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ORIGINAL COMMUNICATION

Predicting neurologic recovery after severe acute brain injury using resting-state networks

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Abstract

Objective There is a lack of reliable tools used to predict functional recovery in unresponsive patients following a severe brain injury. The objective of the study is to evaluate the prognostic utility of resting-state functional magnetic resonance imaging for predicting good neurologic recovery in unresponsive patients with severe brain injury in the intensive-care unit.

Methods Each patient underwent a 5.5-min resting-state scan and ten resting-state networks were extracted via independent component analysis. The Glasgow Outcome Scale was used to classify patients into good and poor outcome groups. The Nearest Centroid classifier used each patient's ten resting-state network values to predict best neurologic outcome within 6 months post-injury.

Results Of the 25 patients enrolled (mean age = 43.68, range = [19–69]; GCS ≤ 9; 6 females), 10 had good and 15 had poor outcome. The classifier correctly and confidently predicted 8/10 patients with good and 12/15 patients with poor outcome (mean = 0.793, CI = [0.700, 0.886], $Z = 2.843$, $p = 0.002$). The prediction performance was largely determined by three visual (medial: $Z = 3.11$, $p = 0.002$; occipital pole: $Z = 2.44$, $p = 0.015$; lateral: $Z = 2.85$, $p = 0.004$) and the left frontoparietal network ($Z = 2.179$, $p = 0.029$).

Discussion Our approach correctly identified good functional outcome with higher sensitivity (80%) than traditional prognostic measures. By revealing preserved networks in the absence of discernible behavioral signs, functional connectivity may aid in the prognostic process and affect the outcome of discussions surrounding withdrawal of life-sustaining measures.

Keywords fMRI · Coma · Consciousness · Brain injury · Machine learning · Resting state

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Introduction

Predicting meaningful functional recovery after an acute severe brain injury is a substantial clinical challenge in the intensive-care unit [1, 2]. Measuring the spontaneous fluctuations of the blood oxygen level-dependent signal using resting-state functional magnetic resonance imaging (rs-fMRI) may improve prognostication for this patient population. Indeed, assessing functional connectivity across well-established resting-state networks may provide objective and quantifiable markers of neurologic damage and inform patient outcomes. To date, task-based fMRI has proved effective for assessing preserved cognitive function in this patient group [3, 4]; however, rs-fMRI has advantages due to its ease of administration and requires no effort by the patient. In fact, there is a growing body of evidence suggesting that the preservation of functional networks—primarily the default mode—in acute disorders of consciousness may

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be necessary to support neurologic recovery due to its proposed role in sustaining consciousness [5–9].

Differences in network connectivity have been established between survivors and non-survivors of acute severe brain injury [6, 10]. However, whether the preservation of functional networks can be used to provide individualized assessments for good neurologic recovery remains to be fully elucidated. Machine-learning approaches are useful in this regard, as they can objectively determine the relationship between network connectivity and patient prognosis, while providing information about the quality and strength of that association [11–13]. Given that 70% of deaths in the ICU following a severe brain injury are from the withdrawal of life-sustaining measures, it is imperative to develop accurate tools to identify patients that have the potential for good neurological recovery to better allocate healthcare resources and avoid premature withdrawal of care [14].

The overarching goal of this study was to determine if functional connectivity measures could predict neurologic outcomes in a heterogeneous cohort of unresponsive critically ill patients. Specifically, a machine-learning classification approach was used to determine if rs-fMRI measures across ten well-established networks could accurately determine if a patient would achieve a meaningful neurological recovery or a poor functional outcome within 6 months of their brain injury (GOS 4–5 and GOS 1–3, respectively). We hypothesized that the analysis of rs-fMRI using machine-learning methods would successfully identify patients with good outcome and that this identification would be dependent on the detection of preserved functional networks.

Methods

Standard protocol approvals

This study received ethical approval from the Health Sciences Research Ethics Board at Western University in compliance with the Tri-Council Policy Statement (TCPS): Ethical Conduct for Research Involving Human guidelines. Written informed consent was obtained from the substitute decision-maker for each patient before study procedures commenced.

Patients

Data was acquired from 27 patients in this cohort study from two ICUs at the London Health Sciences Centre (London, Canada). Patients were enrolled between 2014 and 2017 and January–August 2022. Two patients were discarded due to excessive motion. Demographic and clinical characteristics are outlined in Table 1. Inclusion criteria for this study were: (1) admission to the ICU and unresponsive after a severe brain injury of any aetiology, (2) a minimum age of 18 and maximum age of 80, (3) cardiovascular stability, (4) no prior history of neurological impairment, (5) no contraindication for MRI, (6) a low level of consciousness as the primary reason for the inability to command follow at enrollment and at the time of scan, and (7) sedation was not the primary cause of the low level of consciousness. Patients were ineligible for the study if they were (1) hypothermic and (2) had an unstable cardiac or respiratory status that posed an immediate risk for deterioration and (3) too unstable for MRI due to raised intracranial pressure and an inability to lie flat in the scanner.

Acquisition

A 1.5 T General Electric MRI system was used to acquire structural and functional data. A high-resolution whole brain 3-D T1-weighted axial SGPR pulse sequence was obtained over 4 min. An rs-fMRI scan was acquired with a T2*-weighted acquisition sequence (TR = 2500 ms, TE = 40 ms, matrix size = 64 × 64, slice thickness = 3 mm, in-plane resolution = 3.75 mm × 3.75 mm, and flip angle 90°). The 134 volumes were obtained over 5.58 min. Each volume consisted of 30 oblique interleaved slices. The first two volumes of each patient's scan were discarded to allow for the stabilization of the magnetic field.

Preprocessing

Statistical Parametric Mapping (SPM 8, http://www.fil.ion.ucl.ac.uk/spm) was used for image pre-processing. Functional images for each participant were AC-PC orientated, spatially realigned for motion correction, co-registered to the T1 structural images, segmented and normalized to the SPM echo-planar imaging template, and spatially smoothed using an 8 mm FWHM Gaussian kernel. Movement parameters were included as covariates. Of the 25 patients included for analysis, motion and rotation parameters did not surpass an average of 2 mm or 2°.

Resting-state analysis

An independent component analysis (ICA) was used to decompose the fMRI data into statistically independent spatial and temporal components using the GIFT software package (http://icatb.sourceforge.net). The number of estimated components ranged from 11 to 88. The component results were scaled to *Z*-scores. Next, the components generated for each patient were spatially correlated to ten well-established and widely used resting-state network templates derived from a database of ~ 30,000 controls [15]. The ten templates were representative of the following networks: medial visual, occipital pole visual, lateral visual, default

Table 1 Patient demographic and clinical information

Study ID	Age	Sex	Etiology	Time of scan post-ictus	GCS at scan (E,M,V)	Sedation	GOS
01	25	M	Traumatic brain injury	11 days	4 (2,1,1T)	None	4
02	40	M	Traumatic brain injury	9 days	5 (1, 3,1T)	None	4
03	67	F	Hepatic failure	9 days	8 (3,4,1T)	Hydromorphone 0.5 mg/h infusion	4
04	66	M	Intracerebral hemorrhage with bi-hemispheric infarcts involving frontal and temporal lobe	23 days	5 (1,3,1T)	None	2
05	28	M	Status epilepticus	3 months	6 (4,1,1T)	Midazolam 0.5 mg/h infusion	3
06	42	M	Stroke with bilateral deep white matter watershed infarcts	22 days	9 (4,4,1T)	None	2
07	32	M	Status epilepticus	5 months	6 (4,1,1T)	None	2
08	19	M	Traumatic brain injury	10 days	4 (1,2,1T)	None	4
09	59	F	Brain abscess	13 days	9 (4,4,1T)	None	3
10	30	M	Intracerebral hemorrhage involving left occipital lobe	8 days	7 (2,4,1T)	Fentanyl 50 µg/h infusion	2
11	20	M	Traumatic brain injury + cardiac arrest	21 months	8 (4,3,1T)	None	2
12	30	M	Infection (secondary to brainstem tumor)	3 days	6 (4,1,1T)	None	3
13	36	M	Hepatic failure	6 days	6 (1,4,1T)	Fentanyl 25 mg bolus	1
14	67	F	Herpes simplex virus encephalitis	22 days	6 (1,4,1T)	None	4
15	38	F	Intraventricular hemorrhage with deep white matter infarcts	32 days	7 (2,4,1T)	None	3
16	55	M	Cardiac arrest	4 days	3 (1,1,1T)	Propofol 3 mg/kg/h infusion	5
17	34	M	Traumatic brain injury	26 days	8 (4,3,1T)	None	4
18	33	M	Traumatic brain injury	17 days	9 (4,4,1T)	None	4
19	34	M	Cardiac arrest	7 days	3 (1,1,1T)	Propofol 3 mg/kg/h infusion	2
20	41	M	Traumatic brain injury with bilateral subdural hematoma/subarachnoid hemorrhage	2 days	3 (1,1,1T)	Propofol 3 mg/kg/h infusion	3
21	68	M	Stroke with infarct in the pons	22 days	4 (1,2,1T)	None	2
22	61	M	Cardiac arrest	6 days	6 (1,4,1T)	None	1
23	56	M	Stroke with left-side cerebellar infarcts	5 days	5 (1,3,1T)	None	1
24	69	F	Cardiac arrest	4 days	3 (1,1,1T)	Propofol 3 mg/kg/h infusion	4
25	41	F	Stroke (bilateral cerebellar infarct)	2 days	3 (1,1,1T)	Propofol 3 mg/kg/h infusion	3

mode, cerebellar, sensorimotor, auditory, executive control, and right and left frontoparietal. The component with the highest mean spatial correlation to each of the ten templates of interest was extracted as the resting-state network for that patient. These components were visually inspected to ensure that they accurately reflected the desired network. These component correlation values were subsequently used in the machine-learning analysis to predict functional outcomes.

Outcome measures

A patient's clinical outcome was determined by their best Glasgow Outcome Scale (GOS) score within 6 months following their injury [3, 16]. A GOS between 4 and 5 was classified as good outcome, whereas a GOS of 1–3 was scored as poor outcome. During pre-processing and ICA analysis, investigators were unaware of patient outcomes and medical staff completing behavioral assessments were unaware of imaging results.

Outcome prediction

All machine learning was conducted on Python (Version 3.8.12) using sci-kit learning packages [17]. The Nearest Centroid classifier was used to compute the mean value (centroid) of training examples for both labels (good and bad outcomes) across each dimension (ten resting-state networks) in the data. Then, on the test set, the Euclidean distance between each centroid and patient data is computed, where test examples with a smaller distance to the centroid are assigned the corresponding label. Prediction accuracy was measured using balanced accuracy, which is measured as

$$\frac{\text{sensitivity} + \text{specificity}}{2},$$

where sensitivity was measured as correct *and* confident predictions of good outcome and specificity as correct *and* confident predictions of poor outcome (see "Statistical evaluation of prediction performance" for quantifying correct and confident predictions). Predictions that were inaccurate *or* not confident were labeled as incorrect (the opposing label).

Machine-learning procedure

The performance of the Nearest Centroid classifier was estimated using repeated ($N = 1000$ iterations) stratified threefold cross-validation. On every iteration, the data were randomly split into three partitions in which the ratio of patients with good and poor outcomes were equal. For each of the three folds, the classifier was trained on two of the partitions (16–17 patients) and tested on the remaining (6–7 patients)—yielding three balanced accuracy scores (one for each fold). A large number of iterations were used to compute the distribution of balanced accuracy scores, so it could be trained on different subsets of patients. Group-level accuracy was measured as the average balanced accuracy score on the test partitions across all folds and iterations. Confidence in an individual's predicted outcome was defined as the proportion of the 1000 iterations in which the classifier predicted a certain outcome. For example, a patient who was predicted to have a good outcome on 800/1000 iterations would be classified as good outcome with 80% confidence.

Influential resting-state networks

The networks that were significant predictors of functional outcome were determined by evaluating the centroids (mean of each of the ten resting-state networks) with the largest difference between good and poor outcome groups. The true difference in the centroid value between the good and poor outcome groups was statistically evaluated by comparing it to differences in the centroid values computed via permutation testing (see "Statistical evaluation of prediction performance").

Statistical evaluation of prediction performance

Permutation testing was used to evaluate the significance of group-level accuracy, individual patient's confidence score, and resting-state network predictors. This method is a nonparametric approach to statistical testing that allows the generation of a null distribution based on permutations of the existing data. In this case, the identical machine-learning approach (as detailed in "Machine-learning procedure") was used, except that the patients' true outcomes were shuffled on each iteration. This approach was applied for 1000 iterations which generated distributions of group-level balanced scores and individual-level predictions which can arise from random permutations of the data. Comparing the individual- and group-level accuracy scores to their respective null distribution captures spurious associations between resting-state networks and functional outcome as well as controlling for unequal group sizes [18, 19].

For the group-level balanced accuracy scores to be significant, the mean balanced accuracy score across all non-permuted iterations had to fall outside 95% of the null distribution. For the individual prediction, if the proportion of correct classifications for a patient was larger than 97.5% of the null distribution, then the patient was correctly (and confidently) classified. However, if the proportion of correct classification was less than 2.5% of the null distribution, then the patient was incorrectly (and confidently) classified. If the proportion fell within the null distribution, no relationship between resting-state networks and outcome could be reliably drawn for that patient, resulting in an incorrect prediction regardless of the actual outcome the classifier.

Permutation testing was also used to determine resting-state networks that were statistically significant predictors of neurologic recovery. Null distribution of differences between centroids (good and poor outcome) for each resting-state network was computed on the data with shuffled outcome labels. A Z-score was computed between the true difference in centroid value between good and poor outcome and the null distribution of difference scores calculated via permutation testing. Formally, this is calculated as

$$Z = \frac{\mu(\text{Centroid}_{\text{Good}} - \text{Centroid}_{\text{Poor}}) - \mu(\text{Null Centroid}_{\text{Good}} - \text{Null Centroid}_{\text{Poor}})}{\sigma(\text{Null Centroid}_{\text{Good}} - \text{Null Centroid}_{\text{Poor}})},$$

where each value in the equation is a matrix with dimension iterations × centroids × resting-state networks, where μ denotes average over the first dimension and σ denotes taking the standard deviation over the first dimension. Therefore, Z is a vector of Z-scores indicating the importance of

each network for predicting functional outcome. See Supplementary Fig. 1 for additional details.

Results

Patient information

105 patients with brain injury were screened, 69 were eligible, and 57 were enrolled. 30 patients were enrolled but did not complete the study procedures. Supplementary Fig. 5 outlines the reasons patients were excluded, not enrolled, and enrolled but not tested. Twenty-seven patients completed the scan, but two were removed due to excessive motion artifacts. Thus, 25 patients were included in the analysis and presented with the following demographic factors (mean age = 43.68, range = [19–69]; 6 females). Patient etiology consisted of traumatic brain injury (28%), stroke (28%), cardiac arrest (16%), infection (12%), hepatic failure (8%), and status epilepticus (8%). The timing of the scan varied due to the inclusion of three chronic critically ill patients (median = 10.00, range = [2–360 days]). The Glasgow Coma Scale (GCS) score was obtained immediately prior to scanning ($M = 5.68$, CI = [4.87, 6.49], range = [3–9]). 64% of patients were not sedated during the scan ($n = 16$) and the type of sedative varied for the remaining participants. For complete patient information, please refer to Table 1.

Outcome groups' information

No statistical differences in demographic or clinical information were observed between the good outcome ($n = 10$) or poor outcome ($n = 15$) groups, with respect to age (good outcome: $M = 45.00$ CI = [37.67, 52.33]; poor outcome: $M = 42.80$, CI = [36.70, 48.90]; $t(16.91) = 0.314$, $p = 0.76$), sex (good outcome: $n = 10$ (3 females); poor outcome: $n = 15$ (3 females), $t(17.31) = -0.536$, $p = 0.60$), log scan time post-ictus (good outcome: $M = 2.17$, CI = [1.85, 2.50]; poor outcome: $M = 2.83$, CI = [2.20, 3.45]; $t(22.06) = -1.367$, $p = 0.19$), GCS at time of imaging (good outcome: $M = 4.89$, CI = [4.38, 6.22]; poor outcome: $M = 6.07$, CI = [5.16, 6.71]; $t(17.05) = -0.714$, $p = 0.48$), and proportion of patients sedated (good outcome: $n = 4$; poor outcome: $n = 5$; $t(18.65) = 0.323$, $p = 0.75$). Notably, no clinical variables were significant predictors of outcome when evaluated using the machine-learning procedure detailed above and functional outcome prediction using these variables was poor (see Supplementary Fig. 2).

Predicting patient outcome using resting-state networks

Prediction performance and confidence

The classifier predicted outcome well above chance (Balanced Accuracy: Mean = 0.793, CI = [0.700, 0.886], $Z = 2.843$, $p = 0.002$). When it came to correct individualized prediction of outcome, the classifier was confident (Mean = 96.89%, SD = 0.080, Range = [63.50–100%], all $p < 0.01$). However, when the classifier was incorrect, it also was confident (Mean = 91.34%, SD = 0.116, Range = [71–100%], all $p < 0.001$). Altogether, 8/10 patients with good outcome and 12/15 patients with poor outcome were confidently and correctly predicted. See Fig. 1a for individualized accuracy and confidence scores and Fig. 1b for group accuracy.

Influential resting-state network predictors

Predicting functional outcome was largely determined by the three visual networks (medial: $Z = 3.11$, $p = 0.002$; occipital pole: $Z = 2.44$, $p = 0.015$; lateral: $Z = 2.85$, $p = 0.004$; see Fig. 2a for results from all resting-state networks). Each of the visual networks had centroids that had significantly larger mean spatial correlations in the good outcome group than the poor outcome group (see Fig. 2b). Notably, the importance of visual networks in predicting outcome was specific to the neural information obtained as follow-up tests showed no evidence that eye-opening scores on the GCS (GCS-E) predict spatial correlation values of visual networks (see Supplementary Fig. 3 for details). This suggests that patient eye-opening scores at the time of the scan were unrelated to each visual network's spatial correlation. In addition to visual networks, the left frontoparietal network was significant ($Z = 2.179$, $p = 0.029$), whereas the right frontoparietal trended toward significance ($Z = 1.880$, $p = 0.060$) and, like the visual networks, had larger spatial correlations in the good outcome group compared to the poor outcome group. The other networks failed to reach significance (all $p > 0.23$). The three patients misclassified as having good outcome had preserved visual and frontoparietal networks, and the two patients who were misclassified as having poor outcome showed the opposing trend (see Fig. 3).

Discussion

In this study, rs-fMRI was used to assess the functional integrity of the brain in 25 unresponsive patients with severe neurologic injuries admitted to the ICU. A machine-learning approach was employed to predict whether patients would have a good or poor neurologic recovery and to assess the

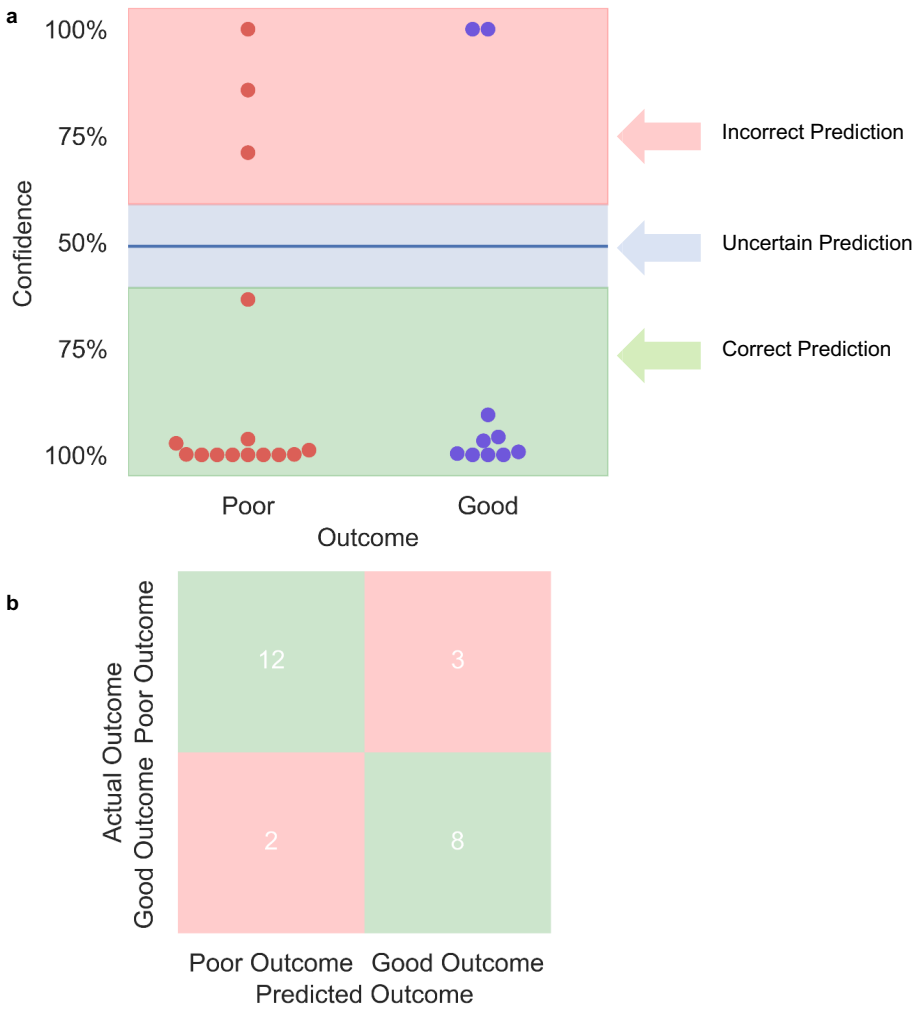

Fig. 1 **a** Dot plot that shows the Nearest Centroid's accuracy and confidence in predicting each patient's functional outcome from ten canonical resting-state networks [10]. Each dot represents a single patient's confidence. The shading of the dot plots indicates whether prediction was correct or not, where the green area represents patients who were confidently and correctly predicted by the classifier, the red area is the opposite, and the blue area is where the prediction of patient outcome could not be distinguished from guessing. **b** Confusion matrix of a patient's true outcome (*y*-axis) and the Nearest Centroid's prediction of that outcome. The numbers indicate the number of patients who were classified in each quadrant. Green shaded regions correspond to accurate predictions, whereas red indicates incorrect predictions

confidence in that prediction. The classifier correctly and confidently predicted 8/10 patients who had good outcome and 12/15 patients who had poor outcome, well above predictions derived from standard clinical variables. The results of this study suggest that rs-fMRI may complement current clinical prognostic tools by providing reliable and individualized assessments of neurologic outcomes.

These findings add to a growing and important body of literature that demonstrates the prognostic utility of rs-fMRI for patients with acute severe brain injuries [5, 8, 10]. While limited in size, this study shows a sensitivity of 80% for predicting good neurological recovery, which is higher than standard clinical tools that are currently used in practice [20]. These results complement a recent study which showed that combined rs-fMRI and EEG models predicted consciousness levels at ICU discharge with high sensitivity (82%) [21]. The results of this study extend these findings by demonstrating that these measures can be used to predict the best functional outcome a patient achieves within 6 months following their injury. The high sensitivity of these measures may be in part because rs-fMRI captures the brain's intrinsic functional connections in a manner that can be objectively quantified, reflecting wide-scale integrity of neuronal function. Hence, if resting-state networks are preserved for a particular patient, the patient may have the capacity to reintegrate wide-scale neuronal function that supports consciousness and good neurological outcome.

The three visual networks examined in this study were found to be significant predictors of neurologic recovery. Importantly, the predictive value derived from these networks was independent of eye-opening at the time of the scan (see Supplementary Fig. 3). Previous research has found preserved functional connections both within and between the occipital lobe and the rest of the brain in acutely unresponsive patients [8], and supported by structural imaging findings that demonstrate changes in forebrain–occipital connectivity in severe TBI patients who regained consciousness [22]. The potential clinical utility for visual networks also draws support from patients with chronic disorders of consciousness, where visual-auditory networks were able to

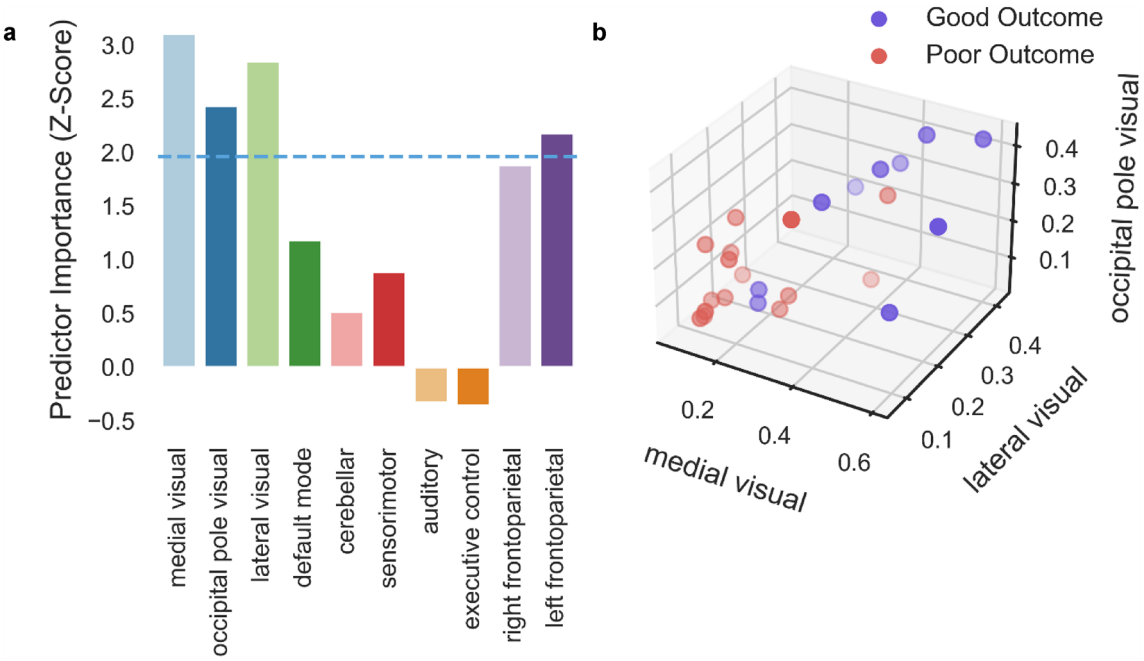

Fig. 2 **a** Bar plot showing the extent to which resting-state networks were predictive of functional outcome. *Z*-scores indicate the degree to which the difference between the good and poor outcome centroid was highly positive (or highly negative) compared to chance, where chance is defined by the centroids computed during permutation testing. Larger *Z*-scores indicate a large centroid difference between good and poor outcome, whereas a large negative difference means the opposite. *Z*-scores above the dashed blue line are significant ($p < 0.05$). **b** A 3-D scatterplot showing the two different outcomes (good outcome in blue and poor outcome in red) plotted as a function of the three networks (medial, lateral, and occipital pole visual) that were most informative in distinguishing between outcomes

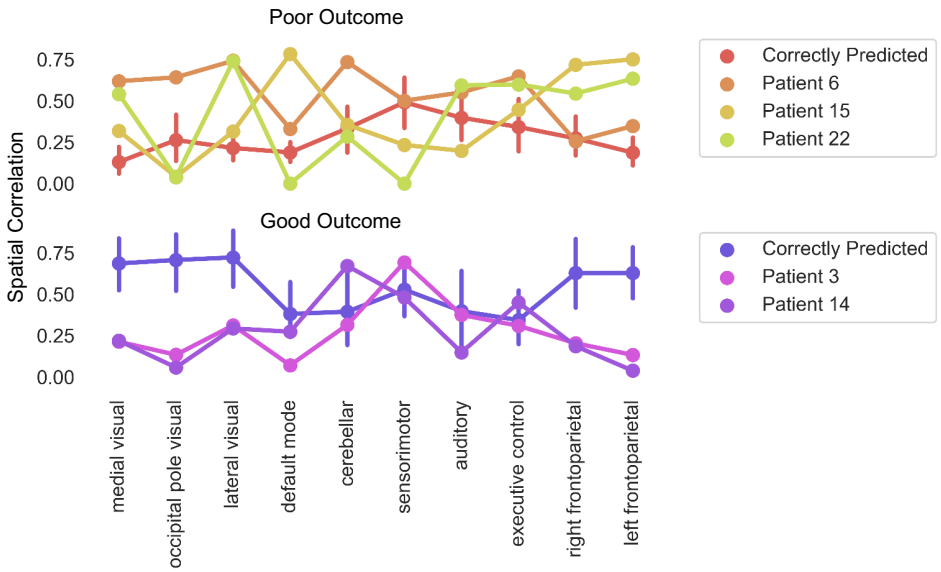

Fig. 3 Pointplot showing the mean spatial correlations (with 95% confidence intervals) for each network. The top plot shows the spatial correlation values for patients with poor outcome and the bottom plot for good outcome. The red and blue lines show mean spatial correlation when patients were correctly predicted by the classifier, whereas the remaining colors were those who were mispredicted (with warmer colors representing mispredicted patients who had a poor outcome and cooler colors were mispredicted patients with good outcome)

differentiate between minimally conscious and unresponsive patients [23]. However, an important distinction is that in the present study, auditory networks were not significant predictors of recovery. Visual networks are also supportive of higher order cognitive properties, such as space, orthography, covert reading, and internally directed thought [15, 24, 25]. The present study also revealed that the left frontoparietal network had prognostic importance, which supports prior findings demonstrating that the preservation of this network is a significant predictor of recovery after anoxic and traumatic brain injury [26]. Additionally, the frontoparietal network has been used as a biomarker for preserved cortical

integrity in chronic disorders of consciousness, likely to its role in goal-directed behavior, working memory, and cognitive control [15, 24, 27]. Taken together, the preservation of these networks suggests that the neural infrastructure for simple and complex perception and cognition may support neurologic recovery.

In contrast to previous rs-fMRI studies with this patient population, the DMN was not a significant predictor of outcome [5–7, 9]. Notably, there was high positive correlation between the default mode network and the medial visual and frontoparietal networks (see Supplementary Fig. 4), which may have lessened the predictive power of the DMN. It may be the case that more detailed information about the DMN (e.g., voxel-wise functional connectivity) is needed to draw out information relevant to predicting outcome. Nonetheless, our results suggest that it may be more useful to examine the predictive value of connectivity across multiple resting-state networks. Future research should incorporate these resting-state networks with additional networks (e.g., the salience network [23]), compute connections within networks and structures [9, 28] known to be associated with supporting consciousness (e.g., the ascending arousal network [22]) to better understand the role these different networks play in supporting neurologic recovery..

This study has a heterogeneous patient population with variable time of scanning, which should be considered as novel and important strengths. The results suggest that the timing of ICU stay should not preclude the need for an rs-fMRI scan and that the prognostic utility of this method extends beyond the acute phase of severe brain injury. While only 12% of the study population was chronically critically ill, the results predicted the correct outcome for these patients, suggesting that future work should include and further explore using rs-fMRI for patients with extended ICU stays. Moreover, the varied sample in this study reflects the practical reality of heterogeneous brain disorders in the ICU. Given that previous rs-fMRI studies have almost exclusively focused on anoxic and traumatic brain injured patients [5, 8–10, 29], this study mirrors a more realistic sample of aetiologies that are seen in the ICU. Future work should investigate the utility of rs-fMRI for other severe brain injuries, such as stroke, hemorrhage, status epilepticus, encephalitis, and metabolic encephalopathies [30].

Importantly, these results demonstrate that rs-fMRI can be obtained with a 1.5 T scanner and are clinically useful at this field strength, which increases the generalizability of these findings. Clinical protocols could include rs-fMRI sequences as they are easy to obtain relatively short and do not require any effort on the part of the patient. Unlike task-based paradigms [3, 4], the results do not depend on command driven brain activity which can be limited by fluctuating levels of consciousness and thus prone to false negatives [31]. While most MRI scanners can perform functional sequences, they rarely come as ‘standard’ and technical expertise is required to analyze and interpret rs-fMRI data. Ultimately, standardized acquisition and analysis will be required to implement these methods across hospitals.

Identifying markers for good functional recovery in acutely unresponsive patients is of paramount importance, because discussions surrounding the continuation or removal of life-sustaining therapies occur in a short time window following the patient becoming unresponsive. Currently, the functional outcome for many ICU patients remains uncertain, and both clinicians and families struggle with whether to maintain or discontinue support. The results of surveys of intensivists, neurosurgeons, and neurologists highlight this issue, finding significant uncertainty concerning prognosis in severe traumatic brain injury, what constitutes good functional recovery, as well as considerable variability in how and whether recommendations to withdraw life-sustaining therapies are made [14, 32]. Our results indicate that quantifying and classifying the presence of rs-fMRI networks can provide useful information to aid in prognostication, which may affect the outcome of these discussions.

Limitations

This study was completed at a single center, and the number of patients included is relatively small, which decreases the generalizability and limits external validity. Furthermore, machine learning can be misleading in smaller samples due to the potential for overtraining [12, 13, 33]. However, the accuracy is in line with similar studies [7–9], and several precautionary steps were taken (e.g., permutation testing, validation against clinical information) to reveal potential biases that could have inflated accuracy. However, large multi-center studies are needed to elucidate the reproducibility of these results and to determine the true prognostic utility of rs-fMRI. The Coma Recovery Scale-Revised was not used to assess for level of consciousness in this patient cohort. Indeed, the use of the CRS-R score would enable stronger conclusions to be drawn from the prognostic value of neural data. For example, while the preservation of visual networks could not be explained by GCS-E scores, they may be explained by CRS-R measures of visual tracking. While the CRS-R is recommended for use with patients with chronic consciousness disorders, it is time-consuming and often difficult to administer in the ICU [34, 35]. Therefore, the GCS score was used to document the patient’s level of consciousness at the time of study enrollment and imaging, but future work should consider the added value of

using CRS-R for bedside measures of conscious awareness. Finally, while our approach obtained high sensitivity and specificity driven by visual and frontoparietal networks, prediction was not perfect. For example, not all patients with preserved visual and frontoparietal networks will recover and not all patients without them will have a poor outcome. Misprediction is meaningful in that it exposes limitations in the exclusive use of rs-fMRI for prognostication. Future work can incorporate other prognostically relevant tools, including blood biomarkers, clinical information, and task-based neuroimaging [36].

Conclusion

In conclusion, machine learning and rs-fMRI can be utilized to provide accurate individualized assessments for neurological outcome from a diverse population of critically brain injured patients. Our results suggest that the preservation of functional networks may serve as a biomarker for good functional recovery after sustaining a severe brain injury. Although promising, more work is required to elucidate the utility of rs-fMRI for providing clinicians with timely prognostic information about the prospect of recovery which may aid with decisions regarding the continuation of care and the withdrawal of life-sustaining measures.

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Data availability The codes used to analyze the data from this study is available at https://github.com/TheOwenLab/Acute-Resting-State. The deidentified fMRI data can be made available from the corresponding author, upon reasonable request.

Declarations

Conflicts of interest The authors declare no conflicts of interest.

Ethical standard The study was conducted according to the guidelines of the Declaration of Helsinki of 1964 and later amendments, and approved by the Health Sciences Research Ethics Board of Western University.

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