Recent Advances in the Assessment and Diagnosis of Disorders of Consciousness: Behavioral and Neuroimaging Applications

Holy Cross Hospital
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Joseph T. Giacino, PhD
Spaulding Rehabilitation Hospital
Harvard Medical School
Boston, MA USA

Disclosure

Dr. Giacino has no significant financial relationship with any commercial or proprietary entity that produces healthcare-related products and/or services relevant to the content of this presentation.

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Continuum of Recovery of Consciousness:
(Adapted from Laureys, 2003)

**Coma**: A state of sustained pathologic unconsciousness in which the eyes remain closed and the patient cannot be aroused. *(MSTF, NEJM, 1994)*

**Vegetative State**: A condition in which there is complete absence of behavioral evidence for awareness of self and environment, with preserved capacity for spontaneous or stimulus-induced arousal *(Aspen Workgroup, JHTR, 1997)*.

**Permanent VS**: A prognostic term that denotes an irreversible state which can be applied 12 months after a traumatic injury and after 3 months following non-traumatic injury in adults and children *(AAN, Neurol, 1995)*.

**Minimally Conscious State**: A condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated *(Giacino, et al., Neurology, 2002)*.
The Problem of Consciousness

“The limits of consciousness are hard to define satisfactorily and we can only infer the self-awareness of others by their appearance and their acts.”

Plum and Posner, 1982
The Diagnosis of Stupor and Coma

Neurobehavioral Approaches to Diagnostic Assessment

Behavior = Gold standard
Neurobehavioral Approaches to Diagnostic Assessment

Evidence of sustained or reproducible command-following or yes/no responses or intelligible verbalization or selective responses to specific environmental stimuli?

No

Absent brainstem function and apnea?

Yes

Pt has sleep wake cycles & opens eyes spontaneously or to stimulation

Brain death

No

Coma

Yes

VS

Yes

Functional communication or functional object use?

No

MCS

Yes

Communication limited to eye movement or blinking

No

Post-Traumatic Confusional State

Yes

Locked-in Syndrome

(Adapted from Ashwal, et al, Sem in Ped Neurol, 2002)
## Summary of Evidence Supporting Measurement Properties of Behavioral Assessment Scales for DOC

<table>
<thead>
<tr>
<th>Scale</th>
<th>Standardized Admin/Scoring</th>
<th>Content Validity</th>
<th>Internal Consistency</th>
<th>Inter-Rater Reliability</th>
<th>Test-Retest Reliability</th>
<th>Criterion Validity</th>
<th>Diagnostic Validity</th>
<th>Prognostic Validity</th>
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<tr>
<td>CRS-R</td>
<td>Acceptable</td>
<td>Excellent</td>
<td>Good (class I)</td>
<td>Good (class II / III)</td>
<td>Excellent (class II / III)</td>
<td>Unproven (class IV)</td>
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<td>Predictive, 30 days post-injury Good vs. Disability and Death (class I)</td>
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*(Seel, et al., Arch Phys Med & Rehabil, 2010)*

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### JFK COMA RECOVERY SCALE - REVISED

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*(Seel, et al., Arch Phys Med & Rehabil, 2010)*

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### JFK COMA RECOVERY SCALE - REVISED

This form should only be used in association with the "CRS-R ADMINISTRATION AND SCORED GUIDELINES" which provide instructions for standardized administration of the scale.

#### Patient Information

<table>
<thead>
<tr>
<th>Patient:</th>
<th>Diagnosis:</th>
<th>Skull:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth:</td>
<td>Date of Admission:</td>
<td></td>
</tr>
</tbody>
</table>

#### AUDITORY FUNCTION SCALE

4. Comprehension to Command *
3. Reproducible Movement to Command *
2. Localization to Sound *
1. Auditory Startle *
0. None

#### VISUAL FUNCTION SCALE

5. Object Recognition *
4. Object Localization (Touching) *
3. Visual Pursuit *
2. Reactions *
1. Visual Startle *
0. None

#### MOTOR FUNCTION SCALE

9. Functional Object Use *
8. Automatic Motor Responses *
7. Object Manipulation *
6. Localization to Visual Stimuli *
5. Flexion (Withdrawal) *
4. Abnormal Finishing *
3. Normal Placed *
2. None

#### MOTOR FUNCTION SCALE

GROSS/MOTOR FUNCTION SCALE

5. Ineffective Localization *
4. Vocalization/Vocal Movement *
3. Ocular Reflex Movement *
2. None

#### COMMUNICATION SCALE

GROSS/MOTOR FUNCTION SCALE

2. Pseudobulbar - Accurate *
1. Non-Functional Intention *
0. None

#### MOTOR SCALE

1. Abolition *
2. Eye Opening to Stimulation *
3. Eye Opening with Stimulation *
4. Intubation *

#### TOTAL SCORE

(Giacino, Kalmar, Whyte, Arch Phys Med Rehabil, 2004)
Coma Recovery Scale- Revised: Psychometric Characteristics


Table 4 - Item parameters and fit statistics for the CRS-R (N=258, analysis no. 4).

<table>
<thead>
<tr>
<th>CRS-R subcales</th>
<th>Location</th>
<th>SE</th>
<th>Fit residual</th>
<th>$\chi^2$</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS-R Adrenalin</td>
<td>-0.941</td>
<td>0.124</td>
<td>-0.036</td>
<td>4.808</td>
<td>0.179</td>
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<tr>
<td>CRS-R Motor</td>
<td>-0.025</td>
<td>0.082</td>
<td>0.641</td>
<td>3.492</td>
<td>0.322</td>
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<tr>
<td>CRS-R Visual (CRS-R Hommeignon)</td>
<td>0.087</td>
<td>0.100</td>
<td>-0.207</td>
<td>1.692</td>
<td>0.439</td>
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<tr>
<td>CRS-R Anxiety</td>
<td>-0.064</td>
<td>0.102</td>
<td>0.037</td>
<td>4.554</td>
<td>0.175</td>
</tr>
<tr>
<td>CRS-R Omo-motor</td>
<td>0.027</td>
<td>0.117</td>
<td>0.943</td>
<td>6.657</td>
<td>0.539</td>
</tr>
<tr>
<td>CRS-R Visual (Anoetom- Aisomo)</td>
<td>0.164</td>
<td>0.171</td>
<td>-0.094</td>
<td>4.093</td>
<td>0.252</td>
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<tr>
<td>CRS-R Communication</td>
<td>2.166</td>
<td>1.177</td>
<td>-0.044</td>
<td>6.013</td>
<td>0.206</td>
</tr>
</tbody>
</table>

Table 5: Test-Retest Reliability of Dichotomized CRS-R Subscale Scores (n=20).

<table>
<thead>
<tr>
<th>CRS-R Subscale</th>
<th>Cohen $\kappa$</th>
<th>95% CI</th>
<th>P*</th>
<th>Rater Agreement</th>
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<tbody>
<tr>
<td>Auditory</td>
<td>0.63</td>
<td>0.50</td>
<td>0.77</td>
<td>0.95</td>
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<tr>
<td>Visual</td>
<td>0.50</td>
<td>0.36</td>
<td>0.68</td>
<td>0.89</td>
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<tr>
<td>Motor</td>
<td>0.50</td>
<td>0.36</td>
<td>0.68</td>
<td>0.89</td>
</tr>
<tr>
<td>Omo-motor</td>
<td>0.30</td>
<td>0.15</td>
<td>0.52</td>
<td>0.73</td>
</tr>
<tr>
<td>Communication</td>
<td>0.63</td>
<td>0.50</td>
<td>0.77</td>
<td>0.95</td>
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</tbody>
</table>

Table 6: Frequency of Test-Retest Agreement in Diagnosis (n=20).

<table>
<thead>
<tr>
<th>CRS-R Subscale</th>
<th>VS</th>
<th>MCS</th>
<th>MCS+</th>
<th>Total</th>
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<tbody>
<tr>
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<td>8/20</td>
<td>8/20</td>
<td>5/20</td>
<td>21/20</td>
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<td>Visual</td>
<td>8/20</td>
<td>8/20</td>
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<td>8/20</td>
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<tr>
<td>Communication</td>
<td>8/20</td>
<td>8/20</td>
<td>5/20</td>
<td>21/20</td>
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</table>

Table 7: Frequency of Agreement Between CRS-R and DRS-Derived Diagnoses (N=80).

<table>
<thead>
<tr>
<th>CRS-R Subscale</th>
<th>VS</th>
<th>MCS</th>
<th>DRS</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Auditory</td>
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<td>16/80</td>
<td>0/80</td>
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<tr>
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<td>64/80</td>
<td>16/80</td>
<td>0/80</td>
<td>80/80</td>
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<tr>
<td>Motor</td>
<td>64/80</td>
<td>16/80</td>
<td>0/80</td>
<td>80/80</td>
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<tr>
<td>Omo-motor</td>
<td>64/80</td>
<td>16/80</td>
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<tr>
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<td>16/80</td>
<td>0/80</td>
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Table 8: Frequency of Agreement Between CRS-R Subscale and DRS-Derived Diagnoses (n=20).

<table>
<thead>
<tr>
<th>CRS-R Subscale</th>
<th>VS</th>
<th>MCS</th>
<th>DRS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
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<td>5/20</td>
<td>1/20</td>
<td>15/20</td>
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Coma Recovery Scale- Revised: Construct Validity

(Gerard, et al., Arch Phys Med Rehabil, 2014)

Coma Recovery Scale- Revised: Diagnostic Sensitivity/Specificity

(Bodien, et al., Arch Phys Med Rehabil, 2016)
Limitations of Behavioral Assessment

• Behavior is a poor proxy for conscious awareness
  – Eg, Cannot differentiate volitional from involuntary or reflexive movement (eg, smiling)
• May fail to detect co-existing sensory (eg, blindness), motor (eg, contractures) and cognitive impairments (eg, aphasia)
• Subject to subjective bias of examiner
  – No standard of care for examination procedures or response interpretation

(Giacino & Smart, Curr Opin Neurol, 2007)

Incidence of diagnostic error

- 37% (Childs et al, Neurol, 1993)
- 43% (Andrews et al, BMJ, 1996)
- 41% (Schnakers et al, Brain Injury, 2008)
Neuroimaging Approaches to Diagnostic Assessment

The Broad Spectrum of TBI Pathophysiology

Contusio  TAI  EDH
SA  SDH  Penetrating Injury  Fracture  Dissection
Neuroimaging to Detect Traumatic Axonal Injury

- Conventional MRI

- Advanced imaging techniques
  - Susceptibility-weighted imaging (SWI)
  - Diffusion tensor imaging (DTI)
  - Diffusion tractography
  - Resting state functional MRI (rs-fMRI)
  - Stimulus-based functional MRI (fMRI)

- Limitations, pitfalls and artifacts

The Clinical Challenge
- Traumatic Coma -

- 19yo M unrestrained driver in MVA
- Glasgow Coma Scale score = 6T (E1, V1T, M4)
- Bilateral hemicraniectomies for EDH evacuation (day 1)
Conventional MRI (Day 8)
- T2*-Weighted Gradient-recalled Echo -


R² = 0.39, p<0.001

R² = 0.82, p<0.0001

Duration of Unconsciousness (hours)


Diffusion-Weighted Imaging (Day 8)

Wu et al. Radiology 2009;252: 173-181

Median Whole-Brain and Regional ADCs versus Outcome according to 6-month Modified Rankin Scale Score

Wu et al. Radiology 2009;252: 173-181

Unexpected Recovery from Traumatic Coma

Photos shown with consent from patient and family

Day 254 - Rehabilitation

Day 356 – Home with family

Advanced Imaging Techniques

- Susceptibility-weighted Imaging (SWI) -
Can Advanced Imaging Techniques Improve Prognostic Accuracy?

- 23yo F in traumatic coma (GCS 4T) on day 10 post-injury -

Detecting Traumatic Microbleeds
- Sequence Selection & Field Strength -


Tong et al. Ann Neurol 2004;56:36-50

Edlow, Giacino et al. Neurocritical Care 2013; epub ahead of print.
Advanced Imaging Techniques
- Diffusion Tensor Imaging -

Diffusion Tensor Imaging (DTI)
- Fractional Anisotropy (FA) Maps -

Wiegell et al. Radiology 2000;217:897-903
DTI and Neurocognition in Traumatic DOC
- Tract-based Spatial Statistics -

The DTI IMPACT Score

White Matter ROIs (n= 20)

Severe TBI Cohort (n= 105)

Individual Patient Analysis
**Advanced Imaging Techniques**

- **Diffusion Tractography** -

Diffusion Tensor Tractography
- Background and Principles

Diffusion Tractography in TBI

Newcombe et al. JNNP 2010; 81:552-561

Controls (n=11)  Severe TBI Patients (n=9)  TBI Patients (n=28, severe=23)

An fMRI-based visual cognition paradigm for detection of command-following and communication

N=20 Healthy Subjects

Visual Discrimination - YES

Communication - YES

Visual Discrimination - Places

Communication (False) - Places

Newcombe et al. JNNP 2010;81:552-561
Implications for Clinical Practice

- The sensitivity and specificity of clinical and neuroimaging predictors relevant to patients with DOC remain unknown.

- In the absence of a “gold standard” for predicting outcome, a multimodal approach that combines 1) behavioral, 2) imaging, and 3) electrophysiologic tools is warranted.

- In communicating prognosis, the clinician should a) tie the prognosis to the strength and consistency of the available data and b) indicate the level of confidence in the prognostic assessment.

### Prognostic Confidence Matrix

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<tbody>
<tr>
<td>Imaging +</td>
<td>High</td>
</tr>
<tr>
<td>Imaging -</td>
<td>Low</td>
</tr>
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Integration of Behavioral, Structural & Functional Data
- Traumatic Coma RESPONSE Study -


Multimodal Approach: Clinical-Radiologic Correlations

Day 8
Day 44
Day 198
Day 366

MPFC
PCC
Left 1.5T
Right 1.5T 1.5T 3T

Th Th

Z Score

DRS
CRS-R

Days Since TBI
Summary

• Disorders of consciousness exist along a dynamic continuum of residual cognitive function.
• Diagnostic error remains high among patients with DoC.
• Behavioral assessment remains the gold standard for differential diagnosis.
• Neuroimaging procedures may play a pivotal role in detecting conscious awareness in patients with concurrent sensory, motor and cognitive deficits, but sensitivity and specificity must be carefully considered.
• Multimodal assessment should be conducted to improve diagnostic precision.
• Diagnostic impression should always be framed within the limits of confidence.
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Department of Physical Medicine & Rehabilitation
Harvard Medical School
Spaulding Rehabilitation Hospital
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