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Functional near-infrared spectroscopy: A novel tool for detecting consciousness after acute severe brain injury

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Recent advancements in functional neuroimaging have demonstrated that some unresponsive patients in the intensive care unit retain a level of consciousness that is inconsistent with their behavioral diagnosis of awareness. Functional near-infrared spectroscopy (fNIRS) is a portable optical neuroimaging method that can be used to measure neural activity with good temporal and spatial resolution. However, the reliability of fNIRS for detecting the neural correlates of consciousness remains to be established. In a series of studies, we evaluated whether fNIRS can record sensory, perceptual, and command-driven neural processing in healthy participants and in behaviorally nonresponsive patients. At the individual healthy subject level, we demonstrate that fNIRS can detect commonly studied resting state networks, sensorimotor processing, speech-specific auditory processing, and volitional command-driven brain activity to a motor imagery task. We then tested fNIRS with three acutely brain injured patients and found that one could willfully modulate their brain activity when instructed to imagine playing a game of tennis—providing evidence of preserved consciousness despite no observable behavioral signs of awareness. The successful application of fNIRS for detecting preserved awareness among behaviorally nonresponsive patients highlights its potential as a valuable tool for uncovering hidden cognitive states in critical care settings.

consciousness | coma | brain Injury | fNIRS

Significance

In the intensive care unit (ICU), unresponsive patients with acute brain injury may retain a higher level of consciousness than apparent at the bedside. Our study highlights the utility of functional near-infrared spectroscopy (fNIRS), a portable optical neuroimaging device, for detecting the neural signatures of conscious processing. We identified resting-state networks, sensorimotor and auditory processing, and command-driven brain activity at the individual level in healthy participants. Moreover, we applied fNIRS to detect preserved consciousness in three severely brain-injured ICU patients and found that one patient had fully preserved awareness despite lacking behavioral signs of consciousness. Our study highlights the potential of fNIRS as a valuable tool for identifying hidden cognitive states in patients following serious brain injury.

Functional neuroimaging techniques have significantly enhanced our understanding of residual and covert cognitive processing in patients with a disorder of consciousness (1). A comprehensive array of paradigms has been developed to assess and detect the neural correlates of conscious processing using fMRI and EEG (2–5). These tasks range from the presentation of passive stimuli that enable the assessment of lower-level cortical processing in response to sensory cues (3, 6), to active task-based approaches that allow for the detection of higher-order volitional brain activity to external commands (2, 7). Remarkably, functional neuroimaging tools have demonstrated that approximately 15 to 20% of patients clinically diagnosed as being in a vegetative state (also known as unresponsive wakefulness syndrome) are, in fact, aware, despite the absence of observable behavioral signs (8). This phenomenon, referred to as covert awareness or cognitive motor dissociation (9), has now been corroborated by numerous fMRI and EEG studies (10, 11). An even larger proportion of patients demonstrate covert cortical processing, which is characterized by association cortex responses to auditory stimulation (e.g., speech), even when no evidence of preserved language function is observed on bedside behavioral examinations (12).

More recently, some of these functional neuroimaging methods have been used to assess residual and covert awareness in unresponsive patients with acute brain injuries in the intensive care unit (ICU), where treatment decisions are typically based on subjective behavioral responses, and prognosis often remains uncertain (13, 14, 15). Both fMRI and EEG have been used to identify covert awareness in acutely ill patients in the ICU (16, 17), and such findings are predictive of functional recovery (18). However, fMRI is expensive, immobile, susceptible to motion artifacts, and carries a high risk for adverse events, which limits its utility in critically ill populations (13). EEG, although portable, suffers from low spatial resolution and high sensitivity to environmental noise, making recordings within an ICU environment challenging. These limitations suggest that alternative neuroimaging techniques need to be developed for the assessment of covert cognitive function in the ICU.

Functional near-infrared spectroscopy (fNIRS) is an optical neuroimaging technique that has few of the limitations of fMRI and EEG in an intensive care setting and can be used to measure neural activity with no safety risks or disruptions to patient care. fNIRS is portable, relatively inexpensive, and provides good temporal and spatial resolution (19, 20).

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Like fMRI, fNIRS infers brain activity through neurovascular coupling by estimating concentration changes in oxygenated (HbO) and deoxygenated (HbR) hemoglobin (19, 20). Although fNIRS has been employed extensively across diverse populations and with various paradigms to assess cognitive function (21), its potential value in a critical care setting for accurately measuring residual and covert awareness is yet to be elucidated. To establish fNIRS as a reliable assessment tool in the ICU, it is essential to conduct a thorough examination of individual subject reliability, particularly given the unique challenges of understanding cognition in critical care patients (22). Unlike the predominant group studies in fMRI, EEG, and fNIRS, there is a notable difficulty in identifying methods and paradigms that yield consistent results at the individual participant level (22).

In this series of studies, we evaluate whether fNIRS can detect the neural signatures of conscious processing in healthy participants and then use these methods to assess brain activity in acutely brain injured patients in the ICU. First, we explore whether fNIRS can reliably identify neural activity in healthy participants at the individual-participant level using a series of validated fMRI paradigms that have been developed to hierarchically assess residual and covert awareness in patients with disorders of consciousness. Specifically, in a cohort of healthy participants, we evaluated neural activity at rest to assess resting-state connectivity (Study 1), during a passive task-based paradigm assessing sensorimotor processing (Study 2), during a passive task-based paradigm assessing auditory processing (including speech processing and language processing) (Study 3), and during two active task-based covert mental imagery tasks (motor imagery and spatial navigation) (Study 4). Second, we demonstrate the clinical utility of these approaches for investigating residual and covert awareness in three ICU patients with an acute severe brain injury (Study 5). The results demonstrate that fNIRS can detect preserved awareness in patients with severe brain injury despite the absence of any observable behavioral responses.

Results

Study 1: Resting-State Networks can be Identified Using fNIRS. In the first study, a 6-min resting-state scan was collected in the absence of any external stimuli to assess functional connectivity in 23 healthy participants (*SI Appendix*, Fig. S1*A*). Using a seed-based approach, spontaneous correlated patterns of brain activity were examined across four well-established resting state networks that have a] cortical presence and are often examined in unresponsive patients with brain injury: sensorimotor, auditory, frontoparietal, and default mode (23, 24). Sensorimotor and auditory networks provide valuable information about the preservation of connectivity within lower-level sensory areas, whereas the frontoparietal and default mode networks shed light on the functional connections that sustain higher-order executive function and internal awareness, respectively (25). Importantly, the detection and preservation of these networks have been demonstrated to be necessary for the recovery of consciousness after severe brain injury (24, 26, 27).

Connectivity was evaluated by calculating the strength of significant correlations for each seed region to the rest of the brain. Multiple seeds were used for each network and the resulting correlations were averaged (*SI Appendix*, Table S1 and *SI Appendix*, Fig. S3). Across healthy participants, resting-state functional connectivity was detected for all networks and was in good spatial agreement with the prior fMRI literature (Fig. 1 *A*–*D*) (25, 28). A description of the brain regions associated with each network can be found under *SI Appendix*, Table S1. Additionally, the single-subject sensitivity across participants was 65.2% for the motor network, 69.6% for the auditory network, and 73.9% for both the frontoparietal and default mode networks.

Study 2: Lower and Higher-Order Sensorimotor Processing Is Detected with fNIRS. A right-hand median nerve stimulation paradigm was used to interrogate sensorimotor processing in 17 healthy participants (*SI Appendix*, Fig. S1*B*). This paradigm has been previously used to evaluate the neural integrity of sensory processing in patients with chronic disorders of consciousness (29, 30). The task elicited a robust significant (pHbO *and* pHbR < 0.05) response in low-level sensory and motor regions, including left (i.e., contralateral) postcentral gyrus (i.e., somatosensory cortex) [$T(16)_{HbO} = 3.62$, $T(16)_{HbR} = -3.24$] and precentral gyrus (i.e., motor cortex) [$T(16)_{HbO} = 3.38$, $T(16)_{HbR} = -2.40$] (Figs. 1*E* and 2*A* and *SI Appendix*, Table 2). Moreover, activity was detected in higher-order association areas, namely the left inferior postcentral gyrus (i.e., secondary somatosensory cortex) [$T(16)_{HbO} = 2.46$, $T(16)_{HbR} = -3.91$], reflecting cortical integration and perceptual processing of the stimuli (31). Importantly, these findings are consistent with previous fMRI investigations showing activity in the same anatomical locations (32, 33), thereby demonstrating that fNIRS can reliably detect the appropriate sensorimotor response to median nerve stimulation. Using a leave-one-out cross-validation approach to assess individual subject sensitivity for all task-based studies, we found that 15 of 17 [88.24% (95% CI: 68.23% to 100.00%)] healthy participants had detectable sensory and motor responses to the task.

Study 3: A Hierarchical Auditory Paradigm Detects Speech and Language-Specific Processing. In the third study, we examined whether fNIRS can detect the neural signatures of auditory processing in 29 healthy participants using a paradigm that consisted of four conditions: complex sentences, pseudospeech, signal correlated noise (SCN), and a silent baseline (*SI Appendix*, Fig. S1*C*) (15, 34–36). The complex sentence and pseudospeech conditions demonstrated bilateral activity in the temporal gyrus. Peak activity was observed over the right middle temporal gyrus [$T(27)_{HbO} = 3.41$, $T(27)_{HbR} = -4.25$] and the left superior temporal gyrus ($T(25)_{HbO} = 6.37$, $T(25)_{HbR} = -5.77$) for the complex sentence and pseudospeech conditions, respectively (*SI Appendix*, Fig. S4 *A* and *B* and Table S3). Of note, there was no discernible group-level activity observed in the SCN condition, indicating that this condition may not effectively evoke detectable auditory responses measurable through fNIRS (*SI Appendix*, Fig. S4*C*). Next, in a manner similar to previous fMRI literature, we combined these conditions to assess speech processing and language processing (3, 15). The SCN condition was not included as there was no significant activity detected at the group level (*SI Appendix*, Fig. S4*C*). To examine speech-specific processing, the complex sentences and pseudospeech conditions were compared with a silent baseline. This contrast revealed widespread and significant activity in the bilateral primary auditory cortices, with peak activity in the left middle temporal [$T(27)_{HbO} = 4.59$, $T(27)_{HbR} = -5.64$] and right superior temporal gyri ($T(27)_{HbO} = 3.93$, $T(27)_{HbR} = -4.22$) (Figs. 1*F* and 2*B* and *SI Appendix*, Table S4). Moreover, 24 of 29 healthy participants [82.76% (CI: 61.04% to 100.00%)] had cortical activity in the speech processing contrast. To isolate higher-order language processing, the complex language condition was compared against the pseudospeech condition, which revealed peak activity in the left middle posterior temporal gyrus [$T(23)_{HbO} = 2.61$ $T(23)_{HbR} = -2.60$] (Figs. 1*G* and 2*C* and *SI Appendix*, Table S5). Notably, only 7 of the 29 healthy participants [24.1% (95% CI: 3.96% to 44.32%)] exhibited detectable activity in

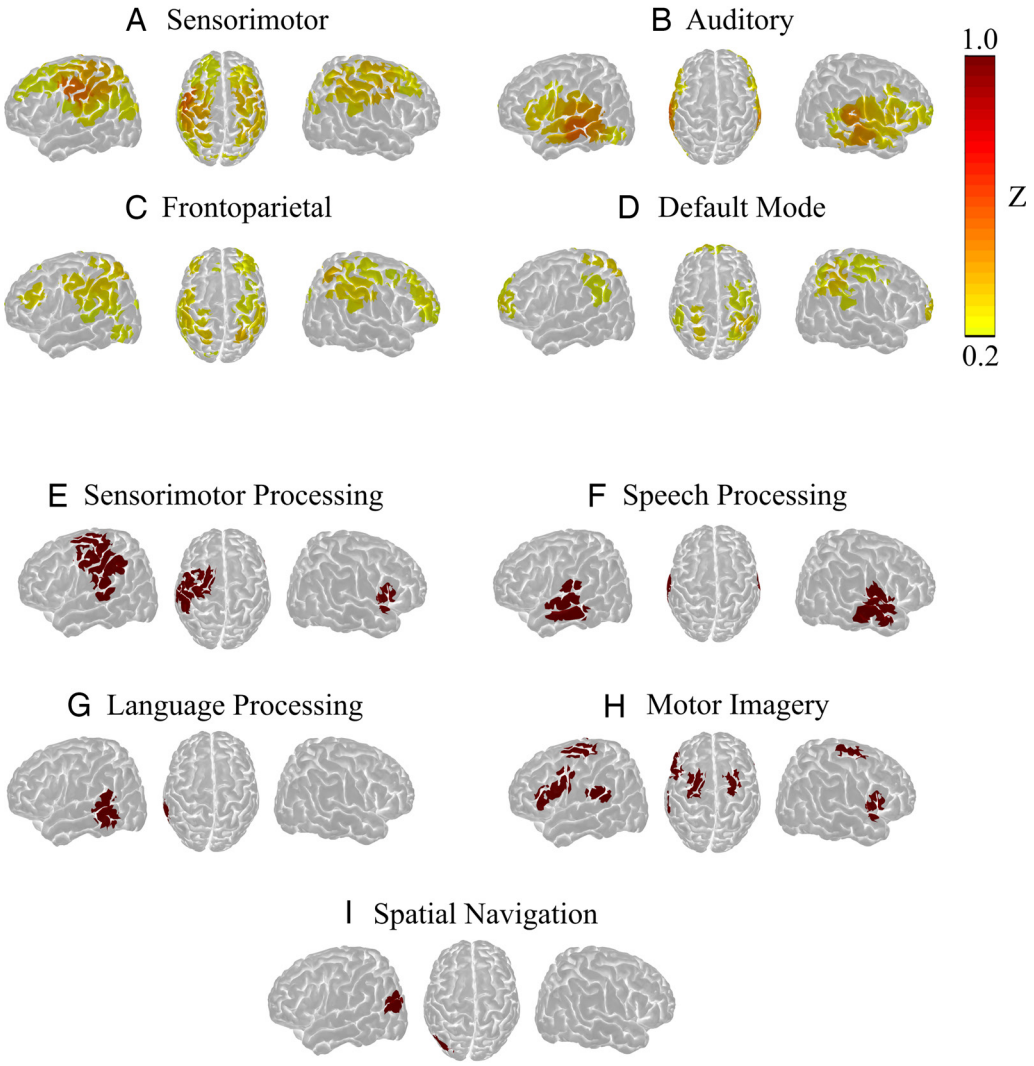

Fig. 1. Healthy participant results for studies 1 to 4. The first two rows show resting-state functional connectivity maps for (*A*) sensorimotor, (*B*) auditory, (*C*) frontoparietal, and (*D*) default mode networks. Each network was extracted with the seed-based approach from the average HbT correlation matrix. Correlation coefficients were converted to Z-scores via an r-to-Z Fisher's transformation and thresholded at Z > 0.2 for display purposes. The remaining rows show binary maps of activity for task-based paradigms: (*E*) Sensorimotor processing, (*F*) Speech processing, (*G*) Language processing, (*H*) Motor Imagery, and (*I*) Spatial Navigation. Each channel (or brain region) was considered activated if it presented a significant characteristic hemodynamic response for both HbO and HbR ($P < 0.05$).

this contrast—a finding consistent with previous reports using a version of this task with fMRI (3, 15).

Study 4: Command-Driven Brain Activity Can be Detected Using fNIRS. In study 4, two command following tasks (motor imagery and spatial navigation) were employed to detect volitional brain activity in 24 healthy participants (*SI Appendix*, Fig. S1*D* and 2*D*) (2, 37). Unlike the passive paradigms used in Studies 1 to 3, these command following tasks rely on participant cooperation and executive processing abilities that dependent upon having preserved awareness, allowing for consciousness to be inferred when the predicted neural responses are observed (38). When participants were instructed to "imagine playing a game of tennis" during the motor imagery task, significant activity was observed in the right frontal gyrus [$T(23)_{HbO} = 2.08$, $T(23)_{HbR} = -2.03$], the left frontal gyrus [$T(23)_{HbO} = 3.80$, $T(23)_{HbR} = -2.24$], and the left supramarginal gyrus [$T(22)_{HbO} = 2.84$, $T(22)_{HbR} = -1.85$] (Figs. 1*H* and 2*D* and *SI Appendix*, Table S6). In the spatial navigation paradigm, participants were told to "imagine walking through your home," and activity was observed in the left middle occipital gyrus [$T(20)_{HbO} = 5.64$, $T(20)_{HbR} = -4.84$] (Figs. 1*I* and 2*E* and *SI Appendix*, Table S7). At the individual subject level, 15 of 24 healthy participants had detectable activity in the motor imagery task [62.5% (95% CI: 41.21% to 83.79%)], whereas only 8 out of 24 participants demonstrated activity in the spatial navigation task [33.33% (95% CI: 20.43% to 46.24%)]. Importantly, the areas of activity detected during both command following tasks were consistent with previous fMRI findings (37, 39, 40). However, sensitivity in the spatial navigation task was significantly lower with fNIRS than with fMRI, whereas sensitivity in the motor imagery task was slightly lower compared to fMRI and EEG (7, 17).

Study 5: Detecting Covert Cognitive Processing in the ICU. In the final study, we sought to determine whether fNIRS could measure and map the extent of preserved cognitive processing in three critically ill patients with severe brain injuries in the ICU (Table 1). No patient showed evidence of behavioral command following from the onset of the brain injury to the time of imaging (*SI Appendix* for detailed clinical profiles and neurological examination results). Fig. 3 outlines a visual schematic of the fNIRS setup with a critically ill patient.

Patient 1. The patient was tested on day 2 of ICU stay while in a coma. The patient did not have detectable activity across any of the passive or active task-based paradigms (Fig. 4 *A* and *B*).

Table 1. Behavioral and neuroimaging diagnosis of the patients tested

Patient number	GCS score	ICU day of testing	CRS-R diagnosis	Speech processing	Motor imagery	Imaging diagnosis	6 mo outcome
1	3 T	2	Coma	Not detected	Not detected	Coma	Death
2	8 T	15	MCS-	Yes	Not detected	CCP	Moderate Disability
3	8 T	7	VS	Yes	Yes	CMD	Severe Disability

Here, we only report neuroimaging results for speech processing and motor imagery, whereas full results from all paradigms can be found intext. GCS: Glasgow coma scale. T: Intubated. CRS-R: Coma Recovery Scale – Revised. VS: Vegetative state. MCS-: Minimally conscious state minus. CCP: Covert cortical processing. CMD: Cognitive motor dissociation.

A correlation-based similarity measure showed that only the frontoparietal network significantly differed from those of healthy controls (*SI Appendix*, Fig. S6).

Patient 2. Tested on day 15 of their ICU stay, patient 2 was in a minimally conscious state minus at the time of testing. Task-based neuroimaging results revealed activity only in the speech processing contrast during the auditory processing task. Neural responses were recorded over the right superior temporal gyrus (T_{HbO} = 2.50, T_{HbR} = −3.01), suggesting that the patient retained the ability to passively perceive speech specific auditory stimuli (Fig. 4*A* and *SI Appendix*, Fig. S7*A*). The neuroimaging results indicate covert cortical processing (12), as no observable behavioral evidence of language expression is present, despite the auditory cortex response to the stimuli remaining intact. The patient did not have a detectable response during the sensorimotor paradigm, language processing contrast, nor the motor imagery or spatial navigation tasks. Resting-state analyses revealed functional connectivity in the default mode network significantly differed from healthy participants ($P < 0.05$) (*SI Appendix*, Fig. S6).

Patient 3. Patient 3 was tested on day 7 of admission to ICU and in a vegetative state at the time of testing. In contrast to patients 1 and 2, robust neural responses were observed in several tasks at all levels of the processing hierarchy, suggesting that this patient's cognitive function remained largely intact despite being unresponsive. Specifically, in the speech processing contrast, a significant change in activity was observed in the left middle temporal gyrus (T_{HbO} =

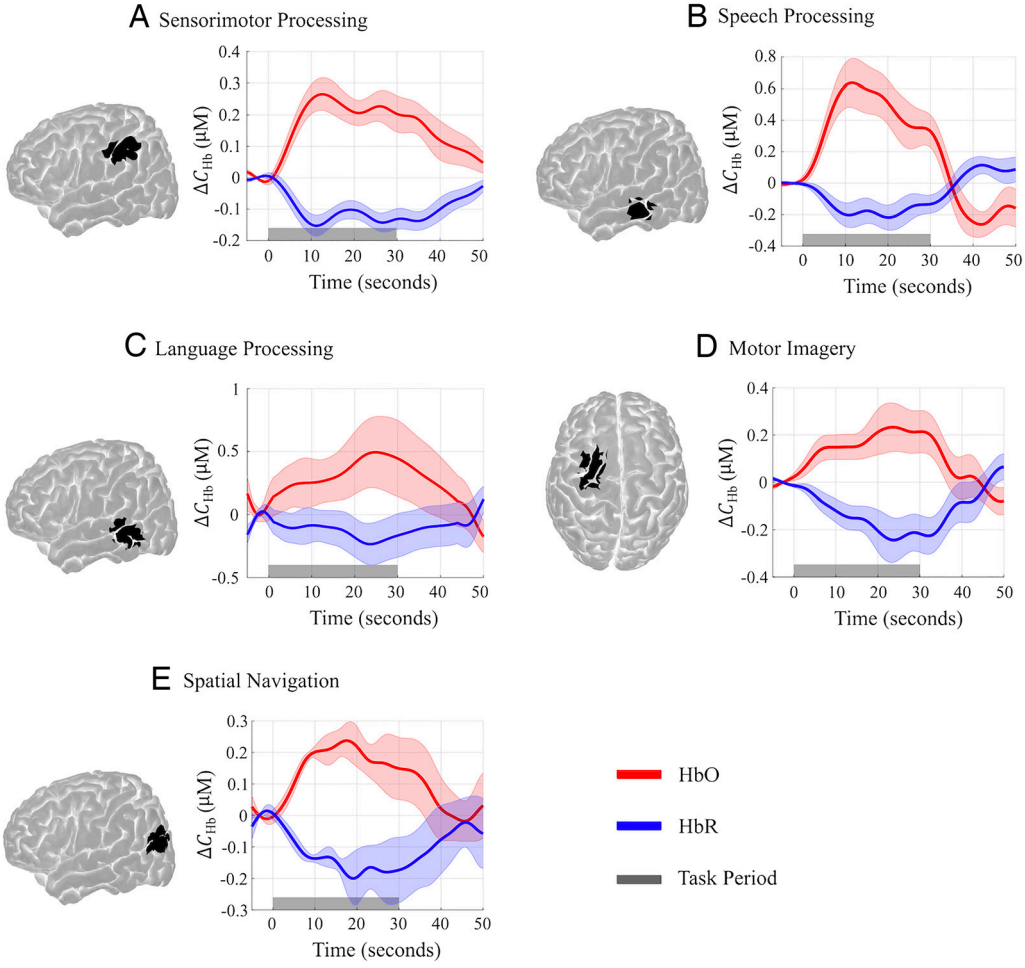

Fig. 2. Group-level healthy participant hemodynamic responses (HRF) at a representative channel for task-based stimuli. (*A*) HRF of the left postcentral gyrus during the sensorimotor task. (*B*) HRF of the left superior temporal gyrus during the speech processing contrast of the auditory processing paradigm. (*C*) HRF of the left middle temporal gyrus during the language processing contrast of the auditory processing paradigm. (*D*) HRF of the left frontal gyrus (i.e., premotor cortex) during the motor imagery task. (*E*) HRF of the left occipital cortex during the spatial navigation contrast. The dark regions in the brain maps represent the channel location inferred with a Monte Carlo simulation using AtlasViewer. Before extracting the hemodynamic responses, HbO and HbR time-series were low-pass filtered at 0.1 Hz for visualization purposes. The average response for language processing (*C*) was smoothed for visualization purposes only.

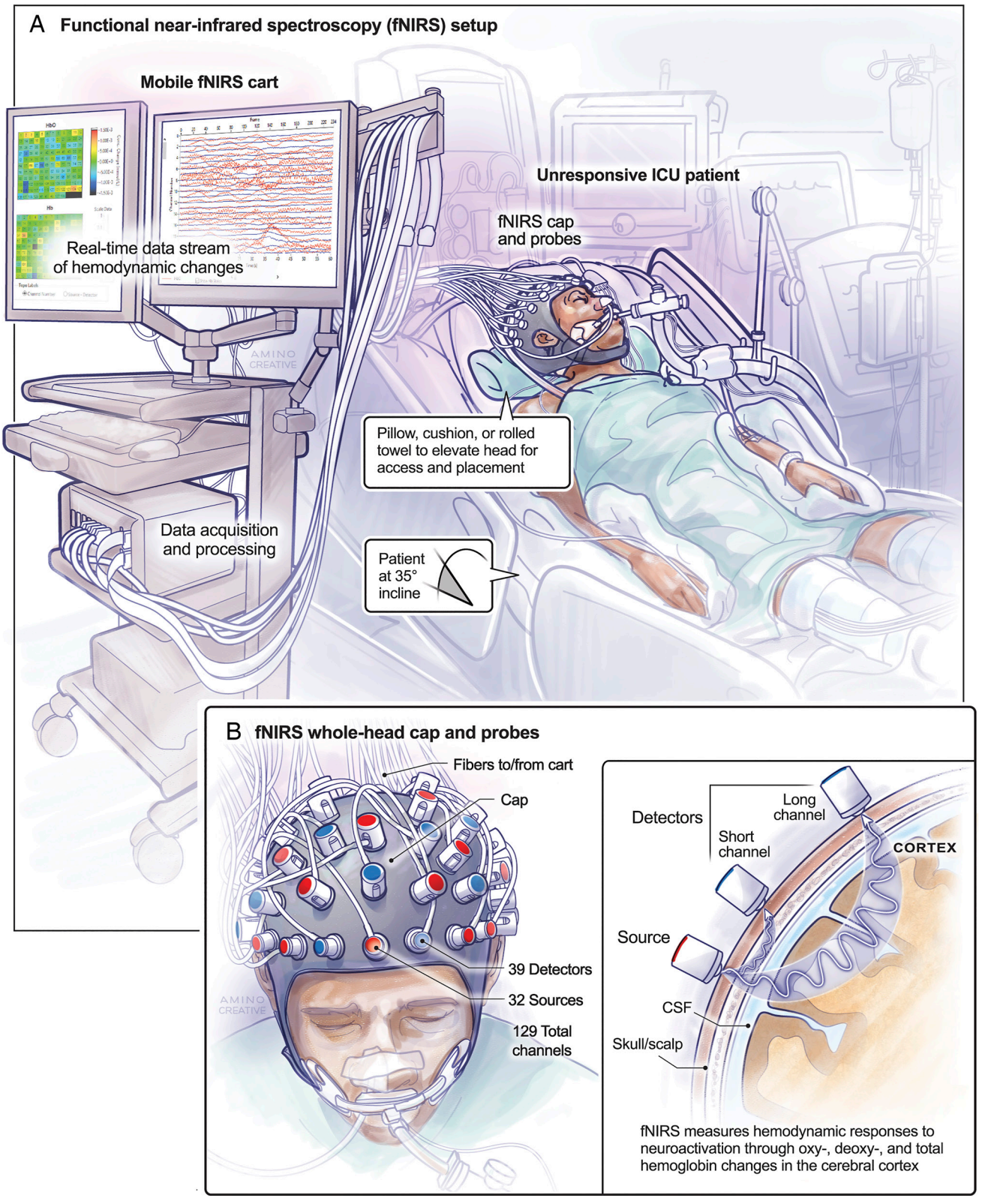

Fig. 3. fNIRS set up and application in the intensive care unit. (*A*) This visual schematic shows a representative severely brain-injured patient undergoing fNIRS testing in the ICU. The fNIRS cap is placed on the patient's head and connects the channels that record changes in oxygenated and deoxygenated blood to a cart beside the patient that holds the fNIRS system and computer, which provide real time measurements of signal quality. (*B*) A close-up representation of the patient wearing the fNIRS cap. The sources (red *top*) emit light into the brain and the detectors (blue *top*) measure the light absorption. The concentration changes measured in oxygenated and deoxygenated hemoglobin are quantified and linked to brain activity through neurovascular coupling. To the right, a schematic of the photon path of the NIR light emitted from the sources. Short channels measure the hemodynamic changes from the extracerebral layers which can be removed during analysis to minimize noise, where as long channels measure the concentration changes in hemoglobin from both the extra- and intracerebral layers. Artwork by Cassio Lynm.

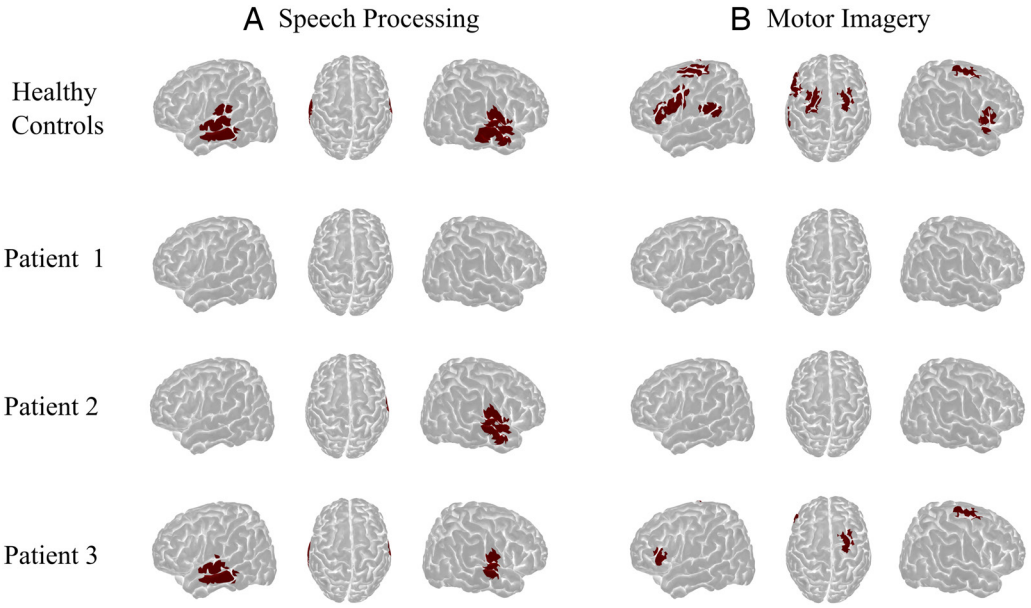

Fig. 4. Individual patient responses to the speech processing, and motor imagery tasks. Stimulus-based fNIRS responses to (*A*) Speech processing and (*B*) Motor imagery. The first, second, third, and fourth rows show the activated channels for the healthy participants, Patient 1, Patient 2, and Patient 3, respectively. Patient 1 had no detectable activity for both tasks, while Patient 2 only had a response to the speech processing contrast. Patient 3 demonstrated similar activity profiles to the healthy control group for all tasks shown.

10.54, T_{HbR} – 11.72), demonstrating residual speech processing abilities (Fig. 4*A* and *SI Appendix*, Fig. S7*B*). In the motor imagery task, the patient had significant activity in the right frontal gyrus (i.e., premotor cortex) (T_{HbO} = 3.96, T_{HbR} = –2.80) and the left frontal cortex (i.e., premotor cortex) (T_{HbO} = 3.36, T_{HbR} = –1.82), indicating that the patient could willfully modulate their brain activity when instructed to do so, despite no signs of awareness at the bedside (Fig. 4*B* and *SI Appendix*, Fig. S7*C*). A successful motor imagery response reflects intention and does not occur in the absence of conscious awareness, suggesting that this patient's true condition was cognitive motor dissociation (38). Sensorimotor activity was not acquired for this patient and there was no significant activity detected in the language processing and spatial navigation tasks. Resting-state analyses revealed preserved connectivity across all networks which were indistinguishable from healthy controls (*SI Appendix*, Fig. S6).

Discussion

In this series of studies, we evaluated whether fNIRS can detect the neural correlates of sensory, perceptual, and conscious processing in healthy participants and in behaviorally unresponsive patients with acute brain injury. Specifically, we tested whether optical imaging can reliably detect brain activity using paradigms commonly used with fMRI to assess perceptual processing and executive function in healthy individuals and patients with disorders of consciousness (2, 15, 41). Across individual healthy participants, we demonstrate that fNIRS can detect commonly studied resting state networks, sensorimotor processing, speech-specific auditory processing and volitional command driven brain activity—albeit with a sensitivity that is lower than some previous fMRI work (e.g., Edlow et al. 2017—68.5%, Fernandez-Espejo et al. 2014—78.5%). On the other hand, we found that fNIRS is less reliable in capturing the neural correlates of language processing or command-driven spatial navigation at the single-subject level.

Importantly, we were able to extend these findings to acute critically ill patients and demonstrate that these fNIRS paradigms can effectively detect covert brain activity in the ICU. We assessed three unresponsive patients with acute brain injury and found that one could willfully modulate brain activity when instructed to imagine playing a game of tennis. The patient generated consistent neuroanatomically appropriate responses across trials; responses that are known to only occur in the presence of conscious awareness (38). Moreover, these findings were supported by the fact that lower-level cognitive processes, such as speech-specific processing, were also detected, as well as intact functional connectivity within resting state networks, both of which are necessary to support higher-order cognitive function. Taken together, the results demonstrate that this patient had a level of awareness that was entirely inconsistent with their clinical examination of consciousness. Of note, Patient 3 had a negative result to the language processing contrast, which is not entirely surprising given the low sensitivity of this condition in healthy controls. In contrast, the task-based data from patient 2 yielded a response in the speech processing contrast, but not in any of the higher-order contrasts. It is critical to note that comparable responses have been observed in healthy individuals under anesthesia (35), implying that these auditory signatures do not signify conscious processing of the stimuli. Nevertheless, this low-level auditory perceptual finding still revealed a level of preserved cognitive function that was not apparent from the patient's behavioral responses, demonstrating that fNIRS can provide additional information about cortical function. Finally, the first patient had no detectable activity to any task-based paradigm.

We opted to report our sensitivity values in healthy participants across task-based paradigms using a binary approach; that is, channels that show concurrent changes in HbO and HbR. This is a conservative approach for reporting cortical activity with fNIRS, which is becoming increasingly recommended by the field (42–44). The results allow us to determine the optimal battery of tasks that are suitablee for detecting covert brain activity with fNIRS in patients with severe brain injury. First, we found that the motor imagery task is more effective than spatial navigation for capturing command-driven brain activity with fNIRS. This may be because the motor imagery tasks tend to

recruit cortical structures (37, 39), whereas the spatial navigation task has mostly been associated with deeper cortical and subcortical areas, which cannot be captured with fNIRS (e.g., the parahippocampal gyrus) (45). Our single-subject motor imagery sensitivity values were slightly lower than prior published literature (46–48), likely due to the lack of complete coverage over the supplementary motor area and our conservative reporting method (49). Second, we found that the sensitivity of fNIRS for detecting sensorimotor activity and speech-specific auditory processing across healthy participants was similar to that reported in prior fNIRS literature—likely due to the robust cortical recruitment of these sensory tasks (50, 51). However, our results suggest that fNIRS is not effective at isolating higher-order language processing—a finding that is consistent with prior fMRI studies (3). Furthermore, as with any neuroimaging method, the absence of fNIRS activity should not be equated to of lack of covert cognitive functioning. Indeed, even with fMRI, some healthy controls fail to show any responsivity during the same auditory (3) and command following tasks (39, 52), highlighting that false negatives can occur with functional neuroimaging techniques (53). Therefore, given that the duration of testing at the ICU bedside is an important consideration, our findings suggest using resting state, sensorimotor, speech processing, and motor imagery when evaluating covert cognitive function.

Our findings suggest that fNIRS is a viable tool for improving diagnosis and prognosis in patients with acute brain injuries in the ICU. With respect to diagnosis, we have provided direct evidence that fNIRS can be diagnostically useful; for example, patient 3 was shown to have a level of consciousness that was entirely inconsistent with their clinical diagnosis. While bedside behavioral assessments like the GCS and CRS-R are currently the gold standard for detecting preserved signs of consciousness, they are highly subjective, suffer from poor interrater reliability, and cannot identify covert conscious awareness (22, 54). These limitations have led to a misclassification rate of approximately 40% in this population of patients (55). With respect to prognosis, the use of fNIRS in this context finds support from fMRI studies where preserved cortical activity detected using similar paradigms presented in this paper are predictive of recovery in both chronic (3, 34) and acute brain injury (15, 18, 26). Nevertheless, while the results of this study suggest that fNIRS can detect covert brain activity in acutely unresponsive patients, future studies with larger sample sizes are needed to fully elucidate its prognostic potential (56).

There are both advantages and disadvantages of using fNIRS in the ICU to probe for residual and covert awareness. fNIRS is tolerable to motion and has adequate spatial and temporal resolution, and data acquisition does not suffer from major sources of interference, all of which can impede functional neuroimaging studies using fMRI and EEG with critically ill patients (13). Additionally, the portability of fNIRS allows for repeated testing on multiple days or at different times during the day, thus allowing fluctuations in awareness to be captured. Repeated testing also reduces the likelihood of false negatives (56). fNIRS can also be used in patients with incompatible implanted hardware, those who are too medically fragile for hospital transport, and patients with raised intracranial pressure, which prevents testing with fMRI in a considerable proportion of this population (13, 57). fNIRS does have limitations, including the difficulty of its use in patients with physical barriers to optode placement, such as patients with decompressive craniectomies, c-spine injuries, and external ventricular drains, and the possibility that patients with a subdural hematoma may have inconclusive results due to the prevention of appropriate diffusion of NIR light in this context.

Conclusion

We propose fNIRS as a method for detecting residual and covert cortical processing in acutely unresponsive patients in the ICU. By combining a portable optical neuroimaging technique with established paradigms that probe for increasing levels of neural function, we demonstrate that fNIRS is a viable alternative to fMRI for detecting the neural correlations of conscious processing in both healthy participants and patients with severe brain injuries. These findings have important practical and ethical implications for the patient's standard of care and quality of life and may open a window to future use of fNIRS brain–computer interfaces for rudimentary mental communication (58).

Method

Participants. Ethical approval for this study was obtained by Western University's Health Sciences Research Ethics Board. Written informed consent was provided by all healthy participants. Control participants were right-handed, native English speakers, had no history of neurological disorders, and had self-reported normal hearing. The substitute decision-makers provided consent for the three patient participants in this study. Across studies 1 to 4, 23 (11 females, 21 to 31 y/o), 17 (12 females, 20–48y/o), 30 (15 females, 20 to 48 y/o), and 24 (12 females, 21 to 31 y/o) healthy participants participated in the resting state, sensorimotor processing, auditory processing, and covert mental imagery tasks, respectively. Three acutely unresponsive patients in the ICU participated in study 5 (*SI Appendix*, information for detailed clinical information).

Procedures. A comprehensive and well-validated battery of fMRI paradigms was used to assess the reliability of fNIRS for capturing the neural correlates of conscious processing, where each successive study required a greater level of cognitive processing to produce a neural response (*SI Appendix*, Fig. S1 and S2) (*SI Appendix*, information for in-depth descriptions and administration of each paradigm). In study 1, a 6-min resting-state scan was acquired to evaluate the intrinsic functional connectivity of the brain (59). For study 2, sensorimotor processing was assessed using a right-hand median nerve stimulation paradigm (29, 30). Study 3 consisted of a hierarchical auditory paradigm to assess speech processing and language processing (15). For study 4, covert command following was assessed with motor imagery and spatial navigation tasks (2, 37, 39). In study 5, the tasks in studies 1 to 4 were used to assess three acutely unresponsive patients in the ICU.

Data Acquisition. Data were acquired using a four-wavelength NIRScoutXP system (NIRx Medical Technologies, LLC) with a sampling rate of 3.9 Hz and lasers centered at 785, 808, 830, and 850 nm. To establish which cortical areas fNIRS would be sensible for each task, we opted to employ a full coverage of the frontal, parietal, and temporal areas, with 32 sources and 39 detectors, resulting in a 129-channel setup (121 long channels and 8 short channels). The fibers were affixed to the head using an EEG cap (EASYCAP, GmbH) and positioned according to the 10 to 20 international system for EEG electrode placement (*SI Appendix*, Fig. S3). For the patients, the study was conducted at the bedside in the Medical Surgical Intensive Care Unit at University Hospital, London, Ontario, Canada. The patient's bed was elevated to a 30° angle, and a pillow was placed behind the patient's back and neck to elevate the head to access the optodes across the entire head (Fig. 3).

Data and Statistical Analyses. Please refer to *SI Appendix* for a more detailed description of the data analysis. The data were preprocessed using functions adapted from HomER2 (60). First, channels with low signal-to-noise ratio (SNR < 8, mean divided by SD) were removed and light intensity of the remaining measurements were converted to optical density. Next, motion artifacts were corrected with spline interpolation followed by wavelet decomposition (61). Changes in HbO and HbR were computed using the modified Beer–Lambert Law, with the differential path length factor calculated for each participant as a function of age (62).

For the task-based paradigms, hemoglobin time courses were band-pass filtered between 0.005 to 0.5 Hz and detrended (for the auditory processing, the high-pass filter was not employed because of the low frequency of repetition of the task). Statistics of activation was inferred with the GLM method using an AR-IRLS solver in which short channels were incorporated as regressors of noninterest

(63). Group-level results were calculated with a weighted linear regression that corrects the different errors of each channel in the first level across different participants. At the group and individual levels, a channel was considered as activated if there was significant increase in HbO and a concurrent significant decrease in HbR ($P < 0.05$, inferred with a one-tailed t test). Specifically, for language processing at the group level, only HbR was considered to evaluate activated channels due to challenges associated with this contrast. For assessing the sensitivity of each task, we verified how many participants had at least one activated channel that overlapped with the activated channels for the group using a leave-one-out approach (i.e., the group results were performed without data from the participant that was being evaluated).

For the resting state, hemoglobin time courses were band-pass filtered between 0.009 and 0.08 Hz. Scalp hemodynamics was removed with short-channel regression, and hemoglobin time series were prewhitened to remove temporal autocorrelation. Resting-state functional connectivity networks were extracted by computing the Pearson correlation coefficient across the HbT time series of each channel and using a well-established seed-based approach (59, 64–66). To evaluate the similarity across participants for each seed-based network, we computed the Pearson correlation coefficient across all possible pairs of participants. With the leave-one-out approach, the fNIRS sensitivity in detecting resting state networks was defined as the percentage of participants that had similarity distributions (22 pairs) that did not differ from the group distribution of the remaining participants (231 pairs). Significance was inferred by a two-sided t test with p-value less than 0.05 after FDR correction considering 23 independent comparisons.

Data, Materials, and Software Availability. All code and toolboxes used in this study have been deposited in Github (https://github.com/TheOwenLab) (67). Study data is available from the corresponding author upon reasonable request due to ethical contrains (67).

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