Serial multimodal functional brain network evaluation in children with acute disorders of consciousness, covert consciousness, and brain death: a novel demonstrative case series

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Abbreviations:

acute brain injury (ABI)

Brain death (BD)

blood oxygen level dependent fMRI signal (BOLD)

brain death (BD)

brainstem auditory evoked responses (BAER)
blood oxygen dependent signal (BOLD)
Cognitive motor disassociation (CMS)
continuous video EEG (vEEG)
cerebral perfusion pressure (CPP)
default mode network (DMN),
disorders of consciousness (DOC)
drug resistant epilepsy (DRE)
electrocerebral silence (silence)
electroencephalogram (EEG)
epileptiform activity (Epil)
frequency (freq)
functional MRI (fMRI)
head of bed angle from horizontal (HOB)
hypoxic ischemic insult/encephalopathy (HI)
increased (inc)
language (lng)
locked-in syndrome (LIS)
minimal activity (min)
minimally conscious (MC)
multimodal brain network evaluations (MBNE)
neurovascular unit (NVU)
pathological connectivity (PC)
Pneumothorax (PTX)
resting state fMRI (rs-fMRI)
rs-fMRI generated cortical networks (RSN)
somatosensory evoked responses (SSEP)
task-based functional MRI (tb-fMRI)
transcranial motor stimulation motor evoked potentials (TCeMEP)
unresponsiveness wakefulness (UWS)
visual evoked responses (VEP)
withdrawal of life-sustaining therapies (WLST)

ABSTRACT

Background: Although disorders of consciousness (DOC) are common manifestations after acute brain injury (ABI) in the pediatric population, there are no definitions or consensus reports regarding disorders in neonatal, pre-language children or older pediatric patients. Adult guidelines support multimodal brain network evaluations (MBNE) by functional MRI (fMRI) and EEG to diagnose DOC and covert consciousness. However, the utility in children is unknown. The feasibility and application of serial MBNE to characterize DOC in children with ABI will be discussed using illustrative case studies.

Methods: MBNE was performed without sedating medications in three pediatric patients, who were hospitalized in the Phoenix Children's Hospital pediatric ICU between April 2017 and August 2021, (2 months, 6 and 11 years of age), with ABI-DOC and outcomes described. Diagnostic studies were integrated into clinical care, including continuous video electroencephalogram, visual/somatosensory/brainstem-auditory evoked responses, developmentally appropriate active and passive task-based functional MRI (tb-fMRI), and resting state fMRI (rs-fMRI). Tb-fMRI included passive movements of the hand, passive checkerboard visual stimulation, active command to imagine moving the arm, command to move the arm, move the leg, repeat words (subvocalize), and listen for animal words in lists of common words.

Results: Initial (patient 1, 2, and 3 on day 2, 19, 4) and repeat (patient 1 and 2 on day 10, 254) MBNE were performed. Initial clinical examinations included observed unarousable unconsciousness in all children. In patient 1, repeat MBNE reflected covert consciousness after treatment with antiseizure medication (day 6-10) of pathological rs-fMRI signals suggesting epileptogenicity in deep brain locations, not seen on EEG. His subsequent improvement was first detected by MBNE, then present on clinical exams later demonstrating regained consciousness, with the capacity for facial communication despite quadriplegia. Withdrawal of life sustaining therapies (WLST) was presented as a care option prior to, but not after, detection of covert consciousness in the acute period. In patient 2, MBNE showed potential for return of consciousness via intact whole brain resting state networks and abnormal rs-fMRI signal, which were treated with antiseizure medication. He had delayed repeat testing due to lack of standardized protocol at that time. He gradually recovered to full consciousness over 63 days, and near complete physical and cognitive recovery over one year, with commensurate rs-fMRI resolution of abnormal signals. WLST was considered amongst care providers, with unclear MBNE influence on the group of providers, though ultimately no formal discussion occurred with the family despite prolonged suppression of consciousness. Patient 3, the youngest, , who had no detectable networks, thus no network evidence of covert consciousness or potential for consciousness by MBNE, a day prior to succumbing to brain death. WLST was discussed with infant's family early in the course prior to and after consistent and poor rs-fMRI results.

Conclusions: Determinations to escalate therapy and continue supportive care were influenced by MBNE. Serial MBNE in children with ABI-DOC is a feasible diagnostic strategy. Potential benefits include more precise DOC endotyping, increased therapeutic options, outcome predictions and more rational withdrawal of support. Discussion of these critical care pathways will facilitate standardization of care among pediatric neurointensivists.

INTRODUCTION

Of the approximately 90,000 pediatric ICU admissions per year in the PANGAEA study, 16.2% have acute brain injury (ABI) with 56% morbidity and 12% mortality.¹ Twenty-five percent of the deaths were withdrawal of life sustaining therapy (WLST) due to poor neurological status, compared to 11% of deaths due to cardiovascular causes.¹ In adult trauma and hypoxic ABI, 50% of WLST occur ≤ 3 days after injury when examination criteria are unstable and not reliable², and 16% of WLST are thought to have had potential for functional recovery, respectively. Though undefined, this is similarly suspected in pediatrics.³ Critically, detection of potential for good neurological outcomes in ABI-WLST candidates with hinges on accurate disorder of consciousness (DOC) diagnosis.^{4, 5}

Unfortunately, the link between pediatric DOC and outcomes is poorly understood due to developmental immaturity, pathological dysmaturity, neuroplasticity, gene-environmental interactions⁶⁻¹⁶, and largely undefined early pediatric DOC, compared to adults.⁵ Consequentially, there is a lack of well validated standardized pediatric DOC exam assessments, with only one study including down to one year of age,¹⁷ leading to extension of largely teenage and adult data in clinical application,^{4, 5} resulting in poorly accurate pediatric DOC classification.^{5, 18} Thus, no clear guidelines regarding early pediatric DOC classifications have yet been suggested. Furthermore, even with clear DOC definitions and validated bedside exam in adults, DOC misdiagnosis is 40%, and prediction accuracy of recovery is only 60-80% in unarousable unconsciousness, and the exam offers no potential for detection of covert consciousness. All pointing to the need for advanced DOC biomarkers above bedside exam alone in children and adults.^{4, 5, 19}

DOC care guidelines suggest novel diagnostic pathways applying state-of-the-art technology such as multi-modal neuroimaging may increase patient-specific accuracy in children.¹⁸ Advances include novel structural/functional brain connectivity biomarkers, such as resting state and task-generated MRI (rs-fMRI, tb-fMRI) and EEG signatures²⁰. For older children and adults, these biomarkers represent functional brain neural circuitry which expands DOC classification (operationally defined herein from adult subacute/chronic DOC criteria⁵) to consider covert states of consciousness.²¹⁻²⁵ However, the optimal timing and validated accuracy of biomarker applications are presently unknown for unknown for all ages.

In considering advance biomarkers for consciousness endotyping in pediatrics, robust diagnostic application relative to normative network development is critical. As such, it is important to note that rs-fMRI networks (RSN) are well detectable by the 2nd trimester. And, normative, developmental, longitudinal and repeat-measures of infant rs-fMRI whole-brain connectivity yield reliable results.²⁶⁻²⁸ In pre-verbal children, rs-fMRI yields reliable network patterns of maturation, predictive of further network maturation in association with developmental outcomes.^{12, 13, 15, 16, 29-58} This approach is diagnostic in pediatrics with and without **milder acute** insults, such as prematurity^{50, 53} or concussion⁵⁹, and in the general pediatric drug resistant epilepsy (DRE) for RSN⁶⁰ and seizure onset zone (SOZ) localization validated against intracranial EEG and surgical outcomes⁶¹⁻⁶³. Validation in these other developmental pathologies increases confidence in application of this in higher stakes severe ABI.

However, there are only a few reported applications of these advanced markers in **severe** ABI of the developing brain. In neonates only two studies evaluate **severe ABI**. One found association between RSN and motor outcomes.⁶⁴ The other evaluated RSN in relation to acute neurological factors (exam, injury severity, and consciousness), outcomes (mortality, development delay, and seizures), and compared RSN to other diagnostics (anatomical MRI, MR spectroscopy, and EEG).⁶⁵ Association was found between the RSN and exam and outcomes, performing comparably or better to other diagnostics. In children with severe ABI, there are two single case reports implicating potential detection of covert consciousness and a DOC treatment opportunity, and one case series poster

finding outcome prediction capacity.⁶⁶⁻⁶⁸ Thus, there are no well validated brain network DOC biomarkers in the severe ABI pediatric population. And, the ultimate ground truth validation of RSN in ABI-DOC, brain death (BD), expected to demonstrate the poorest connectivity⁶⁹⁻⁷⁵, is only reported in an adult case-control study.⁷⁶

Thus, since the optimal tests, timing, and diagnoses for advanced DOC biomarker application are unknown in pediatrics, we present a selected pediatric case series with acute ABI-DOC. We modified the DOC guidelines for developmental level and highlight difference in biomarker impact when applied serially during the early acute period. Through this multimodal brain network evaluation (MBNE) four primary aim areas are assessed: (1) acute period DOC endotyping, (2) neuroprognostication, (3) impact in WLST and BD, and (4) revelation of interventional opportunities. We propose that serial MBNE in pediatric acute DOC may decrease diagnostic errors, and deliver more informed diagnosis, prognosis, and treatment.

METHODS

This report was determined to be a clinical case series of three patients and not human subject research by the Phoenix Children's Hospital IRB, and the families provided approval. Cases were selected with acute coma and findings demonstrative of brain network biomarker potential, who received some of the advanced tests within EAN¹⁸ and AAN³ guidelines.²⁴ The first rs-fMRI performed in 2018 in the pediatric ICU informed clinical practice to consider a broader multimodal and serial application of the testing (patient 2). Of these biomarkers, those clinically available in the Phoenix Children's Hospital ICUs since June 2017, were aggregated into a coma test panel in 2021, intending to standardize clinical approach. The aim was to provide developmentally appropriate acute DOC endotyping to identify patients with preserved neural networks who were unable to normally volitionally respond by exam. The decision to perform these tests and use the results on clinical grounds was made in consultation with the intensivists, with the intention of using the tests to direct management. The fMRI testing in these cases was performed in those determined to be safe for transport and MRI scan, without sedation, following acute DOC onset, as described in **Tables 1 - 3** between April 2018 and April 2021.

The MBNE included patient-tailored application of passive-resting state fMRI (rs-fMRI), continuous video EEG (vEEG), passive-activation (visual evoked responses (VEP), somatosensory evoked responses (SSEP), brainstem auditory evoked responses (BAER), selective passive task based fMRI (tb-fMRI; such as examiner moving the patient's hand), vEEG reactivity to environmental stimulation), and volitional-activated brain network tb-fMRI tests (e.g. asking the patient to repeat words)).

ICU MRI Safety and Anesthesia: The patients were required to be stable for transport to the scanner. Although the selected patients were not receiving sedation during the MRI scan, some pediatric DOC cases may be candidates for the passive-task fMRI and rs-fMRI, despite need for light conscious sedation. Routinely, at PCH, non-ABI patients receive 80-100 mcg/kg/min of propofol during passive task-fMRI and rs-fMRI. Of these, about 1 in 50-80 have lower than expected RSN detection, suspected primarily to larger sedative induction bolus or higher infusion rate titrated by pediatric anesthesiologist to maintain low patient motion, and idiosyncratic sedation effects, with no safety incidences since 2011. However, the BOLD signal reduction from light sedatives in pediatric severe ABI is unknown, and may comparatively reduce detection of true network capacity, leading to greater false negatives. Until better understanding of sedative effect is obtained, if pre-MRI trial of sedative temporary discontinuation fails, then only robust RSN detection with concurrent sedatives may yield helpful information.

EEG and fMRI: EEG-based assessments, tb-fMRI and rs-fMRI sequences parameters, equipment, analysis, and interpretation procedures were performed as reported in our prior work,^{61, 63, 77} with exceptions to the task-based tb-fMRI procedures described below. The rs-fMRI was analyzed in a data-driven whole-brain manner (independent component analysis; ICA) to create the whole brain network profile, as demonstrated in a recent meta-analysis to demonstrate ability to localize seizure onset zones in adults and children.⁷⁸

Tb-fMRI Paradigm: The DOC-arousal protocol was initiated by stating the patient's first name preceding all paradigm and scanner-related instructions and motor commands, using the patient's primary spoken language⁷⁹. Developmentally-tailored tasks adapted from prior work in adults⁸⁰ were implemented. Patients with no history of following commands are not candidates for active task-based command following fMRI. however passive stimuli, such as flashing lights, are still applicable. Instructions and verbal stimuli were delivered using the most frequently spoken language (English). Auditory stimuli and instructions were presented through MR-compatible headphones. Visual stimuli were projected onto a mirror mounted on the head coil, with eyelids taped open by staff during this scan.

Tb-fMRI Sequence and Analysis: SensaVue fMRI equipment (Invivo Corporation, Gainesville, FL, USA) delivered 4.25 minutes, 8 blocks and one task per sequence, 15 seconds of baseline scan discarded, 15s rest, 15s task; TR 3000 msec, TE 35, matrix size 128x128, flip angle 90, slice thickness 4mm, 1.8 x 1.8 x 4 mm voxel, in-plane FOV 230 x 230mm, and ≥ 35 slices, adjusted to patient head size. The tb-fMRI were visually inspected for expected specific recorded real-time network activation at the scanner to account for within-sequence differences associated with inconsistency in activation during different blocks of the same task. Further, offline analysis found activation was within expected limits of signal detection for interpretation.

Offline analysis occurred via SPM12 pipeline consisting of slice-timing correction, realignment, co-registration to patient T1, and spatial smoothing over 8 mm gaussian kernel. First level analysis was performed using a GLM to subtract baseline BOLD signal from task/stimulus period BOLD signal with realignment parameters entered as a regressor. Contrasts were thresholded at $p < 0.005$ (uncorrected), cluster size was thresholded at > 10 voxels.

Tb-fMRI requires 15-30 minutes, depending on the number of tasks performed. The staff training requirements are above those provided in MRI technician training. At PCH, in patient 1, the tb-fMRI was performed by a cognitive neuroscientist and research psychologist with extensive experience in designing and performing tb-fMRI language tasks in children and adults (BLS), under the supervision of the attending neurologist with fMRI expertise (VLB). The order of tasks was selected to place the most cognitively challenging task first to minimize fatigue.

Passive visual stimulation and finger tapping, active arm motor command, with at least one language-related task was delivered in each session. Other tasks were completed as appropriate for the patient. Children unable to follow commands at baseline are not thought to be candidates for active task-fMRI, but passive tasks may still be clinically applicable.^{81, 82} In the first session, additional tasks included leg movement command and subvocalization. In the second session, additional tasks included leg movement command, motor imagery (arm movement), active listening for animal-words in lists of words, and subvocalization.

Table 1. Developmentally tailored DOC tb-fMRI paradigms, network domains, and description.

No.	Network Domain	Passive /Active	Details
1	Visual	P	A moving checkerboard with a red fixation cross was presented during the task active portion, blank grey screen with a red fixation cross was presented during the rest. Before the sequence, patients were instructed to watch the screen. (SensaVue standard)
2	Sensory motor	P	The patients' fingers were moved in a tapping motion by staff during the task active portion. No movement was performed during the rest portion. (Adapted SensaVue standard)
3	Motor arm	A	Patient instructed, "Patient first name, move your arms" during task portion, then told to rest during rest portion.
4	Motor leg	A	Patient instructed, "Patient first name, move your legs" during task portion then told to rest during rest portion.
5	Language reception	A	Active word listening of common animal words: patients were told that they would be listening to sets of words and to listen for the animal words.
6	Language, motor arm, memory	A	Imagine Movement action-rest – arm: patients were instructed before the scan to imagine moving their arm when they heard 'action' and to stop when they heard 'rest'.
7	Language, motor face, memory	A	Subvocalization: patients were presented spoken words and told to repeat each word in their head after they heard it.

FDA-approved sequences are denoted by SensaVue standard or adapted as described, while remaining sequences were without FDA evaluation. Abbreviations: A active, P passive.

RESULTS

Patient 1: A 6-year-old full-term normally developing male, low risk-pregnancy, and no family history of neurological/psychiatric disorders, who was a passenger in a motor vehicle accident, with resultant severe traumatic brain injury (right medulla contusion, diffuse axonal injury including the right splenium of the corpus callosum, bilateral frontal lobes, right centrum semiovale, and left basal ganglia), atlanto-occipital dislocation, and C1-level spinal cord and medullary brainstem lesion with hemorrhage (Figure 1, A1).

Patient 2: An 11-year-old full-term normally developing male, low risk-pregnancy, with family history of death of brother (same parents) secondary to neuroblastoma, in advanced school classes without assistance, and no family history of neurological/psychiatric disorders, who had acute DOC with loss of brainstem reflexes contemporaneous with spontaneous ruptured cerebellar vermian arteriovenous malformation and posterior fossa hemorrhage, brainstem compression, and cardiac rhythm instability. He received emergent posterior craniectomy.

Patient 3: A two-month-old male born at early-term 37 weeks' diamniotic gestation, with high-risk multiple gestation (twin)paternal history of depression. He was reported to be in good health until he was found apneic and unresponsive in prone position after being fed and placed his side for sleep. A family member delivered cardio-pulmonary resuscitation (CPR) until emergency medical services arrived. He was determined to be asystolic, with restitution of cardiac activity after two dosages of epinephrine after 10 minutes. The coroner's autopsy cited undetermined cause of death, potentially asphyxiating sleep environment.

Table 2. Clinical course, team impression, and resulting determinations

Day	Exam(E)/other results	Clinical Impression	Intervention/Tests determined
Patient 1			
0-2	E*: flaccid and unresponsive, with only pupillary constriction to light.**	Coma; injury severity traditionally considered fatal.	WLST considered by team, but life-sustaining measures continued as parents were initially hospitalized. Team decided to perform MBNE
2-5	TCD: no vasospasm;	Coma; continued lack of significant improvement	D2 poor MBNE results and consequent WLST and antiseizure medication treatment options discussed with family
6-10	E: no significant change	Coma; Team convening d2-5 on RS concerning for possibly unidentified seizure focus (Fig 1, A2-3). ^{61, 63, 66}	Team and family determine to give anti-seizure medication (phenobarbital 20, 10, 10, 5, 5 mg/kg/day respectively d6-10)
10	E: No significant change with phenobarbital	Coma; Determined need for repeat testing	MBNE Table 3
10	MBNE significant: Task-fMRI – following commands; Rs-fMRI resolved seizure network	Team agreeing on diagnosis of covert consciousness and determination to communicate this with family	Family informed he is in covert consciousness and waiting with life sustaining therapies and inventions for further recovery reasonable to team and family, but unknown if he would improve on exam.
12-20	E: changed from unresponsive to slow-intermittently-responsive-to-command by deconjugate vertical eye movements, while requiring examiner to hold open eyelids.	UWS ^T to MC by exam, but likely actually better consciousness given tb-fMRI	Planned for d20 occipital-cervical fusion
72-74	E: reduced responsiveness to eye movement commands; EEG depressed activity compared to prior; MRI with severe acute hydrocephalus with new brainstem herniation	Coma to UWS; Hydrocephalus determined	Emergent EVD
75-90	E: continued ventilator dependent and quadriplegic, but trended toward improvement with beginning to mouth words over breath ventilator, eyebrow raise and grimace/smile to command, and small shoulder shrug to command	Conscious	Transfer to inpatient rehabilitation
6 months	E. Eye tracking to play electronic device games, though found not reliable for formal testing. Thus, test format: yes (eyebrow raise)/no (grimace). Average for age: receptive language (single word receptive vocabulary, ability to follow two-step commands), and verbal memory; Intact: orientation, attention, basic visuo-perceptual skills, and simple problem-solving. Below age average: visual reasoning skills. Other higher-level cognitive skills were not assessable given motor-impacting communication limitations.	Conscious with generally good recovery. However, higher complex cognitive capacity, though not tested, is suspected to be impacted to an unknown degree by the TBI.	Discharged to home
Patient 2			
0	E: sluggish pupils, flaccid, unresponsive; CT posterior fossa hemorrhage with mass effect on brainstem	Coma	Posterior craniectomy
1-7	MRI: right cerebellum, midbrain, and tectum isolated infarctions. TCD Serially: initially showed vasospasm, resolved < 7 d;	Serious injury; indeterminate outcome prediction	Anti-vasospasm medication < 7d

0-19	E: Suppressed consciousness, multiple examiners with improving or more severe exam findings even with the same examiner over time ; Movements initially interpreted as consistent with responsiveness but later assessed as indeterminate and possibly subcortical such as repetitive facial frowning.	Coma to MC; unknown degree of reversibility and potential lack of significant recovery, WLST discussed among team members	Given lack of robust recovery, D19 MBNE determined by team to be conducted
19-31	E: lack of significant improvement	Coma to MC; epileptogenic network broadly over fronto-temporal, opercular, thalamic, and brainstem areas with fast-erratic activity (Figure 1, B2-3). ⁶⁶	Results of intact RSN and abnormal rs-fMRI SOZ-like signal discussed with family. Team and family opt to give phenobarbital load; then then scheduled Kepra (20 mg/kg/day) thereafter
31-63	E: Trending toward improvement, but with continued inconsistency across examiners exams and times until d63	Conscious by day 63 on ALL examiner's documentation consistently	Transfer to inpatient rehabilitation
64-12 mo	E: Gradual recovery of brainstem functions to very mild residual dysarthria, proprioceptive and coordination deficits nearly completely resolved, independent in ADLS and ambulation.	Recovery, gradual, with very mild deficits	Discharged to home; 1:1 support at school for safety and carrying backpack
254+	E: Advanced age-appropriate classes in high school, physical education without assistance. Patient recalls being aware of details such as the presence of his father in the evening in the ICU when the room sunlight decreased.	Excellent recovery. Possible prior covert consciousness	MBNE for planned aneurysmal treatment evaluation
Patient 3			
0	E: fixed and dilated pupils, agonal respirations, no purposeful movement.	Coma	thoracocentesis and chest tube PTX; Neuroprotective measures/goals: CPP>55, ICP< 0, HOB 30°, glucose 100-160, Na>40, Mg>2, Hgb >8, PCO2 38-40 mmHg, PO2≈100, T 36.0-37.0°C, Tolerated wean off vasoactive medications within 24 hours.
1	E: seizure versus nonepileptic paroxysmal movements of the right upper extremity with wrist extension and index finger pointing possibly with stimulation, otherwise unchanged exam.	Coma vs UWS	Anatomical MRI
3	MRI: extensive artifact and inconclusive extent of injury.	Given the movements, equivocal imaging, and ongoing breathing pattern, need more information	Team and family decide to perform D4 rs-fMRI with repeat anatomical MRI
4	Rs-fMRI: no detected networks (Figure 2-3, Supplementary Fig 1). Anatomical MRI: bilateral extensive infarction; EEG: low amplitude; E: arm movements ceased.	Confirmatory and consistent test results indicating poor outcome	Family informed of no reasonable hope of recovery. Discussed with family options of WLST verses anticipated unlikely improvement.
5	E: agonal breathing ceased; formal brain death testing by two expert exams on day 5. EEG: electrocerebral silence	BD due to HIE; Rs-fMRI possibly predictive of BD; Cause evaluation in Supplementary Material.	

BLUE text indicative of unique impact by fMRI; GREEN text indicative of fMRI consistency with other tests additive information considered in care determinations. *No significant change in exam unless specified; **Occasional extremely slow eye movement, deconjugate, unclear if to command or random, as not reproducible, and command repeated many times before eye movement change; ^T Although less than 30 days, and case 2 age not in formal DOC definitions, author using MC/UWS terms for brevity of team impression of degree of responsiveness. BD – brain death; CPP cerebral perfusion pressure; HOB-head of bed angle; MC – minimally conscious; PTX – pneumothorax; UWS – unresponsive wakefulness

Table 3. Serial Multimodal Cerebral Functional Testing

CASE #	Function	Test Comment	EEG		Tb-fMRI		Rs-fMRI		Consistency	
			D2	D10	D2	D10	D2	D10	D2	D10
1	Sensory-Motor	SSEP, passive stim	-	-	-	-	-			
		Task based stim			-	+	-	+		
	Auditory/Lng	BAER	-	D72+	-	+	-	+		
	Vision	VEP	+	+	-	+	+	+	EEG/RS > task	
	Modulatory	Sleep Wake Cycle	+	-						
		State Changes	+	+						
		Reactivity	+							
		Background	+	+, R depr						
		Default mode					-	+	EEG > RS	
	Epil/abn		-	-			+	-	RS > EEG	
			D1-6	D64			D19	D254	D1-6, D19	D48, D254
2	Sensory-Motor	SSEP		+			+	+		
		TCeMEP		+						
		CNVII EMG		+						
	Auditory/Lng	BAER					+	+		
	Vision	VEP					+	+		
	Modulatory	Sleep spindle	+							
		State Changes								
		Reactivity	min							
		Background	delta							
		Default mode					+	+(incr freq)		
	Epil/abn		-				+	-	RS > EEG	
			D1-4	D4	D5					
3	Sensory-Motor	SSEP								
		TCeMEP								
		CNVII EMG								
	Auditory/Lng	BAER								
	Vision	VEP								
	Modulatory	Sleep spindle	-		-					
		State Changes	-		-					
		Reactivity	-		-					
		Background	Low amp		silence					
		Default mode		-						
	Epil/abn		-		-					

+ present, - tested and absent, blank cell test not performed, +/- denotes different values of present/not detected (for example) by right and left hemisphere respectively, *abn* abnormal to epileptiform activity by rs-fMRI, *BAER* brainstem auditory evoked response, *CN* cranial nerve, *D* day, *Default mode* (network) by rs-fMRI, *delta* slow delta frequency, *EEG* electroencephalogram, *EMG* electromyogram, *Epil* epileptiform activity, *freq* frequency of blood oxygen dependent fMRI signal, *Lng* language, *min* minimal activity, *incr* increased, *rs-fMRI* resting state functional MRI, *silence* meaning electrocerebral silence, *SSEP* somatosensory evoked potential, *tb-*

Impressions and Plans

Initial (patient 1, 2, and 3 on day 2, 19, 4) and repeat (patient 1 and 2 on day 10, 254) MBNE were performed. Initial clinical examinations included observed unarousable unconsciousness in all children.

In patient 1, repeat MBNE reflected covert consciousness after treatment with antiseizure medication (day 6-10) of pathological rs-fMRI signals suggesting epileptogenicity in deep brain locations, not seen on EEG. His subsequent improvement was first detected by MBNE, then present on clinical exams later demonstrating regained consciousness, with the capacity for facial communication despite quadriplegia. Withdrawal of life sustaining therapies (WLST) was presented as a care option prior to, but not after, detection of covert consciousness in the acute period.

In patient 2, MBNE showed potential for return of consciousness via intact whole brain resting state networks and abnormal rs-fMRI signal, which were treated with antiseizure medication. Change in exam after antiseizure medication was more equivocal, as only change in eye opening pattern was 10 days later, and clear command following 17 days later. Unfortunately, check for early network improvement to treatment by repeat MBNE, as in patient 1 did not occur, due to lack of standardized protocol at that time. He gradually recovered to full consciousness over approximately 63 days. Noting at D50 he possibly followed his first clear command, whereas other prior movements (hand grip, facial grimace, tongue movements) initially thought to be in response to command were later doubted by some providers as more likely due to stereotypical nature and observed response to environment noise or passive movement or touch of limbs (see supplemental material for day by day exam and medications, especially physical medicine and rehabilitation physician note on day 26). He had near complete physical (independent in activities of daily living) and cognitive recovery over one year (is now back in honors age-level classes), with commensurate rs-fMRI resolution of abnormal signals. WLST was considered amongst care providers, with unclear MBNE influence on the group of providers (as a whole). Though ultimately no formal WLST documented discussion occurred with the family despite prolonged suppression of consciousness. MBNE results were discussed with family and the intact networks were thought to be a sign of possible recovery beyond what might have been expected otherwise by the anatomical MRI and current state of recovery.

Patient 3, who had no detectable networks, thus no network evidence of covert consciousness or potential for consciousness by MBNE, a day prior to succumbing to brain death. WLST was discussed with infant's family early in the course prior to and after consistent and poor rs-fMRI results.

DISCUSSION

This novel case series demonstrates serial MBNE is feasible and results changed clinical care. The findings have implications for (1) acute period DOC endotyping beyond the clinical exam, (2) severe ABI developmental network determinates of recovery from DOC, (3) WLST determinations supported by the case with BD, and (3) novel interventions to promote recovery from DOC.

In summary, we present extreme contrasting cases at opposite ends of ABI severity spectrum detected by fMRI. In doing so, we describe the first reported case of a child with covert consciousness identified during acute DOC and the first pediatric patient with fMRI findings prior to brain death. These extremes were commensurate with connectivity severity and outcome. We also affirm our previously reported,⁶⁶ possibly treatable, biomarker of epileptogenesis in acute ABI-DOC detected by rs-fMRI. Lastly, we demonstrate that serial

early application of MBNE in pediatric ABI-DOC may allow early visualization of treatment effect, predictive of outcome.

Rs and task fMRI findings benefit four MBNE Aims

Tb-fMRI detected *covert consciousness in a six-year-old child with ABI-DOC and is expected to perform similarly in children who can follow auditory commands without cue*. Active task paradigms are the highest marker of preserved consciousness because they require contemporaneous active listening and comprehension. Specialized brain network activation is preserved which subserves interpretation of instructions and formulation of responses immediately on command. As seen in Patient 1, each of the five different active commands had 8 repetitions resulting in statistically significant activation in expected respective brain network regions. For example, the arm motor network activated when told to move the arm, as well as the language network activated when told to repeat words. For a patient experiencing DOC by exam, it is extremely unlikely that such reproducible and network-specific results can be obtained by chance. Thus, these activation results indicate covert consciousness, which is not volitionally expressed or detectable by bedside exam due to ongoing efferent motor impairment.

Future real-time applications of active tb-fMRI by the neurointensivist with children with DOC may include assessment of the patient's emotional state and level of understanding regarding their condition, as well as other higher level comprehension tasks. This could be achieved through a structured questionnaire requiring yes/no responses, such as commanding them to move their arm for YES (motor network activation) or repeat the word No (language network activation), as first described by Owen et al.⁸⁰

Regarding prediction, task-induced *activation* above basal network activity requires a greater level of functional brain circuitry energy and coordination above and beyond what is needed for standard rs-vEEG or rs-fMRI. Thus, passive and active tb-fMRI network activation represents complex integration of supporting networks to provide coordinated energy and intact signaling in real time. These responses may be predictive of recovery and outcome during acute pediatric DOC, as in our patient 1.

In contradistinction to the other MBNE tests, rs-fMRI is akin to observing a pulse oximetry reading of the entire brain's networks. As such, each network's degree of normalcy of spatial and oxygen-oscillation patterns stratify both the related functional capacities (e.g. language, cognition, consciousness) and coordinate neuronal brain function. This may in turn be *predictive* of the potential of inter-connected related networks to recover, as experienced by patient 1 and 2, or not recover, as in patient 3.

In addition to the detection of the major preserved networks, rs-fMRI also detects *abnormal connectivity which may block or interfere with other regional efferent activity expression*. Importantly, these abnormal findings nonetheless may reflect a biomarker that potentially can detect a **reversible and possibly treatable** condition showing network improvements possibly responding to treatments over serial measurements. This was demonstrated by patient 1's normalization of blood oxygen level dependent fMRI signal (BOLD) and clinical improvement, despite negative results by other tests that were insensitive to the child's intact network functions.

Surface routine EEG or vEEG studies cannot depict epileptiform activities within the neuroaxis beyond the ability of scalp electrodes to detect. As assessed for patient 1 and 2, rs-fMRI signals are comparatively unhampered by spatial resolution. This property allows detection of either subcortical normal or pathological phenomenon. Compared with surface EEG recordings, rs-fMRI may help better localize injured regions that are not expressed by observable clinical signs,⁸³⁻⁸⁵ or be detectable by surface recording electrodes, given localization to deep brain locations⁸⁶ where injury may reside.⁸⁷

The novel abnormal neuronal signals found in the deep brain regions of patients 1 and 2 fit the criteria of rs-fMRI SOZ found in children with DRE, in that they were grey-matter centric but not in typical RSN or noise spatial or temporal distributions.⁶³ In DRE and patient one, the findings normalized after surgical targeting and antiseizure medication, respectively.^{61-63, 78, 88} These atypical rs-fMRI signals may represent **early epileptogenesis, which may not even be epileptiform yet**, within abnormal neural networks that could be potentially improved by treatments that suppress pathological neuronal over-excitation during ABI.^{66, 78}

Thus, rs-fMRI may differentiate treatable and transient conditions that respond to more effective neuroprotection before transitioning to an irreversible chronic condition, such as chronic DOC or epilepsy. The temporal improvement detected by both rs-fMRI and tb-fMRI networks was more profound and more tightly measured in time in patient 1 than patient 2.

Further, given lack of examination consensus among practitioners at the bedside for these children, serial use of MBNE in a timely fashion early during the disease process could guide the neurointensivist to use rs-fMRI to detect earlier pathologic changes that would be more responsive to more effective neuroprotective interventions. RSN normalization preceded exam improvement in patient 1 and points out the advantage of serial assessments to anticipate potential recovery.

More accurate classification of DOC using rs-fMRI whole-brain network patterns is supported by patient 2's report after his recovery of his memory of preserved consciousness while in the ICU, at which time intact resting state networks were documented. Patient 1's preserved task-fMRI findings after resolution of his apparent rs-SOZ after treatment adds another pediatric ABI-DOC classification category given his improved condition to covert consciousness.

Plausibility: Connectivity in Children with Brain Death Compared with Recovery

In contrast to the more favorable outcomes of patient 1 and 2, patient 3's lack of detectable RSN represent irreversible unconsciousness associated with permanent loss of brain function consistent with brain death (BD). Following a profound HI insult because of presumed accidental asphyxiation, patient 3 ultimately exhibited neurological exams, apnea tests, laboratory findings, MRI, EEG, and TCD results consistent with BD.

More specifically, his abnormal rs-fMRI the day prior to BD consisted of the absence of local or long-range network connectivity derived from data-driven whole brain connectivity. These severely abnormal findings accurately reflected his subsequent BD status, not confounded by factors that could impede rs-fMRI BOLD signal detection such as sedatives, low hemoglobin, altered ventilation, cardiovascular effects, or tested metabolic/genetic disorders.

Clinical applications of rs-fMRI across the range of DOC categories from recovery to BD are supported by patient 3's findings. The age of insult and resulting whole brain network profile post-ABI-DOC in survivors and outcomes may reveal age-dependent nuances to outcomes, perhaps even more so that initial blunt mechanism of injury. Principles of developmental neuroplasticity include critical/sensitive periods during the first thousand days defined as from conception to 2 years of age. During this early part of the lifespan, eighty percent of brain development has been achieved, resulting in permanent brain connectivities throughout childhood into adulthood. Subsequent diseases or adverse conditions can further alter brain circuitry affecting quality of life and outcome¹⁰³.

Thus, this diagnostic biomarker will be particularly applicable when assessing the complex DOC endotype (characterization of consciousness capacity by advanced biomarkers) of prematurity and neonatal ABI, combining gene-environment interactions across pregnancy and into the premorbid postnatal life prior to DOC.^{12, 13, 15, 16, 29-58, 65} Developmental and

destructive processes are expressed by this complex DOC endotype, which conventionally are often applied less specifically to the term encephalopathy of prematurity.⁸⁹

These concepts need to be applied to serial DOC assessments at the time of acute illnesses to accurately predict reversibility or permanence, especially given the potential for secondary injury mechanisms, as in patient 1, who developed secondary hydrocephalus. For adults and teenagers, rs-fMRI appears to discriminate along the BD to recovery DOC continuum that is consistent with bedside exams, and improves outcome prediction.^{3, 76, 90-94}

For neonates and infants, rs-fMRI also potentially improves the clinical correlation, given the immature child's more limited neurological exam repertoire to better predict outcome from acute brain insults.^{12, 13, 15, 16, 29-58, 65} Trimester-specific gene-environment interactions followed by postnatal diseases and adverse conditions during neonatal and infancy periods will be incorporated into the clinical correlation of abnormal rs-fMRI results. Neurological examination findings elicited at the bedside are dependent on brain maturity and the decision to withdraw life-sustaining therapy is challenging.

Determination the minimal level of brain network function to predict meaningful neurological recovery is not yet determined by any modality for all ages.^{3, 95-97} Brain network function requires viable neuronal connectivity. Even in patients with BD more immediate necrotic cell death has not yet occurred for 32-66% of the brain tissue.^{98, 99} Neuronal viability may be preserved despite risks for delayed apoptotic and autophagic programmed cell death. Preserved brain function in an adult BD case presented by Boly et al,⁷⁶ illustrates how there may be preserved local connectivity in the posterior cingulate, without long-range connectivity in the default mode network (DMN). Also, supportively, in adults with acute through chronic phases of brain injury from anoxia, trauma, and cardiac arrest, connectivity in the regions associated with the DMN was predictive of recovery of consciousness.^{90, 92, 100, 101}

However, in considering DMN-centric evaluation in early age pediatric ABI, one important distinction is that long-range connectivity is undergoing significant maturational changes during this time period^{102, 103}, and whole brain connectivity, rather than a specific region to region connection, is more reliable.^{26, 28} Thus, a data-driven whole brain approach may be best in infants and young children undergoing ABI-DOC connectivity evaluation. Such a whole-brain network pattern evaluation in the very young is thus more likely to avoid falsely negative results anticipated since selective short and long-range connectivity has not yet been completely developed in this age group which may be preserved.^{102, 103}

Therefore, a whole brain data-driven rs-fMRI analysis approach may be more applicable to the pediatric population. In patient 3, the whole brain approach allowed evaluation of all known network regions confirming severe progression of total cell death. Even regional connectivity was not detected, as confirmed by later documentation of total brain infarction on MRI and absence of anterograde blood flow by TCD. Since the rs-fMRI was obtained the day prior to when total brain infarction was visualized, and agonal breathing still occurring, such findings may be predictive of progression to BD.

As Shewmon et al,¹⁰⁴ reported, the minimum network activity for meaningful recovery may be determined using rs-fMRI DOC classification, justifying withdrawal of life-sustaining therapies. This network-centric approach may recalibrate the intensivist's intervention strategies involving clinical decisions for withdrawal of life-sustaining therapies (WLST) as well as prognostic discussions with families regarding survival with recovery potential (adult level B evidence).⁵ When considering pediatric-relevant network-based biomarkers during the acute phase after ABI, accurate WLST determinations are crucial. Further studies are warranted to determine the reliability of rs-fMRI during acute periods of brain injury in the pediatric population when compared with examination and other confirmatory studies before determining irreversible DOC and BD.

The diagnostic approach of the BD-DOC continuum after severe brain injury includes potentially treatable disorders. Cognitive motor disassociation (CMD), locked-in syndrome (LIS), and seizures all represent mimics of presumed irreversible unconsciousness.^{105, 106} These disorders can appear similarly unresponsive on exam. Given that 49% of adult DOC carry a misdiagnosis rate, higher percentages may exist during childhood given brain immaturity to express DOC.^{3, 95, 96, 107, 108} As with the patients in this series, unresponsiveness with spontaneous and/or stimulus-induced movement may be interpreted as purposeful, or alternatively as a seizure, or non-epileptic reflexes/automatisms. These paroxysmal events occur in 20-50% of patients after BD,^{69, 70, 72, 73, 75} contributing to misdiagnosis, particularly in the pediatric population.^{70-75, 95, 99, 109-113} This challenge underscores the applicability MBNE with rs-fMRI and tb-fMRI studies to serial assessments.

Pediatric Impact Using Advanced Biomarkers

Advances in multimodality neuromonitoring methods beyond conventional MRI and EEG can help with early diagnosis and timely interventions that could change outcomes for children in the early years of brain development and maturation. In a recent review (2008-2017) these authors highlight gaps in research pertaining to rs-fMRI, based on early brain functional developmental studies in the first few years of life.¹¹⁴ Two large multicenter database projects include the Human Connectome Project (dHCP, 2014-2020) and the Baby Connectome Project (BCP), both of which contribute to the field of developmental neuroscience and neuroimage computing (Zhang et al., Howell et al.).^{114, 115}

The BCP is investigating links between brain connectome and behavioral development (together with genomic testing) during critical periods of early developmental neuroplasticity. These studies will help expand our understanding of how to apply highly sophisticated MRI techniques for this age group. Creating abnormal structural/functional connectivity datasets to complement the normative databases will require relational database development that integrates demographic and clinical information as a function of age, location of injury and etiology. These data can be applied to better diagnose and offer neurotherapeutic interventions for children who express neurodevelopmental, epileptic, and behavioral/cognitive disorders.

Ethical Consideration

We are entering a new frontier of pioneering research and clinical implementation of MBNE warranting careful ethical approach. The ability to test brain networks with increasing precision prompts the consideration of shift toward network-informed neuroprognostication. The hope is that more objective data from MBNE may provide more useful data to navigate determinations of the patient's long-term interests and to do no harm.

The ability to provide evidence of remaining networks may reinforce the position to continue support, as with patient 1. However, given the current paucity of validation of the findings, using the absence of detecting networks as data to justify *proceeding* with WLST or BD is not currently advised until there is substantially more data regarding the accuracy and sensitivity. There are additional concerns about using MBNE to “enhance” the accuracy of BD determination. For example, tests such as EEG for BD confirmation were considered a “more sensitive” methodology but in the end did not add accuracy but often introduced artifact and uncertainty. Ancillary tests (e.g studies of cerebral perfusion) are only advised when it is not possible to perform a rigorous BD examination including apnea testing.. Introducing a new

ancillary test could prompt demands from families to use these techniques or result in some physicians electing to modify existing BD guidelines and protocols. In patient 3, who had severe HIE, fMRI networks did not factor into BD, and the purpose was not to propose use of MBNE to validate BD, but rather to validate the test.

Currently, the nature of the brain injury, particularly in pediatric patients, is critical for prognosis, relying on the degree of reversibility to help determine outcome or whether to proceed with a BD examination. For example, blunt trauma (patient 1) or a hemorrhage from an AVM (patient 2) has higher meaningful recovery potential than out of hospital arrest with prolonged hypoxic-ischemic injury (patient 3). In patient 1, there was perceived futility for the high velocity nonpenetrating trauma with near transection of the cervical-medullary junction, which is irreversible and severe, prompting the discussion of WLST. Alternatively, because of the traumatic nature alone, some may always continue full support through the acute period.

Thus, positive MBNE may come to be integrated in such determinations earlier than negative findings, and much work is needed to gain increased confidence.

Limitations and Opportunities

Future work is needed validate rs-fMRI abnormal connectivity in acute pediatric DOC populations. Abnormal neuronal vs non-neuronal connectivity needs to be better differentiated in ABI likely using spatial distributions, as there is some temporal overlap between these signals.^{61, 63} Neuronal-based pathology has greater respect for network and gray-matter spatial pattern boundaries (Figure 1, A2-3 and C2). Non-neuronal pathological connectivity (PC) is identified in gross brain tissue regions commensurate to the respective extracellular pathological components (Figure 1, B2). This is particularly relevant within the neurovascular unit (NVU) at the blood brain/CSF barriers where neuronal and angiogenic structures interact within close proximity. Differences in the NVU exist between maturing and adult brain^{116, 117}. The rs-fMRI findings in the acute DOC populations combine neuronal cell properties (e.g. seizure) and non-neural properties (e.g. vascular, compressive, and traumatic - based pathological phenomenon. PC may block transmission of ongoing brain network activity across cell membranes affecting efferent communication and phenotypic expressions.

Multicenter collaborative trials and pooled data analyses will help achieve better understanding and offer insights with statistically more substantial datasets to plan diagnostic and therapeutic protocols. Risk-benefit ratios must always be a consideration even in low risk clinical settings. However, present studies are primarily in children starting at 7 years, with paucity of studies in younger children stating during neonatal and early childhood ages. The design of any prospective single center or multicenter protocol requires comprehensive descriptions of the patient populations to achieve more accurate inclusion and exclusion criteria. This is highlighted for the present case series by patient 3. This child was born at a near-term gestational age after a problematic pregnancy complicated by multiple gestation status and prenatal substance use. Altered embryonic/fetal brain development may accompany multiple gen-environment interactions to adversely affect this child's developing nervous system within the maternal/placental/fetal triad across the three trimesters of pregnancy. Even without neonatal medical complications, such children may suffer consequences of acute brain injuries requiring pediatric intensive care. These children have pre-morbid altered brain connectivity that respond differently to acute events than patients 1 and 2. This will be reflected by the serial fMRI studies obtained, and influence survival and

quality of life. Medically fragile children, particularly those born premature have a greater likelihood to require pediatric intensive care and experience worse outcomes. Further advances in pediatric neurocritical care are needed.¹¹⁸ Cross-disciplinary training of neonatal and pediatric neurointensivists will contribute to more timely and effective interventions with improved outcomes.¹¹⁹

Transport considerations are practical challenges to address for research and clinical purposes. Rs and task-fMRI require transport to the scanner requiring 20 minutes of scan time each. General anesthesia interferes with connectivity. Ideally, the patient should not be receiving sedating medications. If sedative medications are clinically needed otherwise, they should be administered at levels expected to produce no more than conscious sedation^{61-63, 77, 88} and ideally reduced or off at least 2 hours prior to rs-fMRI scan time, based on our experience (VB). These patient-related restrictions limit clinical test application.

Given the unique challenges of tb-fMRI in children, future studies are needed to determine the optimal tasks and task order in tb-fMRI and for a given patient (for example, developmental capacity). For example, it may be optimal to perform passive tasks in some cases first to establish baseline activation to stimulus. However, lack of activation in one domain does not preclude activation to another and testing response to sound itself (in the absence of language) in the MRI is difficult. Importantly, lack of activation during tb-fMRI should not be immediately interpreted as lack of cognitive activity or consciousness as this method has higher specificity than sensitivity.

While the dominant paradigm for identifying covert consciousness with fMRI includes motor and spatial imagery tasks without constant prompting during the task period, this has been primarily been performed in adults. Due to consideration for the acute stage of DOC and young age of the patient (7yo), tasks with lower cognitive load were also included. Patient 1's active-task fMRI responses were most robust during the arm motor command, followed by the subvocalization task. Future multi-center studies should identify optimal developmentally appropriate tasks in children with suspected DOC/ABI and interpretation of results.

In comparison to rs-fMRI, SSEP, VEP, and BAER are bedside tests each focus on single network queries of brain function with complementary information together with fMRI findings. When the results are compared, greater insight regarding the peripheral, brainstem and cortical levels of the neuroaxis can be considered. The test results for the children in this series indicate high spinal cord (patient 1 – SSEP) and brainstem (patient 1-BAER) connectivity blocks, with ongoing cerebral visual network activity (VEP, rs-fMRI), with changes commensurate with each child's clinical condition (patient 1 tb-fMRI and rs-fMRI improvement; patient 2 rs-fMRI improvement). However, BAER was initially negative in patient 1, potentially due post-traumatic inner ear effusions, and patient 3 possibly due to confirmed tympanic membrane rupture. Thus, the team avoided concluding deafness erroneously in patient 1, which may lead to decreased incentive for bedside auditory based stimuli and for-going audio-based tb-fMRI, though in patient 2, less conclusive information is known.

CONCLUSION

Serial MBNE in pediatric acute DOC is shown to improve DOC endotyping including the diagnosis of covert consciousness. More aggressive therapeutic opportunities and more accurate prognosis regarding recovery and brain death can be achieved. Integration of demographic/clinical information prior to and during the acute illness is essential for diagnostic and statement strategies to be patient-centric for the pediatric patient, particularly during the first thousand days.

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Figure 1. Patient 1 and 2 Images. In column 1 are sagittal anatomical MRI. In columns 2 and 3 are representative fMRI images and network blood oxygen level time courses (BOLD) wherein the y axis is normalized BOLD and the x axis is time in seconds over 10 minutes.

Patient 1: (A1) Acute spinal cord level C1 and medullary brainstem lesion with posterior fossa mass effect and hemorrhage; (A2-3) Rs-fMRI pathological connectivity (PC) in right and left temporal, brainstem broad regions with pattern of alternating relative activation (RED) and deactivation (BLUE), consistent with seizure onset zone (RS-SOZ). (A4) RS-SOZ BOLD time course which is fast, and erratic compared to normal. Patient received antiseizure medication between time point 1 and 2. (A5-6) tb-fMRI auditory command of repeating words with activation in bilateral motor face region (real-time) (A5) and command to moving hands with activation in bilateral motor hand region (aggregate) (A6). (A7) Patient representative normal rs-fMRI BOLD time course.

Patient 2: (B1) Cerebellar and brainstem mass effect and lesion secondary to posterior fossa arteriovenous malformation hemorrhage with posterior craniectomy. (B2-3) Rs-fMRI PC in prefrontal-temporal RS-SOZ and co-occurring typical language network. (B4) RS-SOZ BOLD time course with abnormal fast activity. Patients receive antiseizure medication between time point 1 and 2. (B5-6) Rs-fMRI normalized frontal activity with typical appearing right hemispheric sensory-motor hand and left hemispheric language networks and (B7) normalized representative BOLD time course.

Figure 2. Patient 3 Anatomical Images. MRI on day 3 (A1-B3) and day 4 (C1-C5), wherein the day 3 findings were more localized and by day 4 there was clear evidence of total brain infarction. A1-A2 and A3-A4 are paired DWI and ADC images showing reduced correlating diffusivity in both basal ganglia, thalami, dorsal brainstem, medial cerebellar hemispheres, frontal lobes, central sulci, and hippocampi. A5 is a T2 image showing increased signal and edema in same regions at A1-A4, without midline shift. B1 is an MR angiogram showing grossly unremarkable flow related signal in the anterior and posterior circulation. B2 is a sagittal image showing the ventricles and extra axial spaces were relatively normal, without herniation. The MRI interpretation stated that the brain parenchymal imaging was “not diagnostically evaluated on this exam to fully characterize”, and “artifact limit(ed) assessment”. Thus, given the acuity of the course, a second MRI was performed on day 4 of admission to confirm findings, assess for interval evolution. C1-C2 and C3-C4 are paired DWI-ADC images showing that all brain parenchyma was now infarcted, with greatly increased edema such that there was flattening of the cerebral sulci, smaller sized ventricular system and narrowing of the basilar cisterns. C5 shows there was decreased size of the ventricles, especially the 4th ventricle, and mild inferior herniation. There were no intracranial blood products. The arterial blood flow on day 3 MRA stopped by day 4 (see transcranial doppler result in text).

Figure 3. Patient 3 compared to age-matched control functional images. Patient noise related IC (A1-A3) and a control normal term neonate 5 days old sample of normal networks for comparison (B2-B5). Because all the patient's IC were noise as seen in Figures 3-5, this image set is shown to demonstrate a contrast against normal at a larger view. A1-A3 show a representative noise related IC of the patient wherein the axial, coronal, and sagittal noise IC in RED is overlaid on the patients T1. The red stripes across the brain best appreciated on the coronal image do not conform to established physiological neuronal networks. A2 is a BLUE graph of the power spectrum of the frequencies from the ICs time course. Normal power spectrum for blood oxygen level dependent brain networks signal is generally ≤ 6.78 Hz/100. Thus, A2 has shifted power spectrum toward the higher end, whereas B4 is in the normal range. A3 and B5 are the patient and normal BOLD normalized time courses respectively, where the y-axis is BOLD signal level of the shown IC, and x-axis is time over 10 minutes. Normal BOLD has a slow oscillatory pattern as seen in B5, whereas A3 is overtly regular, with faster cadence, as reported in cerebrospinal fluid pulsation related noise^{61, 63, 120}. Patient motion during rs-fMRI was less than 0.2 mm in any direction.

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SUPPLEMENTARY MATERIAL

Patient 1 clinical initial interventions: head of bed elevated, normoglycemia, goal sodium > 140 mmol/L, magnesium > 2 mmol/L, partial pressure of carbon dioxide 35-40 mmHg, oxygen saturation near 100%, hemoglobin > 8 mg/dL, temperature goal 36 – 37°C.

Patient 3: Additional History: Positive infant death risk factors: white male, twin-gestation, 3 weeks early – 37 weeks gestation, and not sleeping on his back.

Maternal/placental/fetal triad data, including preconception status: mother reports receiving prenatal care throughout, with several normal ultrasounds. In the last week of pregnancy, she had proteinuria, but no elevation in blood pressure, nor seizure. Had spontaneous labor, then cesarian section with no complications. Mom was 42 years, and dad 39 at conception.

Maternal birth history: 8 pregnancies, 1 spontaneous miscarriage in first trimester, 1 abortion.

PMHx: patient's birth weight was 7 lbs, 13 oz, 53 cm length; and twin was 6 lbs, 12 oz; both breast fed with supplemental formula; no feeding issues; several scheduled well visits to pediatrician unremarkable; circumcision without complication. State mandated screens negative. No genetic testing.

Family Hx: Mother was a smoker prior to the pregnancy. Father had adult onset insulin dependent diabetes. Mother report a history of dad having delusions, but neither she nor he have had any psychiatric formal diagnoses. Mother denied emotional/mental related symptoms. Paternal grandfather with major depressive disorder. Mothers first child was born when she was 15 years old. She has 6 children who are alive, age 2 mo – 24 years, are heathy, with no developmental, behavioral, educational issues

Education: mother and father finished high school in regular classes without extra help. Mother had some college.

Autopsy: reported negative by mother.

Vitals: 4.98 kg, 58 cm height, head circumference 38.5 cm, temperature 32 °C on arrival then averaging 37 °C afterwards, HR 120-210 bpm, RR 30s, mean blood pressures 49-96 with average in 60-70 range, urine output 1.7 cc/kg/hour average, and cerebral oximetry was 94% on day 4. **Ventilator Settings:** servo mode, SIMV, PRVC, PS, rate 26-30 (decreased to 5 only for BD apnea test), FIO2 40, tidal volume 35 mL, PEEP 5 cm H2O, pressure support 8 cm H2O, peak inspiratory pressure 22 cm H2O. **Medications:** Day 1, epinephrine iv, norepinephrine bitartrate iv then discontinued. Day 4, fentanyl 20 mcg iv once, ampicillin-sulbactam 220 mg iv, furosemide 4 mg iv once.

Exams with reported relevant unique or validating findings between providers and over time: **Ophthalmology:** Day 1, No response to light OU, external exam quiet with normal cornea and conjunctiva, optic nerve with normal cup-to-disk ratio 0.05 bilaterally, normal retina, vasculature, and macula, no papilledema, and no retinal hemorrhage. **Neurosurgery, Trauma Service:** Day 1, Glasgow coma scale (GCS) 3, anterior fontanelle open and soft, exams without evidence of trauma. **Intensivist:** Day 1-3, GCS 3, unresponsive to stimulation, no movement, no brainstem reflexes. Day 2-4, persistent agonal breathing at RR 8 bpm. Day 4-5, cessation of agonal breathing. **Day 5, complete brain death exam including apnea test with preoxygenation to PaO2 > 200 mm Hg was without respiratory effort and showed rise in PaCO2 > 20 mm Hg, and confirmation by EEG with electrocerebral silence. Thus, he was declared brain dead.**^{96, 121} The brain death exams: pupils were 4 mm and fixed to light, absence of ocular movement to oculoccephalic testing. There was absence of: corneal reflexes, facial movement to noxious stimuli, pharyngeal-gag, and tracheal-cough response, and oculoccephalic and oculovestibular reflexes. **Neurology:** Day 1, non-dysmorphic, fontanelle flat, normocephalic, no neurocutaneous stigmata, no brainstem reflexes, no movement, flaccid deep tendon reflexes, and flaccid tone. Day 2, unchanged except for **spontaneous movement of right hand/wrist, with external rotation and extension intermittently without clear provocation, no reliable reproduction of movement to noxious stimuli.** Day 3-4, fontanelle bulging, agonal breathing above the ventilator, no movements, mild to moderate generalize muscle tone. Day 5, exam consistent with brain death.

Laboratory: Day 1, initial pH was 6.88, lactic acid 9.9 mmol/L, glucose 276 mmol/L, and bicarbonate < 10 mmol/L. The metabolic panel showed (in units of mmol/L unless specified) sodium 145, potassium 4.6, chloride 119 (mild elevation), CO2 18 mmHg, anion gap 8, glucose 136 (mild elevation), blood urea nitrogen 20 mg/dL, creatinine 0.41, BUN/Cr ratio 49 (10-28 normal), and calcium 8.3 mg/gL. Ammonia was 67 (11-50 umol/L), amylase 9 (1-50 U/L), lipase 19 (10-53 U/L), procalcitonin 23.62 – elevated (0.00-0.05 ng/mL), aspartate and alanine aminotransferase 162 and 253 IU/L, total bilirubin 0.3 mg/dL, alkaline phosphatase 253 U/L, albumin 2.2 g/dL, and total protein 3.8 g/dL. His serum complete blood count on day 4 of admission showed hemoglobin of 9.6

gm/dL (normal), white blood cell count of 6.0 k/uL (normal), platelet count of 33 K/uL (low), red blood cell morphology of burr cells, fragments, and polychromasia (mild abnormalities). His PT was 19.8 sec, INR 1.7, APTT of 37.2 sec (mild elevation). D-Dimer was 7.8 ug/ml FEU (marked elevation). Tracheal cultures reveal contaminants of *Staphylococcus aureus* and *Klebsiella oxytoca* and negative viral panel. Urine and blood cultures were negative. Arterial blood gas on Day 5 showed pH 7.41, partial pressure of CO₂ 29 and O₂ 78 mmHg, base deficit 6.0, oxygen saturation 98%, oxyhemoglobin 2.0%, methemoglobin 1.2%, and deoxyhemoglobin 2.0%. Day 1 urine analysis was unremarkable except with 3+ of glucose, protein, hemoglobin, and ascorbate (which can cause false positive results for urine containing blood). **Toxicology:** Day 1, toxicological evaluation of urine gas chromatography-mass spectrometry was positive for amphetamine, methamphetamine, and niacinamide, which is reported to be a 70% match compared to internally developed spectral libraries by Sonora Quest, which is an unconfirmed medical screen, and is not approved by the FDA, and is regulated under the Clinical Laboratory Improvement Amendments as qualified to perform high-complexity testing for clinical purposes, and is not investigational or for research. However, confirmatory tests were negative by quantitative liquid chromatography-tandem mass spectroscopy amphetamine ≤ 50ng/mL (positive cutoff is 200 ng/mL), and MDA, MDEA, MDMA, methamphetamine, and phentermine were < 200 mg/mL. Fentanyl urine screen was negative. **Electroencephalogram:** Flat and featureless, no evidence of cerebral activity or seizures at any point during recording. Electrocerebral silence by video monitored electroencephalogram according to ACNS guidelines, 18 channel EEG with ECG and pulse oximeter monitors, with testing for reactivity to exogenous stimuli on Day 5. **Body Imaging:** CT of the abdomen and pelvis with contrast was consistent for findings suggesting shock (interloop fluid and ascites with no free air, fluid filled and hyper-enhancing bowel wall) and no evidence for solid organ injury. Chest x-rays over the course were consistent with improving atelectasis, underlying edema, and resolved left pneumothorax. Renal ultrasound demonstrated increased cortical echogenicity of uncertain significance, either due to age or medical renal disease. **Central Nervous System Imaging:** Day 1, CT of the head showed a nondisplaced midline occipital bone fracture, and nonspecific scattered areas of hypoattenuations involving the periventricular white matter and basal ganglia, concerning for hypoxic injury. CT of the cervical spine was normal. Day 3-4, anatomical MRI images and descriptions are shown in **Figure 1**, showing initially more focal injury that progressed by the next day to total brain infarction. Day 5, transcranial doppler ultrasound (TCD) showed reversal of flow during diastole of bilateral middle cerebral arteries, consistent with markedly high increased intracranial pressure, and seen in adults with brain death.¹²² Day 4, whole brain rs-fMRI was acquired and analyzed as previously reported (**Figure 2, Figure 3-5**).^{61, 63} It showed no detectable local or long-range neuronal networks and all of the independent components detected were consistent with sources of noise as previously reported.^{61, 63, 120}

S-Figures 1. Resting State fMRI Independent Component Network Results for the patient's IC 1-30. Thumbnail views of all resulting independent components (IC) are shown, each with a single IC in the axial, coronal, and sagittal views. Each IC's corresponding time course of blood oxygen dependent (BOLD) are shown in the RED graph with normalized BOLD on y-axis and time over 10 minutes on the x-axis. Also, each IC's corresponding power spectrum of time course frequencies are shown in the BLUE graph with power on the y-axis and frequency in Hz/100 on the x-axis. The results are consistent with artifactual and physiological noise with no IC spatially conforming to any known brain network or atypical brain network. The time courses and power spectrums demonstrate highly regular generally fast signal compared to normal brain networks by rs-fMRI.

Patient 2 Daily Summary of Exam, Examine Specialty, Sedating and neuroactive medications

NS-1-5: Neurosurgeons

ICU-1: ICU provider

MED-1-3: Hospitalist/ICU provider

PMR-1: Physical Medicine and Rehabilitation Physician

PT-1: Physical Therapist

Disorder of Consciousness (DOC) Operational Definitions

- Coma: eyes closed, not clearly withdrawing (must be abduction to pain – flexion can be triple flexion (reflex) versus withdrawal (purposeful))
- UWS: unresponsive wakefulness syndrome, means eyes open but not clearly following a command
- MCS: minimally conscious syndrome, means eyes open and intermittently follows some command such as squeeze hand or move mouth
- Conscious – awake and consistently following commands

Day	examiner	Medications	Exam quotes	DOC
1	NS-1	PRN rocuronium 60 mg IV q1 PRN morphine 3 mg IV q2	Posterior craniectomy, “sudden onset of headache, rapid loss of consciousness with a 7 cm posterior fossa hematoma with brainstem compression, hypertension and relative bradycardia taken emergently for EVD placement and posterior fossa decompression (craniectomy) and expansion duraplasty. taken to an outside ER where his GCS was reported a 7 . He was intubated. CT head obtained with continued posterior hematoma, cerebellar edema, intraventricular hemorrhage, hydrocephalus, brainstem compression. ventricular tachycardia, right pupil was noted to be dilating	coma
2	NS-1	Dexmedetomidine 0.2 mcg/kg/hour IV PRN fentanyl 60 mcg q1 PRN rocuronium 60 mg IV q1 PRN morphine 3 mg IV q2	Intubated/Sedated. Pupils 3mm reactive bilaterally.	Coma
3	NS-1	Dexmedetomidine 0.2 mcg/kg/hour IV Fentanyl 0.5 mcg/kg/hour of 50 mcg/mL PRN fentanyl 60 mcg q1 PRN rocuronium 60 mg IV q1	Intubated/Sedated. Pupils 3mm reactive bilaterally.	Coma
4	NS-1	Dexmedetomidine 0.2 mcg/kg/hour IV Fentanyl 0.5 mcg/kg/hour of 50 mcg/mL	GCS: E1M1V1 . Intubated/lightly sedated. Pupils 3mm reactive bilaterally. +corneals	Coma
5	NS-1	Dexmedetomidine 0.4 mcg/kg/hour IV Fentanyl 0.5 mcg/kg/hour of 50 mcg/mL	GCS: E1M1VT . Intubated/sedated. Pupils 3mm reactive bilaterally. +corneals	Coma
6	NS-2	Dexmedetomidine 0.4 mcg/kg/hour IV Fentanyl 0.5 mcg/kg/hour of 50 mcg/mL	Still on DEX and Fent: Intubated/sedated. B/I LE flexor response, minimal finger movement on deep stimuli on L UE. No movement noted on Rt UE, Pupils 3mm reactive bilaterally. +corneals	Coma vs UWS
7	NS-3	Dexmedetomidine 0.4 mcg/kg/hour IV Fentanyl 0.5 mcg/kg/hour of 50 mcg/mL	Intubated/sedated. opens eyes to stimuli/call, B/I flexor response of all 4 extremities, Pupils 3mm reactive bilaterally. +corneals	UWS
8	NS-1	Dexmedetomidine 0.1 mcg/kg/hour IV	Intubated/sedated. Occasionally opens eyes to voice , pupils reactive	UWS

9	NS-1	OFF continuous SEDATION, rare occasional prn	Intubated/sedated. Occasionally opens eyes to voice, pupils reactive. Squeezes hands to commands (?), minimal movement bilateral LE	MCS-
10	NS-1	1 dose morphine 60 mcg IV	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Squeezes hands (Not specifying to command or reflex?).	UWS vs MCS
11	NS-1	OFF continuous SEDATION, rare occasional prn	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Occasionally squeezing hands (unknown if to command). Flexes to painful stim.	MCS or UWS
12	NS-1	OFF continuous SEDATION, rare occasional prn	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes to painful stim.	UWS
13	NS-4	OFF continuous SEDATION, rare occasional prn	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
14	NS-4	OFF continuous SEDATION, rare occasional prn	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
15	NS-1	OFF continuous SEDATION, rare occasional prn	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
16	NS-3	OFF continuous SEDATION, rare occasional prn	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
17	NS-1	OFF continuous SEDATION, rare occasional prn	Intubated/ minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
18	NS-4	OFF continuous SEDATION, rare occasional prn	minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
18	ICU-1	OFF continuous SEDATION, rare occasional prn	Recommend discussion with palliative care and support decision making	
19	NS-2	OFF continuous SEDATION, rare occasional prn	minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim	UWS
20	NS-2	OFF continuous SEDATION, rare occasional prn	minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim	UWS
21	NS-2	OFF continuous SEDATION, rare occasional prn	minimally sedated. Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim	UWS
22	NS-1	OFF continuous SEDATION, rare occasional prn	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim. Left had contracts into grip, but did not open to command. No commands on right or LE.	UWS vs MCS
23	NS-1	OFF continuous SEDATION, rare occasional prn	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim. Left had contracts into grip, but did not open to command. No commands on right or LE.	UWS vs MCS
24	NS-1	OFF continuous SEDATION, rare occasional prn	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim. Possibly starting to follow commands by sticking out tongue (?).	MCS
25	NS-1	Zolpidum 5 mg	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim. Possibly starting to follow commands by sticking out tongue.	MC

25	NS-5	Zolpidum 6 mg	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim. Possibly starting to follow commands by sticking out tongue (?) .	MCS
26	PMR-1	Zolpidum 5 mg	low level neuro status. opens his eyes , but doesn't follow commands or initiate movement . " Her Exam: NEURO: , no visual tracking, atypical grimace -like movement with his mouth/lips : Intermittent lower face grimace/"angry face" , sometimes often triggered by manipulation or touch of a limb, or in response to a command.	UWS vs MCS
27	NS-5	Zolpidum 7 mg	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim. Possibly starting to follow commands by sticking out tongue.	UWS vs MCS
28	NS-5	Zolpidum 8 mg	Occasionally opens eyes to voice , pupils reactive. Flexes weakly to painful stim. Possibly starting to follow commands by sticking out tongue (not consistent).	MCS+?
29	NS-1	Zolpidum 9 mg	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
30	NS-1	Zolpidum 9 mg	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
31	NS-1	Zolpidum 10 mg	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
32	NS-1	Zolpidum 11 mg; keppra 60mg/kg	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	USW
33	NS-1; MED-1	Zolpidum 18 mg phenobarbital 20mg/kg with some ?improvement keppra 20mg/kg divided BID x 3-4 weeks plan	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim. Glasgow coma scale: 8 Neuro: asleep Zolpidum stopped due to lack of clear improvement in arousal and possibly worse as determined by the neurocritical care and intensivist teams together.	UWS
33	MED-1			Coma to UWS
34	NS-1	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
35	NS-1	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
36	NS-1	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
37	NS-1	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
38	NS-1	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
39	NS-1	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
40	NS-1	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
41	NS-4	Keppra 20 mg/kg divided bid	Occasionally opens eyes to voice, pupils reactive. Flexes weakly to painful stim.	UWS
42	NS-4	Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours, pupils reactive. Flexes weakly to painful stim.	UWS

43	NS-4	Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours, pupils reactive. Flexes weakly to painful stim.	UWS
44	NS-1	Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours , pupils reactive. Flexes weakly to painful stim.	UWS
45	NS-1	Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours , pupils reactive. Flexes weakly to painful stim.	UWS
46	NS-1	Dexmedetomidine 0.4 mcg/kg/hour IV Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours, pupils reactive. Flexes weakly to painful stim.	UWS
47	NS-1	Dexmedetomidine 0.6 mcg/kg/hour IV Meperidine Injectable 3 mg IV Every 2 hours PRN once Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours, pupils reactive. Flexes weakly to painful stim.	UWS
48	NS-4	Oxycodone 2.5 mg NG tube q4 prn Dexmedetomidine 0.8 mcg/kg/hour IV Fentanyl 50 MCG IV Every 1 hour PRN Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours, pupils reactive. Flexes weakly to painful stim.	UWS
49	NS-4	Dexmedetomidine 0.8 mcg/kg/hour IV Fentanyl 50 MCG IV Every 1 hour PRN Keppra 20 mg/kg divided bid	Opens eyes spontaneously during day hours, pupils reactive. Flexes weakly to painful stim.	UWS
50	PT-1	Dexmedetomidine 0.8 mcg/kg/hour IV Fentanyl 50 MCG IV Every 1 hour PRN Oxycodone 2.5 mg NG tube q4 prn Keppra 20 mg/kg divided bid	Turns head side to side when asked (possibly first clear time of following a command?)	MCS
51		Oxycodone 2.5 mg NG tube q4 prn Keppra 20 mg/kg divided bid		
52		Keppra 20 mg/kg divided bid		
53	PT-2	Keppra 20 mg/kg divided bid	Able to sit strapped in wheel chair with full support of head and body	MCS
54		Keppra 20 mg/kg divided bid	Transfer to re-hab unit	
55	MED-2	Keppra 20 mg/kg divided bid	NAD, non-toxic, no major responses to stimulation, seems awake with eyes open; no verbalization, increased tone	UWS vs MCS
56	MED-2	Keppra 20 mg/kg divided bid	NAD, non-toxic, no major responses to stimulation, seems asleep; no verbalization, increased tone	UWV vs MCS
57	MED-1	Keppra 20 mg/kg divided bid	NAD, non-toxic, appears alert; no verbalization, increased tone, moves head laterally, on cue, intermittently	MCS+
58	MED-1	Keppra 20 mg/kg divided bid	NAD, non-toxic, appears alert; NAD, non-toxic, appears alert	UWS

59	MED-1	Keppra 20 mg/kg divided bid	NAD, non-toxic, appears alert; no verbalization, increased tone, moves head laterally, on cue, intermittently	MCS+
60	MED-1	Keppra 20 mg/kg divided bid	NAD, non-toxic, appears alert; no verbalization, increased tone, moves head laterally, on cue, intermittently	MCS+
61	MED-1	Keppra 20 mg/kg divided bid	NAD, non-toxic, appears alert; no verbalization, increased tone, moves head laterally, on cue, intermittently	MCS+
62	MED-1	Keppra 20 mg/kg divided bid	NAD, non-toxic, alert but nonverbal, no agitation; no verbalization, increased tone, moves head laterally, on cue, intermittently	MCS+
63	MED-1	Keppra 20 mg/kg divided bid	NAD, non-toxic, alert but nonverbal, no agitation; no verbalization, increased tone, moves head laterally, on cue, intermittently	MCS+
64	MED-3	Keppra 20 mg/kg divided bid	NAD, non-toxic, alert but nonverbal, no agitation, sitting in shower chair; no verbalization, increased tone, moves head laterally, on cue, intermittently	MCS+
65	NS-1	Keppra 20 mg/kg divided bid	no verbalization, increased tone, responds in a delayed fashion to questions with a head nod	Conscious