EEG Monitoring for Assessment of Consciousness in Comatose Patients

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- Co-Editor: Stupor and Coma, 4th Edition
Disorders of consciousness

- Acutely/ICU:
  - Coma
  - Eye opening
  - Attending/tracking
  - Simple/complex commands, orientation

- Chronic: unresponsive wakefulness (UW) / persistent vegetative state (PVS), minimally conscious state (MCS +/−)
Consciousness: Arousal vs Awareness

In ICU:
Early recovery
Phase after
Acute Brain injury

Modified from Laureys et al, Lancet Neurol 2004
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
Content processing

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")

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
- Unable to prognosticate. Mostly self fulfilling prophecies
- Very delayed recovery described for TBI, CA, SAH, other etiologies
Covert consciousness: Are some patients awake that look comatose?

Intraoperative awareness: rare (<1%) Avidan et al NEJM 2011

Chronic DOC

Functional MRI

Goldfine et al, Clin Neurophys 2011

Functional EEG

Monti et al, NEJM 2010
Cognitive Motor Dissociation

Total functional loss

Cognitive function

Normal

Motor function

Total functional loss

Cognitive motor dissociation (CMD)

Consistent goal-directed functional movements

No motor function

VS

MCS

CLIS*

Severe to Moderate Cognitive Disability

Full Cognitive Recovery

LIS*

Schiff JAMA Neurol 2015; Schiff and Fins Curr Biol 2016
Consciousness in the ICU

- RASS score (Richmond Agitation-Sedation Scale): Sessler et al, AJRCC 2002
- GCS (Glasgow Coma Score): Teasdale and Jennett Lancet 1974
- FOUR score (Full Outline of Unresponsiveness Score): Wijdicks et al, Ann Neurol 2005
Coma Recovery Scale-Revised

- Developed to assist with diff dx, prognostication and treatment planning in DOC
- Primarily TBI patients
- 23 items in 6 subscales: auditory, visual, motor, oromotor, communication, arousal functions
- Hierarchical assessment of impaired consciousness
- Able to differentiate VS and MCS
- Established standard for DOC studies

Giacino et al, Arch Phys Rehab Med 2004
Acute Severe Brain Injury

- Resting EEG: assessment and prediction
- Task related modulation of brain activity in unresponsive ICU patients
- Linking functional EEG with functional imaging
Generated by complex interaction btw thalamic burst neurons, cortex, and basal forebrain, all of which receive substantial inputs from the ascending arousal system.
Brief intro to computational EEG analysis

Power spectral analysis

- delta (2–4 Hz)
- theta (4–7 Hz)
- alpha (8–13 Hz)
- gamma (30-50 Hz)

- Complexity analysis: permutation entropy
- Information sharing (coherence, wSMI) functional connectivity between brain regions
- Phase-amplitude coupling: decreased phase-amplitude modulations may represent alterations of thalamo-cortical as well as intracortical connectivity

Fast Fourier Transform
Resting EEG

Anesthesia

Power

Coherence

Supp et al, Curr Biol 2011

Chronic DOC

Coherence analysis

Leon-Carrion et al Brain Res 2012

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

Median explained variance and SD of the partial least squares model.
- 500 repetitions using the first 4 principal components on 90% of the data
- Estimating explained variance using the remaining 10%

Claassen et al Ann Neurol 2016
Complexity and Information sharing measures: coma vs command following (N=83)

Theta Permutation Entropy

Theta weighted Symbolic Mutual Information

Alpha Coherence with Fz

Acute DOC: entropy

Gossieres et al. Funct Neurol 2011
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

33% misclassified?
Prediction of recovery of consciousness

Mesocircuit integrity vs outcome after CA (N=36)

<table>
<thead>
<tr>
<th>Confusion matrix</th>
<th>Best spectra: C,D</th>
<th>Best spectra: A,B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good outcome (CPC 1-3)</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Bad outcome (CPC 4-5)</td>
<td>3</td>
<td>20</td>
</tr>
</tbody>
</table>

Correlated (p=0.0011) with clinical outcome at discharge (CPC)

Forgacs et al Ann Clin Transl Neurol 2017

Vegetative state Based on clinical exam

Based on EEG

VS | MCS
---|---
67% (50) | 33% (25)

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

Never improve | Unknown outcome
Acute Severe Brain Injury

• Resting EEG: assessment and prediction
• Task related modulation of brain activity in unresponsive ICU patients
• Linking functional EEG with functional imaging
Resting state MRI

- Based on fluctuations in blood oxygen level dependent (BOLD) signal
- Analysis: Seed based/ROI vs ICA/PCA
- Identified up to 20 RS networks

Raichle et al PNAS 2001; Fox and Raichel Nat Rev Neursc 2007; Biswal et al.PNAS 2010; Damoiseaux et al.PNAS 2006; Mantini et al.PNAS 2007; Shirer et al.Cerebral cortex. 2012
Impaired consciousness after hemorrhagic stroke (N=25, 9 coma)

**Functional connectivity** differences between comatose and non-comatose:

- ICA: dual regression against template of standard RS networks (GLM using *fsl_glm*. p<0.05 FDR) -> 6 networks impaired in coma

<table>
<thead>
<tr>
<th>Right Executive</th>
<th>Cognitive Control</th>
<th>SMA</th>
<th>Visual Lateral</th>
<th>Visual Occipital</th>
<th>Visual Medial</th>
</tr>
</thead>
</table>

- Seeds: voxels in each network that distinguished comatose and awake
- **Within these networks included the premotor cortex, the dorsal anterior cingulate gyrus, and the supplementary motor area**
- All analyses controlled for FDR, motion, sedation, etiology characteristics
Impaired consciousness after hemorrhagic stroke (N=25, 9 coma)

Right Executive

EEG:
- Coherence calculated in 2-sec bins for 30 min block
- Bootstrap distributions of coherence between F4-Fp2 at 4-7 Hz

- Functional MRI techniques allow independent confirmation of hypotheses developed using EEG
- This allows better spatial resolution
- When combined with DTI imaging may allow us to identify underlying structural causes

Mikell et al Stroke 2015
Task based EEG and fMRI to detect covert consciousness

- Small study of TBI patients (N=16)
- EEG/MRI approx day 9+/-5

Edlow et al, Brain 2017
Task based EEG and fMRI to detect covert consciousness

CRS-R
- coma (n = 2)
- VS (n = 3)
- MCS - language (n = 3)
- MCS + language (n = 4)
- Post-traumatic confusion (n = 4)

ICU EEG/fMRI assessment at 7 days
- CMD in 4 patients
  - 3 recovered at 6 mon
  - 1 died at 6 mon

Edlow et al, Brain 2017
From models to prediction to intervention
Single Cases

Stimulating the central thalamus Directly

Schiff et al. TNS 2012

Schiff et al. Nature 2007
From models to prediction to intervention
Single Cases

Proposed "mesocircuit" model underlying forebrain dysfunction and interventions in severe brain injuries

- Frontal cortex
- Parietal/occipital/temporal cortex
- Striatum (MSN)
- GPi
- Central thalamus
- DBS activation (Glutamatergic afferents)

Inhibition
Excitation

Pre VNS

3 months post VNS

Pre cuneus
Thalamus

Stimulating the thalamus
Via the vagus nerve
From models to prediction to intervention

Single Cases

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
Challenges Assessment of consciousness in the ICU setting

- **Is the patient conscious or not?** “the family reports that he/she is following commands”
- **Arousal versus content** processing?
- **Does the patient comprehend?** (aphasia, locked in, learned stereotyped behavior mimicking comprehension)
- **Cognitive Motor Dissociation**: If the patient comprehends: is he/she only unable to execute the command?
- **Test-retest?** Important for shift changes, different skilled providers, different styles/techniques to examine
- **Fluctuations** in exam versus true improvement/worsening, medication/metabolic/brain physiology/structural effects
- **Confounders**
Conclusions

• Consciousness in ICU setting poorly studied
• May need additional tools to complement behavioral assessments, EEG promising
• Combined multimodal assessment (behavioral, electrophys, imaging): maybe a thumbprint of recovery identifiable
• Promise of interventions in the acute stage that may yield positive impact on outcome, may have to be tailored to individual patient
• Our pre-accepted concepts of recovery and prognosis are likely all based on circular reasoning and self fulfilling prophecies
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