Impairment and Recovery of Consciousness

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Disclosures

- Foundation funding: DANA, McDonell
- Advisory Board for clinical trials planning: SAGE (past)
- Site-PI for RCTs: SHINE, I-SPOT, ESETT, Intrepid; former: HASTIER, SAGE, i-DEF, EDGE
- Co-Editor:
  - Stupor and Coma, 4th Edition
  - Seizures in Critical Care. A Guide to Diagnosis and Therapeutics, 3rd Edition
- Shareholder iCE Neurosystems
Challenging assessments of consciousness in the ICU

- **Is the patient conscious or not?** “the family reports that he/she is following commands”
- **The patient opened his/her eyes. Is she/he conscious?**
- **Does the patient comprehend?** Think aphasia, locked in, learned stereotyped behavior mimicking comprehension.
- **Fluctuations in consciousness.** Delirium, true improvement/worsening, medication/metabolic/brain physiology/structural effects
- **In pre-rounding the patient was following commands but now she/he is not.** Important for shift changes, different skilled providers, different styles/techniques to examine.
- **Confounders** (sedation, renal or liver failure, infection/inflammation)
Why bother with consciousness in the ICU?

- Prolonged impairment is frequent with or without brain injury
- Even fluctuating states of consciousness, i.e. delirium, a/w poor outcome
- Weighs heavily in GOC discussion
- WLST most common mode of death in acutely brain injured patients
- Unable to prognosticate. Mostly self fulfilling prophecies
- Very delayed recovery described for TBI, CA, SAH, other etiologies
Multiple ascending pathways
- Brainstem: mesopontine tegmentum
- Projecting to basal forebrain, thalamus, and cerebral cortex

Neurotransmitter
- Upper brainstem and posterior hypothalamus: noradrenaline, serotonin, dopamine, histamine
- Hypothalamus: orexin, melanin-concentrating hormone
- Basal forebrain: acetyl choline, GABA

 ascension arousal system

Cerebral cortex as parallel processor

- Thalamic relay nuclei project sensory input to cortex
- Columns of neurons analyze sensory input independently/in parallel
- Exchange information between different neuronal columns
- Global integration of this information
- Re-assimilated into one conscious state ("the binding problem")


Parvizi et al. PNAS 2006
Models: Impairment of consciousness

Brain stem structures

Thalamus

Subcortical structures/central thalamus

Global workspace theory

Parvizi & Damasio Brain 2003
Lukenhoff et al Ann Neurol 2015
Schiff et al. 2014
Dehaene et al PNAS 1998
When do intensivists encounter conditions of impaired consciousness?

• Most of the conditions we encounter in the Neuro ICU
• Primary: Traumatic brain injury, brain hemorrhages, stroke, encephalitis, sepsis
• Secondary: Elevated ICP, seizures, herniation, cerebral edema
Injury rarely causes isolated effects: Location vs mass effect

Awake
- 30 ml ICH
- 32 ml edema

Comatose
- 17 ml L ICH
- 112 ml edema
Impairment is not static

Herniation syndromes

- Subfalcine
- Uncal
- Central transtentorial
- Tonsillar
- Upward herniation

Claassen et al, Merritt Neurology 2016
Can we develop more objective, possibly continuous assessments of consciousness?

- Behavioral assessments
- MRI
- EEG
Resting EEG

Anesthesia

Coherence analysis

Chronic DOC

Coherence analysis

Supp et al, Curr Biol 2011

Leon-Carrion et al Brain Res 2012

Purdon et al. PNAS 2013
Resting EEG in SAH: correlation with acute impairment of consciousness (N=83)

Arousal (vs coma): increase power
- Central gamma
- Post alpha
- Diffuse theta/delta

Commands (vs coma): increase
- Central gamma power
- Post alpha power
- Alpha (theta) permutation entropy

Claassen et al Ann Neurol 2016
Resting EEG in SAH: correlation with acute impairment of consciousness (N=83)

Claassen et al Ann Neurol 2016

Sitt et al, Brain 2014
Predicting future wake up: chronic DOC

Average Measures

<table>
<thead>
<tr>
<th>Frequency Power</th>
<th>Connectivity</th>
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<tbody>
<tr>
<td>$</td>
<td>\delta</td>
</tr>
<tr>
<td>$</td>
<td>\alpha</td>
</tr>
<tr>
<td>$SE$</td>
<td>$PE \theta$</td>
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Stats

<table>
<thead>
<tr>
<th>VS</th>
<th>MCS</th>
<th>CS</th>
<th>H</th>
<th>VS-MCS</th>
<th>Regress</th>
</tr>
</thead>
</table>

Classified from EEG

<table>
<thead>
<tr>
<th>Clinical</th>
<th>VS</th>
<th>MCS</th>
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</thead>
<tbody>
<tr>
<td>CS + H</td>
<td>11% (4)</td>
<td>89% (34)</td>
</tr>
<tr>
<td></td>
<td>67% (50)</td>
<td>33% (25)</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>VS</th>
<th>MCS</th>
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<tbody>
<tr>
<td></td>
<td>24% (16)</td>
<td>76% (52)</td>
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</table>

% diagnosed (n patients)

Sitt et al Brain 2014
Predicting future wake up: chronic DOC

Clinical
CS + H
MCS

VS
MCS

33% misclassified?
Predicting future wake up: chronic DOC

Vegetative state
Based on clinical exam

Based on EEG

Improved to an MCS or a CS in less than 16-42 days

Sitt et al Brain 2014
Can we actively test for consciousness using the EEG?

- Hidden command following
Hidden command following

• 1st case of uncovering hidden command following Owen et al, Science 2006
• Cognitive motor dissociation (CMD) Schiff JAMA Neurol 2015
  – Impaired ability to express preserved or recovered command following
  – Detection of command following using fEEG or fMRI
• Feasibility of task-based EEG/MRI to identify CMD in chronic TBI patients Goldfine et al, Clin Neurophys 2011; Curley et al, Brain 2018
• In the ICU: Edlow et al, Brain 2017
  – fMRI possibly more sensitive than EEG in early brain injury (4/8 with MRI)
  – fEEG more practical in the ICU (but 0/7 with EEG)
• Chronic DoC 15% have CMD using fEEG or fMRI Kondziella et al, JNNP 2016
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Goldfine et al, Clin Neurophys 2011  Monti et al, NEJM 2010
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**Methods**

**Study design:** prospective observational cohort study of unconscious, acutely brain injured ICU patients admitted to the Neuro ICU July 2014-September 2017

- Inclusion criteria: (1) no command following on Coma Recovery Scale-Revised (CRS-R), (2) acute brain injury, (3) continuous EEG
- Exclusion criteria: (1) age <18 years, (2) pre-existing disorder of consciousness, (3) pregnant, (4) deaf, (5) did not want to participate in study

**Data collection in patients:**

- EEG recorded while presenting repeated motor imaging paradigm
  - International 10–20 System with 21 electrodes, Xltek-Natus,ON,Canada
  - Single-use headphones (E-A-RTONE™ 3A or 5A Insert Earphones)
  - Triggers from presentation computer
- Motor imagery paradigm:
  - 8 trials alternating "keep opening and closing your right hand" with "stop opening and closing your right hand"
  - Total of 6 blocks obtained alternatingly asking the patient to move the right and left hand
- Serial CRS-R scores during interruption of sedation
- Confounders: sedation, metabolic derangement
- GOS-E at 12 months

**Healthy volunteers** (N=10)
Methods

A. Data acquisition: EEG motor imagery paradigm

B. Data preparation: 10-sec periods of EEG following end of each command segmented in five 2-sec long epochs

C. Epoch classification
   - Spectral analysis (PSD) applied for each electrode, resulting in 76 features (19 electrodes x 4 frequency bands)
   - Classification: using a support vector machine (SVM) to determine the ability to distinguish between active (hand opening-closing) and passive (rest) tasks
   - Classifier performance: based on AUC
   - Classifier reliability: determined using permutation testing (with randomly shuffled labels)
66 year old man with severe brain injury

- 1\textsuperscript{st} visit: left occipito-parietal deep ICH with extensive IVH c/b hydrocephalus, VPS, Afib, HTN, HLD, DM2 diet controlled, CAD/MI s/p 3v CABG, depression, and BPH -> recovered
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- 2\textsuperscript{nd} visit: Severe TBI with SAH/SDH/ICH, multiple contusions with edema c/b convulsive
66 year old man with severe brain injury

- 1\textsuperscript{st} visit: left occipito-parietal deep ICH with extensive IVH c/b hydrocephalus, VPS, Afib, HTN, HLD, DM2 diet controlled, CAD/MI s/p 3v CABG, depression, and BPH -> recovered
- 2\textsuperscript{nd} visit: Severe TBI with SAH/SDH/ICH, multiple contusions with edema c/b convulsive seizure

3 weeks later has not woken up
Auditory command: “open and close your right hand”
15% of patients had CMD after applying FDR: 
39% (N=5) of SAH, 20% (N=3) of TBI, 15% (N=4) of ICH, 14% (N=2) of other, and 6% (N=2) of CA patients

<table>
<thead>
<tr>
<th>Demographics</th>
<th>CMD (n=16)</th>
<th>Not CMD (n=88)</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;63 years</td>
<td>5 (31%)</td>
<td>40 (45%)</td>
<td>1.1 [0.3 - 3.9]</td>
</tr>
<tr>
<td>Female</td>
<td>7 (44%)</td>
<td>39 (44%)</td>
<td>1.0 [0.3 - 3.5]</td>
</tr>
<tr>
<td>Length of hospital stay&gt;14 days</td>
<td>9 (56%)</td>
<td>40 (45%)</td>
<td>1.5 [0.5 - 5.3]</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>15 (94%)</td>
<td>81 (92%)</td>
<td>0.8 [0.0 - 6.9]</td>
</tr>
<tr>
<td>Behavioral assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission GCS &gt;7</td>
<td>4 (25%)</td>
<td>30 (34%)</td>
<td>0.6 [0.1 - 2.4]</td>
</tr>
<tr>
<td>Median CRS-R score &gt;2</td>
<td>7 (44%)</td>
<td>43 (49%)</td>
<td>0.8 [0.2 - 2.7]</td>
</tr>
<tr>
<td>Worst CRS-R score &gt;1</td>
<td>8 (50%)</td>
<td>41 (47%)</td>
<td>1.1 [0.3 - 3.9]</td>
</tr>
<tr>
<td>Best CSR-R score &gt;3</td>
<td>9 (56%)</td>
<td>35 (40%)</td>
<td>1.9 [0.6 - 6.7]</td>
</tr>
<tr>
<td>EEG studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of EEG studies</td>
<td>3 [1, 4]</td>
<td>2 [1, 3]</td>
<td>2.1 [0.6 - 7.3]</td>
</tr>
</tbody>
</table>
Temporal pattern of classification

(A) Classifier performance for each trial averaged over recorded blocks in controls. The Y-axis indicates the prediction for a given epoch to correspond to a movement (higher number) vs a non-movement instruction (lower number).

(B) Epoch classifications over time in CMD patients (Note that y-axis scale different btw controls and patients).

Temporal pattern
Clinical state and sedation

Behavioral categories (based on CRS-R):
- Conscious: accurate communication
- MCS-plus: reproducible movement to verbal command or intentional communication
- MCS-minus: fixation and/or visual pursuit
- Unresponsive wakefulness syndrome (UWS) spontaneous or elicited eye opening
- Coma: absence any of the above

Sedation categories:
- Black: none
- Green: pushes of sedative medications
- Blue: low doses of continuously administrated sedatives
- Orange: moderate doses of continuously administrated sedatives

Model performance (AUC) did not differ between different levels of sedation (ANOVA, F(3, 236)=0.47, P=0.70).
Outcomes

Clinical command following

• Half of the CMD (N=8) and a quarter of the non-CMD patients (N=22) followed commands clinically before discharge

• Command following was first detected 6 days (IQR 2.0,8.3) after CMD diagnosis vs. 12 days (IQR 9.3,19.5) in the non-CMD patients (time after last EEG)

Long term functional outcome

• GOS-E 12 months after injury: 44% of CMD and 14% of non-CMD patients had a GOS-E > 3 (OR 4.6, 95%-CI 1.2-17.1, P=0.01)
Cognitive Motor Dissociation

- Consistent goal-directed functional movements
- No motor function
- Total functional loss
- Cognitive function
- Normal
- Motor function
- Total functional loss
- Cognitive motor dissociation (CMD)
- VS
- MCS
- CLIS
- LIS
- Coma
- Severe to Moderate Cognitive Disability
- Full Cognitive Recovery
- *Brain Death

Schiff JAMA Neurol 2015; Schiff and Fins Curr Biol 2016
From models to prediction to intervention

Schiff et al. TNS 2012
From models to prediction to intervention
Single Cases

Stimulating the central thalamus Directly
From models to prediction to intervention
Single Cases

Stimulating the thalamus
Via the vagus nerve

Schiff et al. TNS 2012

Corazzol et al. Current Biol 2017
Stimulating the thalamus mechanically

- Low intensity focal ultrasound (LIFUP)
- Pulse repetition 100Hz, pulse width 0.5ms.
- Patient:
  - TBI initial GCS 3, ED GCS 7
  - 10 ultrasound applications, derated spatial-peak temporal-average intensity 720mW/cm², each 30 s, separated by 30 s pauses
  - Sonication within 3TMRI
  - At time of US in MCS: CRS-R of 15 (day prior), CRS-R 14 (day of), CRS-R 13 (day of), CRS-R 17 (day after)
TBI:
- Amantadine 200–400 mg/day at 4-16 wks post-injury
- Unable to follow commands or communicate reliably
  - 184 patients

Stimulating the frontal lobe via dopaminergic pathways

From models to prediction to intervention
Larger RCTs

Giacino et al. NEJM 2012

Schiff et al. TNS 2012
Conclusion

• Imprecise assessments of consciousness: standardize your approach
• Currently poor at predicting recovery, need better multimodal tools
• CMD can be identified early after brain injury using routine EEG recordings combined with simple motor imagery paradigms
• Tap into CMD for communication?
**Research Fellow:** Benjamin Rohaut
**Data science:** Andrey Eliseyev, Kevin Doyle

**Director of research:** Angela Velazquez
**Research coordinators:** Caroline Couch, Adu Matory

**Student researcher:** Joshua Okonkwo

**Neurosurgery:**
- E Sander Connolly

**Neuro ICU Nurses**

**Electrophysiology**
- Epilepsy attending/fellows/techs: Kelly Burger

**Neuro ICU attendings:** David Roh, Soojin Park, Sachin Agarwal

**External collaborators:**
- **WCMC:** Niko Schiff
- **Paris:** Lionel Naccache, Jean-Rémi King