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SHORT COMMENTARY

Parallel EEG-fNIRS assessments of covert cognition in behaviorally non-responsive ICU patients: A multi-task feasibility study in a case of acute motor sensory axonal neuropathy

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Abstract

Background Repeat neurological assessment is standard in cases of severe acute brain injury. However, conventional measures rely on overt behavior. Unfortunately, behavioral responses may be difficult or impossible for some patients. As a result, patients who recover consciousness before the ability to express so may go undetected. Recent studies have demonstrated the efficacy of incorporating functional neuroimaging into clinical assessment protocols. The objective of the current study is to assess the feasibility of a multi-task, multimodal bedside technique to evaluate sensory and cognitive function in behaviorally non-responsive patients.

Methods We deployed a novel assessment paradigm to evaluate sensory and cognitive processing in one 63-year-old unresponsive patient with acute motor sensory axonal neuropathy (AMSAN). We collected parallel bedside EEG-fNIRS activity during hierarchical auditory processing, movie listening, and motor imagery.

Results We found appropriate hemodynamic activation in the patient's middle and superior temporal gyri to simple sounds and activation in their superior temporal gyrus, left angular and precentral gyri during speech. During movie listening, the patient produced patterns of EEG and fNIRS activity that were statistically indistinguishable from healthy controls. The patient also showed appropriate fNIRS and source-localized EEG activation of motor areas during motor imagery. Upon recovering, the patient correctly recalled multiple aspects of our assessment procedures.

Conclusion In sum, our assessment protocol effectively captures neural markers of sensory and cognitive function in behaviorally non-responsive patients. Crucially, while AMSAN is distinct from brain injury, the patient's assumed dissociation between behavior and awareness provided an ideal test case to validate our protocol.

Keywords Neural assessment · EEG · FNIRS · Coma · AMSAN

Regular neurological assessment is essential for the effective management and treatment of patients with severe brain injuries. In the intensive care unit (ICU), behavioral examination and bedside physiological monitoring are used to establish neurological status. Standardized assessment tools such as the Glasgow Coma Scale (GCS; [1]), the Full Outcome of

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UnResponsiveness (FOUR) score [2]), and more recently, the Coma Recovery Scale-Revised Accelerated Standardized Testing (CRSR-FAST; [3]) enable critical care professionals to rapidly identify altered levels of consciousness and quantify their severity. However, such bedside assessments rely, in large part, on overt behavior, which is often absent or unreliable in critically ill patients [4, 5]. As a result, they may underestimate a patient's conscious state or cognitive capabilities and, in turn, their potential for recovery. This has significant implications in critical care settings where diagnosis and prognosis guide decision-making around how and, crucially, whether to continue medical treatment [6, 7]. Considering the prevalence and variability of withdrawal of life-sustaining measures in the ICU [8, 9], it is imperative that diagnoses and prognoses are made with the best available tools and information. Here, functional neuroimaging could play a key role.

Updated practice recommendations of the American and European Academies of Neurology now recognize that functional neuroimaging has a potential diagnostic role in non-responsive patients with disorders of consciousness (DOC; [10, 11]). While the evidence cited by both bodies comes from nearly two decades of neuroimaging research in *chronic* DOC, recent studies have begun to incorporate these methods into the standard diagnostic protocols for *acute* severe brain injury. Findings from functional magnetic resonance imaging (fMRI) and quantitative electroencephalography (EEG), and most recently functional near-infrared spectroscopy (fNIRS), suggest that neuroimaging can significantly improve the detection of preserved cognition and awareness in acute DOC patients [12–16]. Moreover, uncovering the complex neural dynamics that support residual cognition has been shown to more accurately inform outcome prediction than conventional assessments alone [17, 18]. Furthermore, as is the case in chronic DOC [19], employing multiple complementary and validated neural assessments and imaging modalities in the ICU may improve diagnostic and prognostic accuracy in acute severe brain injury [20, 21].

To this end, we developed a battery of tasks that combines EEG and fNIRS—a portable imaging technique often considered to be the "optical equivalent" of fMRI—with validated assessments of cognition and awareness, repeat testing, and complementary analysis procedures (see 22 for details). In this proof-of-concept case study, we present findings from a 63-year-old woman (hereafter referred to as Patient CC) with severe acute motor and sensory axonal neuropathy (AMSAN) who completed three tasks from our neural assessment protocol. AMSAN is a rare and severe form of Guillain-Barré syndrome (GBS) involving axonal injury of motor and sensory fibers in the peripheral nervous system. Compared to other forms of GBS, symptoms of AMSAN progress rapidly and may result in widespread paralysis requiring prolonged hospitalization and respiratory support [22]. Although distinct from a disorder of consciousness, as the central nervous system is spared, severe GBS and its variants can produce a dissociation between behavior and awareness comparable to a complete Locked-in Syndrome (LIS; 24). During our assessments, CC experienced a state of complete LIS, lacking all motor control, including ocular movement.

In this report, we describe the results of our investigation into CC's cognitive state during the peak severity of her AMSAN symptoms. Using high-density EEG and fNIRS, we recorded CC's electrocerebral and hemodynamic activity during three tasks from our bedside assessment battery: hierarchical auditory processing [13], an auditory narrative [23, 24], and motor imagery [25, 26]. Once CC could respond (Day 30), we also administered a brief memory assessment to explore whether she could recall her time in hospital or events related to our testing procedures. We predicted she would: (1) produce neural responses during the auditory hierarchy, movie-listening and motor imagery tasks that were statistically indistinguishable from those of healthy controls and (2) accurately recall the events surrounding her time in hospital and our assessment procedures. In this case, it would provide strong converging evidence that our neural assessment battery provides rapid and accurate characterization of the conscious state and residual cognitive function retained by non-responsive ICU patients beyond what can be inferred using standardized clinical techniques alone.

Methods

Patient information, disease progression, and assessment timeline

Patient CC was a 63-year-old woman admitted to the ICU for rapidly ascending paralysis, including respiratory muscles. Shortly after intake, her neurological status declined sharply. All motor responses, including brainstem reflexes, were absent (i.e., complete paralysis) by the end of the first day, requiring intubation. Computed tomography and MRI scans on Day 02 and Day 03 were unremarkable, and both infectious (e.g., rabies, botulism) and vascular etiologies (e.g., stroke) were ruled out. Electromyography (EMG) performed on Day 05 revealed absent motor responses with reduced sensory amplitude in the left foot and left radial nerve, as well as absent sensory responses from the left median and ulnar nerves. Together, the findings were in keeping with the diagnosis of AMSAN. By Day 22 and after appropriate treatments were completed, CC regained the ability to move her head and respond appropriately to conversations using head nods. The results of a repeat EMG assessment on Day 27 were identical to the one performed on Day 05. On Day 61, a third EMG revealed improved motor and sensory

responses in her upper limbs but not her lower extremities. CC was discharged to an in-patient rehabilitation facility on Day 73. By Day 84, CC was able to sit up, feed herself, and engage in sustained conversations but had not regained mobility in the lower half of her body. At 12 months, CC had made a near-full recovery; she was living independently, had regained upper and lower limb control, and experienced only minor residual numbness in the tips of her fingers and toes.

We performed our bedside neural assessments over two days. On post-admission Day 05, we collected EEG and fNIRS activity during a passive auditory move-listening task, EEG activity during resting state, and an active motor imagery task. On Day 07, we performed a different passive hierarchical auditory perception task, the resting-state condition, and the active motor imagery task with fNIRS. During both sessions, CC was behaviorally unresponsive, with a GCS score of 3 T [27], Coma Recovery Scale-Revised (CRS-R; 46) score of 0, and a Full Outline of UnResponsiveness (FOUR; 13) score of 2 (Eye Response 0, Motor Response 0, Brainstem Reflexes 2, Respiration Patterns 0). At 12 months, CC had a GCS score of 15, a CRS-R score of 23, and a FOUR score of 16. Finally, we administered a brief memory assessment on Day 30 to determine whether CC could recall the events surrounding her time in ICU. See Table 1 for a summary of hospitalization and testing timeline. Ethics approval for this study was granted by the London Health Sciences Research Ethics Board.

Hierarchal auditory paradigm

We used an auditory paradigm to assess the neural correlates of auditory perceptual processing at three levels: sound, speech, and language comprehension [13]. These levels index increasingly complex auditory processing, enabling measurement of the preservation of auditory functioning in patients. The stimuli consisted of white noise, pseudo-word stories, and short stories presented in a block design. Each stimulus lasted 30 s and was preceded and followed by 30 s of silence. The total duration of hierarchical auditory assessment was 15 min and 30 s.

Table 1 xxxxx

	Disease progression	Diagnostic results	Behavioral findings	Neural assessments
Day 0–1	Admitted to ICU for rapid onset paralysis, deteriorating neurologic status	Absent brainstem, motor reflexes	GCS = 3	—
Day 2—3	—	Unremarkable CT, MRI; infectious, vascular etiologies ruled out	—	—
Day 5	Diagnosed with AMSAN	EMG absent motor responses, absent sensory responses in L median, ulnar	GCS = 3; CRS-R = 0; FOUR = 2	EEG[1,2,3], fNIRS[1]
Day 7	—	—	GCS = 3; CRS-R = 0; FOUR = 2	fNIRS[2,3,4]
Day 22	Regained ability to move head and respond with nods	Clear behavioral signs of awareness	—	—
Day 27	—	EMG impaired motor, sensory responses	—	—
Day 30	Able to nod and shake head for "yes", "no"	—	—	Memory recall task
Day 60–61	Able to form short sentences	Improved motor, sensory responses in upper limbs; lack of motor responses in lower limbs	—	—
Day 73	Discharged to rehabilitation facility	—	—	—
Day 84	Able to sit up, feed themselves, participate in sustained conversation, no lower limb mobility	—	—	—
Day 377	Near complete recovery. Able to live independently. Some residual numbness at the end of fingertips and toes	—	GCS = 15; CRS-R = 23; FOUR = 16	—

AMSAN acute motor sensory axonal neuropathy, *CRS-R* coma recovery scale—revised, *CT* computed tomography, *EEG* electroencephalography, *EMG* electromyography, *FOUR* full outline of unresponsiveness, *fNIRS* functional near-infrared spectroscopy, *GCS* Glasgow coma scale, *ICU* intensive care unit, *MRI* magnetic resonance imaging, *1* auditory movie task, *2* Rest, *3* motor imagery, *4* auditory hierarchy

Auditory movie listening task procedures

The auditory movie paradigm used in our assessment protocol has been described in detail elsewhere [23, 24]. Briefly, we presented two versions of a suspenseful audio clip from the movie "*Taken*". One version was the unaltered audio from the movie, whereas the other version was spectrally rotated or "scrambled" to remove any semblance of a narrative while preserving its auditory properties. In this way, the scrambled version acted as an auditory control condition to compare with the original, suspenseful, intact version. Stimulus presentation was controlled using the Psychtoolbox plugin [28] for Matlab ([29]; EEG) and NIRStim (fNIRS) running on a laptop at Patient CC's bedside. We presented both clips through a pair of Etymotic in-ear headphones at a comfortable listening volume. We presented the scrambled version of the audio first to negate any carry-over effects of the narrative on subsequent conditions. Each version of the clip was 5 min in duration, presented serially with approximately 30 s of initial baseline activity and 30 s between clips. The total duration of the auditory movie task was 11 min.

Motor imagery task procedures

The well-established tennis motor imagery paradigm was used to determine whether Patient CC maintained a level of awareness and cognition sufficient to reliably respond to task instructions despite exhibiting no behavioral evidence thereof [25, 26]. On the first day of testing, we performed the EEG and fNIRS motor imagery tasks. Each imaging modality was recorded separately, but the procedures were identical. We presented Patient CC with spoken instructions to "*Rest*" and "*Imagine playing tennis*" in alternating 30 s blocks, with a total of 5 blocks of motor imagery and 6 blocks of rest. The total duration of the imagery task was 5 min and 30 s.

Memory recall assessment procedures

We developed a semi-structured memory assessment that we administered on Day 30 to determine whether Patient CC could remember her time in the ICU or any of our testing procedures. The assessment consisted of seven yes–no questions inquiring about specific events from our assessment. We also included "catch" questions to differentiate her correct recall from spurious responses. For example, we asked, "*Do you remember being instructed to imagine a specific type of movement?*" with two follow-up questions, "*Was the movement imagine playing soccer?*" and "*Was the movement imagining playing tennis?*" If CC remembered the motor imagery task correctly, she would answer "yes" to the first and third questions and "no" to the second (See Table 2). On Day 30, we administered the memory assessment at Patient CC's bedside by reading the questions aloud and recording her answers.

fNIRS acquisition and analyses

Hemodynamic activity was recorded using a continuous-wave fNIRS system (NIRScout, NIRx Medical Systems) at 3.9 Hz with 32 sources and 39 detectors, enabling 121 regular and 8 short channels [30]. The optical probe covered most of the head, including frontal, parietal, and temporal lobes (see Fig. 1 for sensor-detector layout and task design). We preprocessed the fNIRS data following best practices, including removal of channels with low signal-to-noise ratio (SNR < 8, mean divided by standard deviation), motion artifact correction, band-pass filtering (low-pass filter [lpf] and high-pass filter [hpf]), and short-channel regression [29, 31]. We performed motion artifact correction using spline interpolation followed by wavelet decomposition [32], and band-pass filtering was properly adjusted for each task: motor imagery (hpf = 0.005 and lpf = 0.5 Hz), auditory (lpf = 0.5 Hz and detrended to preserve the small task frequency), and movie listening (hpf = 0.005 and lpf = 0.2 Hz). For motor imagery and auditory tasks, we inferred statistical activation with an autoregressive iteratively reweighted least squares (AR-IRLS) method in which short channels were incorporated as regressors of noninterest [32]. A channel was considered activated if there was a significant increase in oxygenated hemoglobin (HbO) and a concurrent significant decrease in deoxygenated hemoglobin (HbR; $p < 0.05$,

Table 2 Memory assessment questions and responses

Question	Day 30
Do you remember being instructed to imagine a specific type of movement?	Yes
Was the movement imagine playing soccer?	No
Was the movement imaging playing tennis?	Yes
Do you remember being instructed to imagine walking through a specific place?	Yes
Was the instruction imaging walking through your home?	Yes
Was the instruction imaging walking through a grocery store/park?	Yes
Do you remember listening to any audio clips?	No

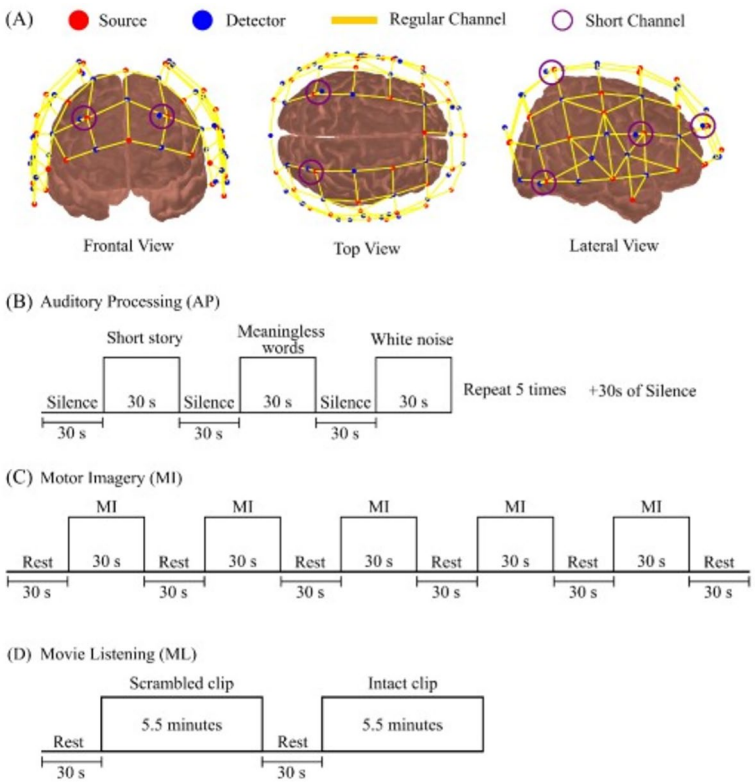

Fig. 1 fNIRS probes and task design. **A** Layout and channel schematics of the fNIRS probes. **B** Task design for the hierarchical auditory processing task. We presented alternating 30 s blocks of silence and auditory stimuli repeated 5 times. **C** Task design for the motor imagery task. Similar to the auditory hierarchy paradigm, we presented alternating 30 s blocks of task instructions (e.g., "*rest*", "*imagine playing tennis*"). **D** Task design for the movie listening task. We presented the scrambled audio before the intact to account for potential carry-over effects of the narrative. Both audio clips included 30 s of silence at baseline

FDR corrected, one-tailed t-test). We recently validated this approach in a cohort of healthy controls [16].

During the movie listening task, we measured neural activation using inter-subject correlation (ISC; see Hasson et al., 2005 for details). For each channel, we correlated the patient's HbO and HbR activity with the average activity from a previously collected sample (n = 26) of healthy controls (see [33]) and averaged the resulting ISCs across HbO and HbR. To focus on higher-order cognitive processing of the movie, our analysis used a region of interest (ROI) of six channels that showed significantly higher ISCs in the healthy controls during the intact movie condition compared to the scrambled movie condition. To determine if the pattern of patient's ISCs within the ROI were within healthy control norms, we calculated a "consistency" score, which is the normalized dot product of the patient's ISCs with the control's group averaged ISCs. Higher scores indicate greater similarity with controls, and we statistically evaluated whether Patient CC's score fell within the distribution of healthy controls (where $p < 0.05$ would indicate a deviation). This approach was previously validated in healthy controls (see [33] for more details). In addition to the consistency measure, we conducted a one-tailed *t*-test to compare the ISCs between the intact and scrambled conditions. Last, we considered an individual channel activated if the difference in ISCs between intact and scrambled conditions, for both HbO and HbR, exceeded the null distribution of these difference scores derived through permutation testing (using a cutoff of $p < 0.05$).

EEG acquisition and analyses

We recorded CC's EEG activity using a 129-electrode HydroCel Geodesic sensor net (Magstim, UK) and the Netstation EEG acquisition software. During the recording, the EEG signals were sampled at 250 Hz and referenced online to the vertex electrode (Cz). We maintained electrode impedances below 50 kΩ during each assessment type and condition. Offline EEG cleaning followed standard preprocessing steps. We re-referenced the EEG to the common average, band-pass filtered the data between 0.5–45 Hz and removed ocular and movement artifacts using automatic artifact detection and manual inspection. Severely noise-contaminated channels were removed from the data and replaced using a nearest-neighbor interpolation procedure. Finally, we performed ICA to remove noise components and de-spiked the data to minimize the influence of non-systematic peaks in EEG amplitude on later analyses [34]. The total duration of EEG setup and testing was approximately 60 min.

First, as in fNIRS, we calculated ISCs between Patient CC and controls during the "*Taken*" audio. We performed a correlated components analysis (CorrCA), the procedures of which have been described in detail previously [23, 35]. In short, CorrCA extracts a pattern of EEG activity that is

maximally correlated across participants. With this component, we can back-project its spatial weights onto the original EEG for each participant—effectively creating a spatial filter—and produce a unique time course of component activity. We then calculate pairwise Pearson's correlations between each participant's component time courses and calculate the absolute mean correlation—the ISCs—for each participant. To reduce bias in our analysis, we perform CorrCA using a leave-one-out procedure and determine statistical significance using a null distribution of correlation coefficients calculated from resampled phase-shifted component time courses. For Patient CC, the procedure was the same, and we calculated her mean ISCs to a previously reported group ($n = 15$; 25) during both the intact and scrambled versions of the "*Taken*" audio.

Second, we performed a source-localization analysis of the EEG during motor imagery. EEG-based decoding of motor imagery often relies on changes in spectral power dynamics across conditions [36, 37]. In addition, recent techniques have incorporated machine learning and classification analyses to detect trial-by-trial performance accuracy (e.g., 37). As one of our primary aims was to establish the convergent validity of our neural assessment protocol, we analyzed CC's EEG activity during the motor imagery task in source space. We applied a weighted minimum-norm estimate (wMNE) solution to localize CC's EEG activity to its likely sources on a standard MNI cortical model comprised of 15,002 flat voxels or "vertices" [38]. We removed the first 1 min. of EEG data from the rest and motor imagery conditions to account for task learning in early trials. We divided the remaining 5 min. of data into 30 s. epochs and applied a 3-vertex spatial smoothing kernel to account for biologically implausible single-vertex activations. From here, we downsampled the data to 1 Hz for computational efficiency and performed a mean subtraction procedure across epochs to identify differences in mean activity between motor imagery and rest. Finally, we calculated a paired two-tailed Wilcoxon sign-rank test with a 5,000 iteration Monte Carlo test of significance to determine whether differences in mean cortical activation differed significantly between the conditions. All source-localization analyses were performed with the Brainstorm toolbox for Matlab [38, 39].

Results

Hierarchal auditory task

Patient CC showed evidence of retained sound processing, showing significant activation in two channels in the right middle temporal gyrus ($t_{HbO} = 2.783$, $t_{HbR} = -3.359$; $t_{HbO} = 2.940$, $t_{HbR} = -4.068$, all $p < 0.05$) as well as one channel in the right superior temporal gyrus ($t_{HbO} = 2.88$, $t_{HbR} = -3.048$, both $p < 0.05$; Fig. 2A). Crucially, the patient's auditory processing was not restricted to simple sounds but also showed evidence of speech-specific responses, as shown by significant bilateral activation in the superior temporal gyrus (left: $t_{HbO} = 2.350$, $t_{HbR} = -3.594$; right: $t_{HbO} = 2.579$; $t_{HbR} = -2.428$, all $p < 0.05$), left angular gyrus ($t_{HbO} = 3.0530$, $t_{HbR} = -2.5797$, both $p < 0.05$), as well as significant activation in the left precentral gyrus ($t_{HbO} = 2.7356$, $t_{HbR} = -3.3774$, both $p < 0.05$) and right superior frontal gyrus ($t_{HbO} = 2.6388$, $t_{HbR} = -2.824$, both $p < 0.05$; Fig. 2B).

Auditory movie listening task

Movie listening produces common maps of cortical hemodynamic activation using fNIRS

Using a two-sample *t-test*, we found that the average ISCs in the intact condition were significantly larger than the scrambled condition, $t(116) = 6.015$, $p < 0.001$, even after considering only the six-channel ROI of higher order regions ($t(5) = 2.461$, $p < 0.05$). Within this ROI, the right middle frontal gyrus ($ISC_{HBO} = 0.4256$, $Z_{HBO} = 1.7603$, $p_{HBO} < 0.05$; $ISC_{HBR} = 0.3220$, $Z_{HBO} = 1.739$, $p_{HBO} < 0.05$) was significantly larger for the intact condition compared to the scrambled condition. Importantly, Patient CC's overall pattern of ISCs within that ROI were well within the typical range observed in healthy controls (*Normalized Dot Product* = 0.014, $Z = 0.879$, $p = 0.388$; see Fig. 2C). Taken together, these results suggest that the patient was engaging with higher order components of the *Taken* audio in a manner that was similar to healthy controls.

Correlated components of EEG activity suggest covert and overt narrative processing

We calculated Patient CC's ISCs with controls in EEG. To accomplish this, we back-projected the spatial weights of two CorrCA components—one for the scrambled condition, one for the intact—calculated across 15 healthy controls in a previous study [38]. Patient CC's ISCs were not significantly correlated with the healthy group during the scrambled audio condition (ISCs = 0.0018, $p > 0.05$ permutation test). However, during the intact audio, her ISCs with controls were statistically significant and, in fact, among the highest across the group (ISCs = 0.0311, $p < 0.05$ permutation test), suggesting comparable processing of the auditory narrative (Fig. 2D).

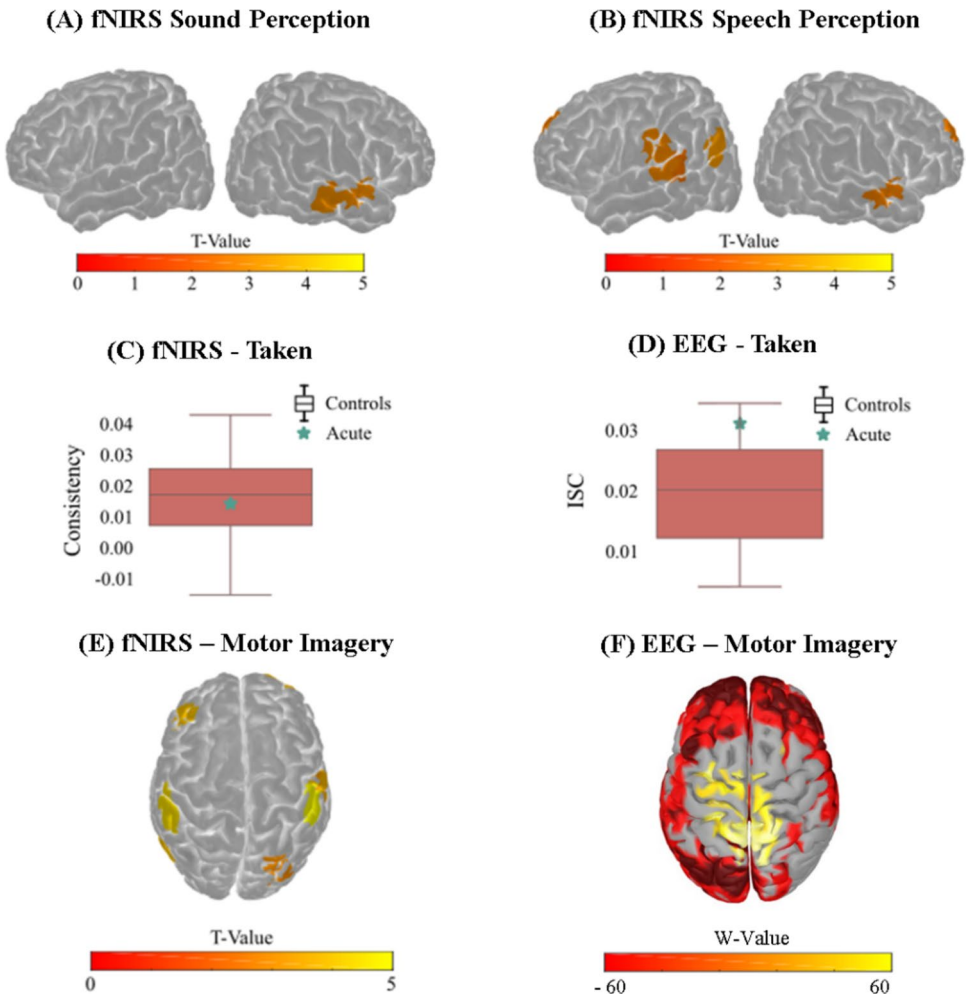

Fig. 2 Significant statistical activation maps and boxplots across task and modality for Patient CC. **A** Significant activation mask for the sound perception condition, where significance is defined as $p < 0.05$ for both HbO and HbR activity. **B** Significant activation mask for the speech perception condition, which compares the speech to pseudo-speech condition, where significance is defined by $p < 0.05$ for both HbO and HbR activity. For all statistical activation maps, lighter colors indicate higher significance. **C** Comparison of the ISC values obtained between Patient CC and controls to the ISCs obtained within controls. Only the first correlated component derived from healthy controls was used to compute ISCs. **D** Comparison of the normalized dot product in Patient CC to what was observed for controls. Only the channels that were significantly larger in the intact condition compared to the scrambled condition were used to compute the normalized dot product. **E** Significant differences in source-localized cortical activity between the averaged rest and tennis epochs for the EEG modality. **F** Significant activation map between the motor imagery and rest condition, where significance is defined by $p < 0.05$ for both HbO and HbR activity

Motor imagery task

Whole brain dynamics of oxy- and deoxyhemoglobin during motor imagery

The cortical profile of motor imagery has been well established in both healthy controls and behaviorally unresponsive patients. We examined whole-brain changes in Patient CC's HbO and HbR activity during motor imagery to explore all task-related hemodynamics associated with the task. We found that HbO in the motor imagery condition increased significantly relative to rest in the following areas: the superior and middle frontal cortices, lateral pre- and post-central gyri, large areas of the parietal cortex, superior and middle temporal cortices, pars triangularis, pars opercularis, and some areas of the occipital lobe ($p < 0.05$, FDR corrected; Fig. 2E). Significant decreases in HbR—the counter dynamics of increased HbR—were less widespread but still covered superior frontal regions, lateral pre- and post-central gyri, supramarginal gyrus, and superior temporal cortex ($p < 0.05$, FDR corrected).

Cortical generators of EEG activity during rest and motor imagery

During rest, we found widespread cortical activations, including anterior frontal, left middle and inferior temporal cortex, right supramarginal gyrus, lateral post-central areas, and isolated islands of activity in the posterior parietal lobe. For motor imagery, most cortical activity occurred bilaterally across the superior parietal cortex and the pre- and post-central gyri—motor areas that were less active during rest (Supplementary Fig. 1). These results also survived significance testing. Indeed, a paired Wilcoxon sign-rank test with permutation testing revealed that motor imagery produced significantly higher cortical activation in medial precentral and post-central cortices, including the SMA, or primary and secondary motor areas (Fig. 2F; see Supplementary Fig. 2 for lateral images). The pattern of cortical activity we observed during the motor imagery task closely resembled that previously observed using fMRI (all contrasts $p < 0.05$, FDR-corrected across vertices).

Memory recall assessment

We administered a brief memory assessment on Day 30, after Patient CC had regained motor function and the ability to communicate, to assess whether she could recall specific events from our assessment protocol (Table 2). On Day 30, CC was able to respond correctly to 5/7 questions. She correctly recalled both imagery conditions but only the instructions from the motor imagery task. She did not remember hearing the audio clips from "*Taken*".

Discussion

In this study, we investigated the feasibility of implementing a multi-task, multimodal neural assessment protocol to confirm suspected conscious awareness in an acutely non-responsive patient in critical care. We presented a case of one patient hospitalized with AMSAN—a rare and severe form of GBS—who exhibited no behavioral evidence of awareness. In keeping with the fact that GBS is a lower motor neuron process with little to no effect on the central nervous system, she produced clear, consistent, and reproducible neural markers of complex cognitive functions during each assessment with both EEG and fNIRS. While the medical team suspected preserved awareness despite the behavioral unresponsiveness, multimodal neuroimaging objectively confirmed that this was the case. For example, significant ISCs with controls during the auditory movie task and appropriate activation of motor cortices during motor imagery provided strong evidence that Patient CC could hear, comprehend language, follow a narrative, and execute (neural) behavior in response to spoken. Moreover, Patient CC's correct recollection of the imagery tasks provides further evidence of her preserved functional capacity in hospital.

Taken together, these results provide two important validations of our neural assessment protocol. First, our findings establish that we can successfully index neural correlates of advanced cognitive function in ICU patients using our assessment battery. The consistency of Patient CC's neural responses across tasks and imaging modalities, her memories from the assessment, and the symptom profile of AMSAN strongly suggest that our tasks effectively captured genuine expressions of preserved cognition in a behaviorally unresponsive patient. It is also important to note here that we have previously reported null results in all three tasks; i.e., ISCs are not always significant [23], and neither the presentation of stimuli nor task instructions automatically elicit appropriate neural activity [13, 26]. Second, comparable ISCs and cortical activations across EEG and fNIRS suggest that each imaging technique captures different aspects of the same underlying cognitive functions. By indexing multiple dimensions of brain activity—electrophysiological or hemodynamic—our approach provides parallel pathways to investigate task-related neural activity, thereby increasing the likelihood of uncovering markers of covert cognition and awareness [40, 41].

While this study presents a comprehensive assessment of a behaviorally non-responsive patient's cognitive state, this is not the first study to investigate residual cognition in acute GBS patients with functional neuroimaging. Indeed, Abdalmalak et al. [42] used time-resolved fNIRS to establish effective communication with one patient with GBS confirmed to be in a functionally locked-in state. By comparing the time course of hemodynamic activity over motor cortex at rest and during motor imagery, Abdalmalak and colleagues showed consistent, time-locked increases in HbO during imagery trials. Furthermore, they successfully decoded "yes" and "no" responses from motor imagery and rest during binary questions about the patient's last name (yes; correct name) and whether they were in pain (no; null "rest" response). Norton et al. [43] recently described similar results in two patients with GBS using motor imagery and spatial navigation tasks in fMRI. Both patients produced significant activation in appropriate motor and spatial navigation areas during the tasks and, in some cases, could modulate their neural activity to answer "yes" and "no" questions from the scanner. Although our motor imagery protocol, as implemented in this study, is limited in this respect, recent work on brain–computer interfaces may provide insights into how to effectively adapt our paradigm to enable effective communication. These may include incorporating training and testing phases, performance feedback, and repeat testing [27, 44–46]. Nevertheless, this study is the first to

our knowledge to employ a multimodal approach (EEG and fNIRS) in this context.

One notable finding in this study was the magnitude of Patient CC's ISCs with controls in EEG. Indeed, CC's ISCs were higher than all but one control participant for the intact audio condition. We have previously reported that, in a sample of chronic DOC patients and one individual with LIS, 30% produced significant ISCs with controls during the "*Taken*" audio (including the individual with LIS). Like Patient CC, the magnitude of their ISCs exceeded those of many healthy controls during the same task. This could be due to several factors, but it is likely that simply having fewer movement-related artifacts in the recordings. The conspicuous absence of hemodynamic activation of dorsal motor regions during motor imagery also warrants further interpretation. Given the anatomical profile of BOLD activity during motor imagery [25, 26], we predicted that we would find similarly localized patterns of fNIRS activation. This was not the case. The most likely explanation for this result was the lack of coverage across central regions of the scalp. With a higher density of fNIRS probes across midline regions, we may have observed an activation pattern that is consistent with previous findings in fMRI. While discerning the source of these discrepancies between assessments is beyond the scope of this study, future research with larger cohorts of patients and discharge follow-ups may provide additional insight into these phenomena.

It is important to reiterate that AMSAN, and GBS more broadly, is not a perfect model for the lack of behavioral responsivity that often follows a severe acute brain injury [47]. However, the results presented here establish the feasibility of using combined EEG-fNIRS to detect overlapping but independent neural correlates of covert cognition. Crucially, we demonstrated that this can be achieved using neural recordings acquired at the bedside of an ICU patient. In combination, our findings provide an encouraging initial validation of our assessment protocol [40]. For patients who are functionally locked-in, whether resulting from disorders like GBS or another neurologic injury, this could provide a pathway to effective communication. With the right task, analysis, and questions, patients may be able to convey their wishes to substitute decision-makers and express any pain or discomfort to healthcare providers. While the results of such assessments should be interpreted with caution—including those presented here—bedside communication with non-responsive patients has the potential to enhance diagnostic accuracy and improve patient management and care. Future work in this area could aim to streamline the practical application of these assessments as well, for instance, by relying on smaller EEG electrode arrays (e.g., 16-channel 10–20 montage). This would reduce the total time required for this assessment, increasing the feasibility of its application in a wider range of patients.

In sum, we presented the first-in-ICU data from our bedside neural assessment battery [40]. We assessed one patient with AMSAN who served as an unresponsive clinical control participant to determine whether we could identify neural markers of preserved sensory function, cognition, and awareness using complementary fNIRS and EEG. Overall, we observed highly consistent results across imaging modalities and tasks. Taken together, our findings strongly suggest that Patient CC remained awake and aware during our neural assessments. In addition, her accurate recall of our testing procedures on Day 30 is a compelling and predictable corollary of preserved awareness. The results of the current study provide initial support for the wider deployment of our EEG-fNIRS neural assessment protocol to further inform standard diagnostic techniques in critical care.

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Declarations

Conflicts of interest We collected this data in April 2022. In September/October of 2022, A. Abdalmalak began working for NIRx Medical Technologies--the manufacturer of the fNIRS system used in this study.

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