stories about the patient prior to the brain injury. Healthy controls listened to a portion of the novel *Alice's Adventures in Wonderland by Charles Lutwidge Dodgson*. We selected the use of a standardized healthy control narrative to avoid personally relevant content that might introduce greater variability of response across the healthy controls [48-50]. For two patient subjects, the narratives stimuli were either not presented or the EEG recordings were excessively noisy. For these patients, we assessed the neuronal response to the novel *Alice's Adventures in Wonderland.* Natural speech stimuli were approximately 2 minutes long and the same stimuli were presented approximately four times to subjects binaurally through headphones at a comfortable sound level of approximately 65 dB. We used the Presentation software (Neurobehavioral Systems, Inc., Albany CA) and the stimuli were time-locked to the EEG recordings.

EEG Data Acquisition

The EEG was recorded with the XLTEK system at a sampling rate of 250 Hz or 256 Hz (Natus Medical, San Carlos, CA). The impedances were maintained at or below 5 kΩ across each of the 37 collodion-pasted electrodes for the duration of the recordings. The electrodes were positioned according to the enhanced 10-20 international system and the reference electrode was positioned at FCz. The EEG data were reviewed with the XLTEK NeuroWorks software (Natus Medical, San Carlos, CA), imported into MATLAB (MathWorks, Natick, MA), transformed to the common average reference, and band-pass filtered between 1-90 Hz. One patient subject's EEG was recorded with 21 electrodes referenced to FCz. The EEG recordings were visually inspected for artifacts and excessively noisy trials were rejected from the analysis. We hand selected all EEG segments used for analysis. Each trial was visually inspected to identify and remove artifacts related to eye blinks, eye movements, and myogenic activity prior to segmentation. Trials with continuous artifact throughout the majority of the recordings were discarded.

fMRI Motor Imagery Paradigm

We conducted fMRI studies in the brain-injured patients (each patient tolerated the study and there were no contraindications for MRI imaging). We acquired the fMRI patient data with the GE 3.0 Tesla Signa Excite HDx MRI system (Milwaukee, WI), the Siemens 3.0 Tesla TIM Trio MRI system (Erlangen, Germany), or the Siemens 3.0 Tesla MAGNETOM Prisma MRI system (Erlangen, Germany). The patients were instructed to

imagine playing tennis and to imagine and attempt to open and close their right hand [with the exception of scan AD2 in which the motor imagery used was swimming]. For the fMRI tasks, the sampling time was TR = 2 seconds. In the Tennis command following task: At 0 seconds, subjects were instructed to 'imagine swinging a tennis racket with your right hand'. At 16 seconds, subjects were instructed to 'stop imagining swinging a tennis racket'. At 32 seconds, the task started over. In the right hand command following task: The subjects were instructed to 'keep opening and closing your right hand … stop opening and closing your right hand'. For both tasks, the sequence was repeated 8 times and the total time duration was 4:16 minutes. A general linear model was utilized to determine blood-oxygenation-level dependent (BOLD) signal differences between the motor imagery task and resting conditions (significant at p=.05 with FDR correction). One patient participated in a different fMRI paradigm and the details were published in a separate manuscript [51].

We utilized the SPM12 software (v. 6225) [5, 52] for the correction of motion artifacts, the implementation of slice-timing correction for interleaved acquisition, and the co-registration of the data to the International Consortium for Brain Mapping – Montreal Neurological Institute (ICBM-MNI) standard space EPI [53]. We applied spatial smoothing with an isotropic 8 mm kernel. The GLM was defined with a hemodynamic response function (HRF) that consisted of two Gamma functions. This was convolved with the block design, a first-order autoregressive model (AR(1)) autocorrelation correction, the six motion parameters that were included as the nuisance regressors, and a constant value as the intercept. Visualization of the SPM was carried out with the

statistical parametric mapping viewing program xjview. A statistical threshold of p=.05 (FDR-corrected) was applied. One patient initially demonstrated task-negative BOLD responses at the time of the NSE measurements; subsequent follow-up fMRI studies in this patient revealed positive BOLD responses. We classify this subject here as fMRI-CF+ based on these later findings; although prior investigations have shown negative BOLD responses in healthy controls in motor-imagery paradigms, negative BOLD signal activation have not been characterized in motor imagery tasks [54, 55].

Natural Speech Envelope-EEG Cross-Correlation Analysis

We utilized a cross-correlation approach to investigate the cortical entrainment to the natural speech envelopes [9-12]. The cross-correlation between the amplitude envelope of the sound pressure tracing recorded during natural speech and the EEG indicates the delay and strength of the neuronal tracking of the speech envelope. We first extracted the NSE by computing the magnitude of the Hilbert transform and band-pass filtered this signal between 2-30 Hz. The natural speech envelope was subsequently down-sampled from 44.1 kHz to 250 Hz to match the EEG sampling frequency. The EEG and NSE from each trial were partitioned into segments of 2.0 seconds duration. For each segment, the cross-correlation function of the NSE and the EEG signal was computed. We then determined the average cross-correlation function across all segments. For our analysis of these cross-correlation functions, we focused on a time window between 0 and 500 msec. For each subject, we computed the latencies and amplitudes of the maximum correlation magnitude of the first and second components of the individual NSE-EEG cross-correlation functions in defined temporal intervals. We label the first and second

components of the NSE response as component latency1 (CL1) and component latency2 (CL2) [9-12].

Many patients have diverse structural injuries that may modulate the strength and the topography of the response. In order to ascertain the strongest auditory evoked response, prior studies have determined the single best channel over the scalp in a predefined region of interest [4, 5, 14, 56-58]. The NSE response is most prominent over the temporal and parietal lobes with sources in the posterior temporal cortices [9, 12]. We defined a region of interest that was composed of the four temporal channels (T3; T4; T5; T6) and their immediate neighboring electrodes. For each subject, we selected the single best EEG channel from this region of interest that had the best-defined NSE response and the greatest correlation magnitude to the NSE. In order to assess the significance of the NSE response, the peak values of the cross-correlation functions were compared with randomized cross-correlation functions that served as a control [9]. The randomized cross-correlation functions were computed by randomly redistributing the values of each cross-correlation segment between the natural speech envelope and the EEG across the time points and averaging across the segments. The chance correlation values across the time lags and EEG channels of the control cross-correlation function generated an approximately normal distribution. We computed the mean and standard deviation of the resultant distribution and determined the 95% confidence range of control cross-correlation values. Peak values in the NSE–EEG cross-correlation function that exceeded the 95% confidence interval were deemed statistically significant at $p \leq 0.05$ following FDR multiple comparisons procedure [12, 59].

QUANTIFICATION AND STATISTICAL ANALYSIS

The statistical analysis was performed on the individual averages of the NSE–EEG cross-correlation functions with the SPSS 24 software package (SPSS Inc., Chicago, Illinois). We computed the latency and amplitude of the maximum correlation for the CL1 and CL2 components. One-way analysis of variance and Tukey-Kramer post hoc tests were implemented to test for significant differences ($p \leq 0.05$) in the latencies and amplitudes of the NSE response components between the brain-injured patient groups of fMRI CF+, EMCS, MCS, and VS patients, and the healthy controls.

DATA AND SOFTWARE AVAILABILITY

Please contact the lead contact (cb647@cornell.edu) for data and software requests.