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

Holy Cross Hospital
Surrey, UK
September 14, 2016

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Disclosure

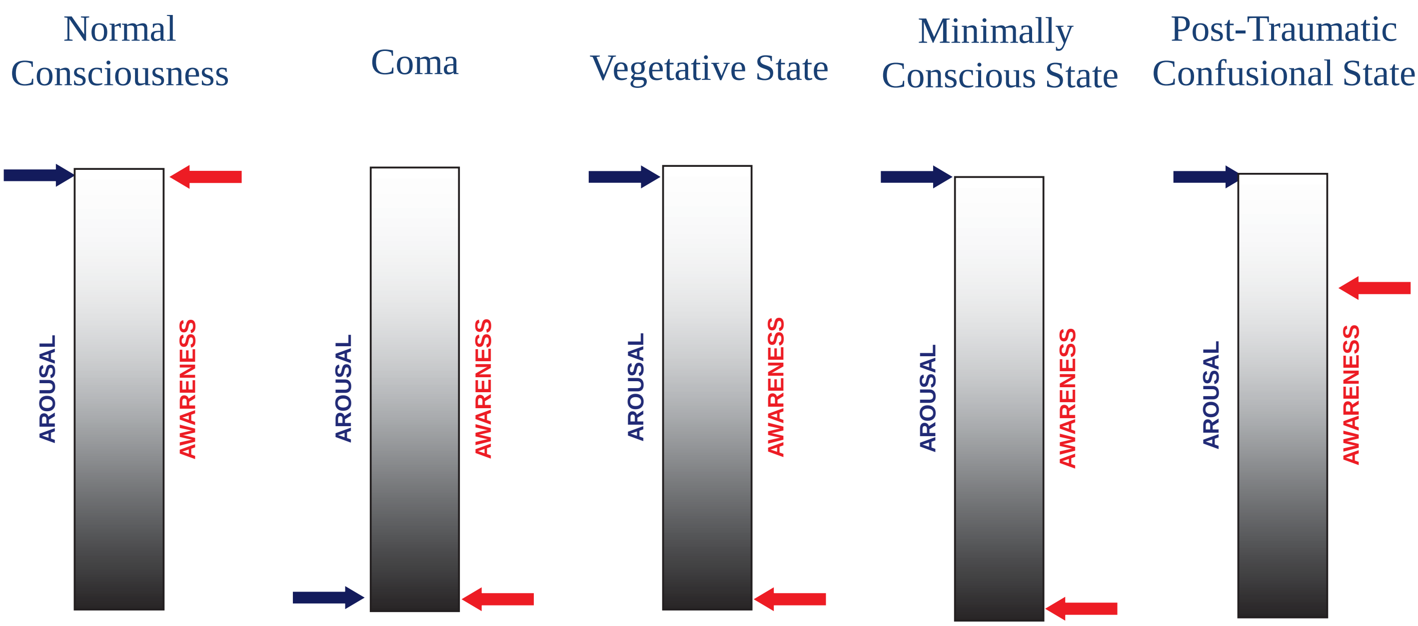
Dr. Giacino has no significant financial relationship with any commercial or proprietary entity that produces healthcare-related products and/or services relevant to the content of this presentation.

Dr. Giacino occasionally receives honoraria for conducting CRS-R training seminars.

Dr. Giacino receives grant funding from the National Institute of Neurological Disorders and Stroke, the National Institute on Disability, Independent Living and Rehabilitation Research, U.S. Department of Defense and the James S. McDonnell Foundation.

Continuum of Recovery of Consciousness:

(Adapted from Laureys, 2003)



Disorders of Consciousness

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

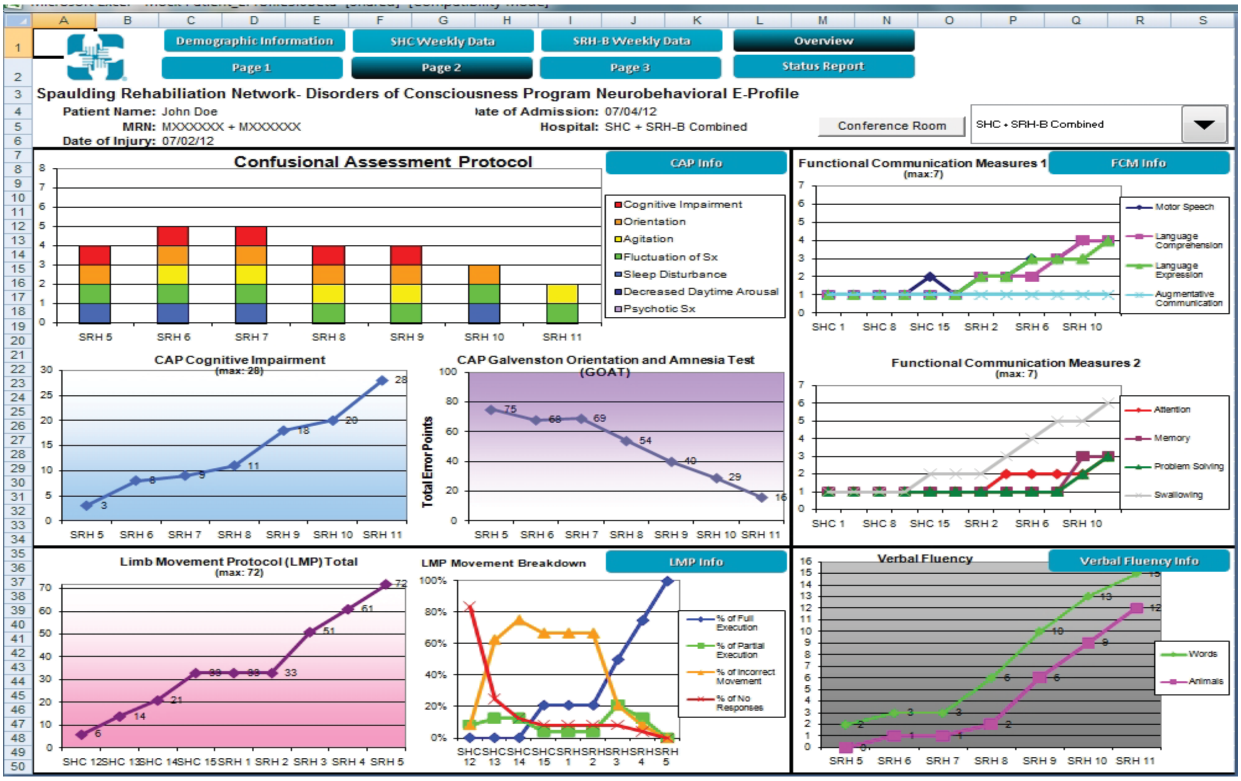
"The limits of consciousness are hard to define satisfactorily and we can only infer the self-awareness of others by their appearance and their acts."

Plum and Posner, 1982
The Diagnosis of Stupor and Coma

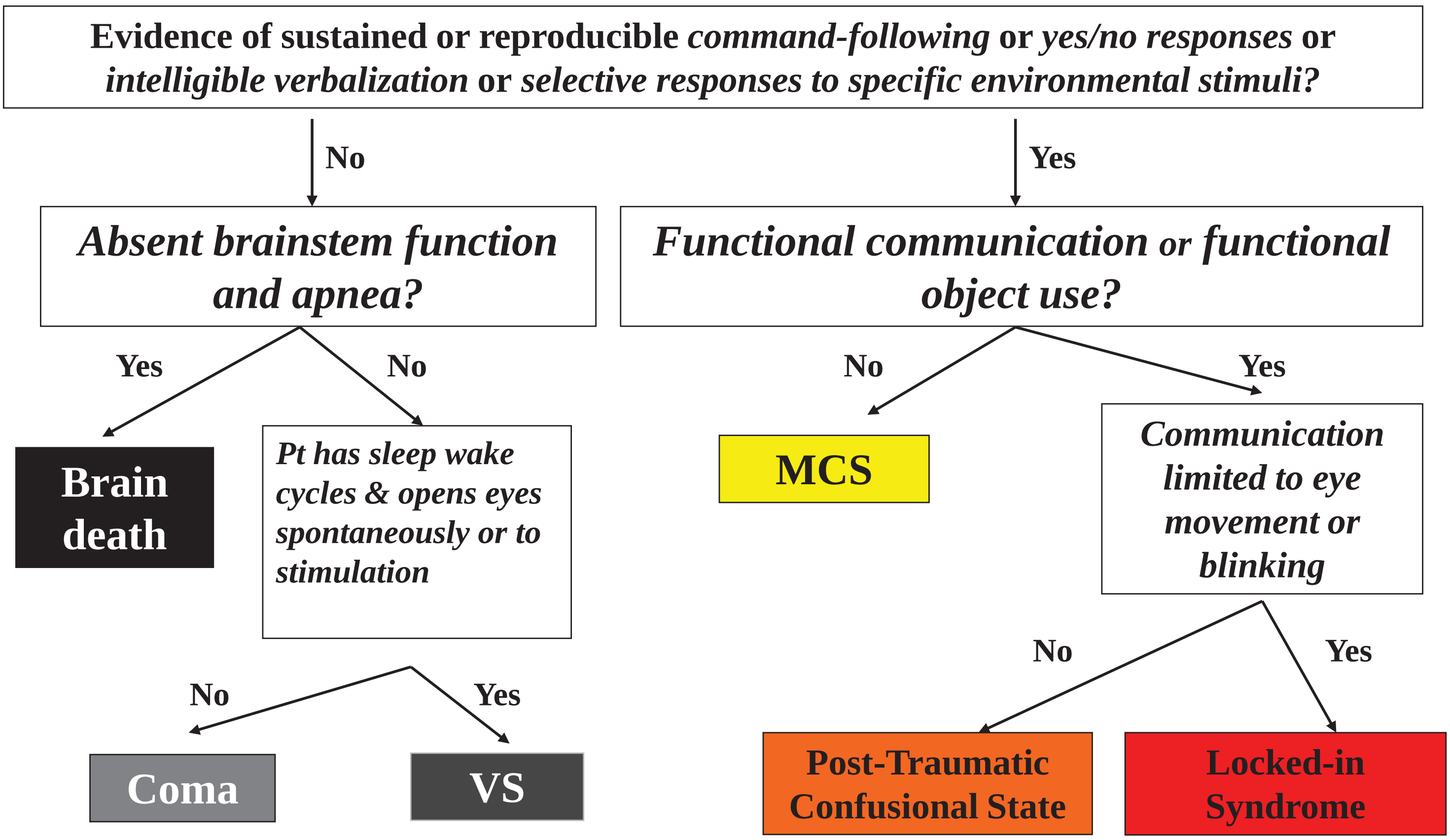
Neurobehavioral Approaches to Diagnostic Assessment

Behavior = Gold standard

Neurobehavioral Approaches to Diagnostic Assessment



Behavioral Algorithm for Differential Diagnosis



(Adapted from Ashwal, et al, Sem in Ped Neurol, 2002)

Summary of Evidence Supporting Measurement Properties of Behavioral Assessment Scales for DOC

Scale	Standardized Admin/Scoring	Content Validity Aspen Criteria	Internal Consistency	Inter-Rater Reliability	Test-Retest Reliability	Criterion Validity	Diagnostic Validity	Prognostic Validity
CRS-R	Acceptable	Excellent	Good (class I)	Good (multiple class II / III)	Excellent (class II / III)	Unproven (class IV)	Unproven (class IV)	Unproven (not studied)
SMART	Acceptable	Good	NA	Excellent (class II / III)	Excellent (class II / III)	Unproven (class IV)	Unproven (not studied)	Unproven (class IV)
WNSSP	Acceptable	Good	Excellent (class I)	Unproven (class IV)	Unproven (class IV)	Unproven (class IV)	Unproven (not studied)	Unproven (class IV)
SSAM	Acceptable	Good	Unproven (not studied)	Unproven (class IV)	Unproven (class IV)	Unproven (class IV)	Unproven (not studied)	Unproven (not studied)
WHIM	Acceptable	Good	Unproven (not studied)	Unproven (class IV)	Unproven (class IV)	Unproven (class IV)	Unproven (not studied)	Unproven (not studied)
DOCS	Acceptable	Acceptable	Good (class II / III)	Unproven (class IV)	Unproven (not studied)	Construct Valid * (class III)	Unproven (not studied)	Unproven (class IV)
CNC	Acceptable	Acceptable	Unacceptable (class II / III)	Unproven (class IV)	Unproven (not studied)	Unproven (class IV)	Unproven (class IV)	Unproven (class IV)
CLOCS	Unacceptable	Acceptable	Good (class I)	Unproven (class IV)	Unproven (class IV)	Strong (class III)	Unproven (not studied)	Unproven (class IV)
LOEW	Unacceptable	Acceptable	Unproven (not studied)	Excellent (class II / III)	Unproven (not studied)	Unproven (not studied)	Unproven (not studied)	Unproven (class IV)
RLS85	Unacceptable	Acceptable	NA	Unproven (class IV)	Unproven (not studied)	Strong (class III)	Unproven (class IV)	Unproven (class IV)
FOUR	Unacceptable	Unacceptable	Excellent (multiple class I)	Good (multiple class I)	Unproven (not studied)	Unproven (not studied)	Unproven (not studied)	Predictive, 30 days post-injury Good vs. Disability and Death (class I)
INNS	Unacceptable	Unacceptable	Acceptable (class I)	Unproven (not studied)	Unproven (not studied)	Unproven (not studied)	Unproven (not studied)	Not predictive, 3 mos. Post-discharge Independent vs. Disability (class I)
GLS	Unacceptable	Unacceptable	Unproven (not studied)	Unacceptable (class II / III)	Unproven (not studied)	Unproven (not studied)	Unproven (not studied)	Not predictive, 6 months post-injury Good/Mod Dis. vs. Severe Dis./PVS (class III) Predictive, 6 months post-injury Good/Mod Dis. vs. Sev Dis./VS/Death (class III)

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

Coma Recovery Scale- Revised

JFK COMA RECOVERY SCALE - REVISED ©2004

Record Form

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

Patient:	Diagnosis:	Etiology:
Date of Onset:	Date of Admission:	

Date															
Week	ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
AUDITORY FUNCTION SCALE																
4 - Consistent Movement 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: Reaching *																
3 - Visual Pursuit *																
2 - Fixation *																
1 - Visual Startle																
0 - None																
MOTOR FUNCTION SCALE																
6 - Functional Object Use †																
5 - Automatic Motor Response *																
4 - Object Manipulation *																
3 - Localization to Noxious Stimulation *																
2 - Flexion Withdrawal																
1 - Abnormal Posturing																
0 - None/Flaccid																
OROMOTOR/VERBAL FUNCTION SCALE																
3 - Intelligible Verbalization *																
2 - Vocalization/Oral Movement																
1 - Oral Reflexive Movement																
0 - None																
COMMUNICATION SCALE																
2 - Functional: Accurate †																
1 - Non-Functional: Intentional *																
0 - None																
AROUSAL SCALE																
3 - Attention																
2 - Eye Opening w/o Stimulation																
1 - Eye Opening with Stimulation																
0 - Unarousable																
TOTAL SCORE																

Denotes emergence from MCS†
Denotes MCS *

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(Giacino, Kalmar, Whyte, Arch Phys Med Rehabil, 2004)

Coma Recovery Scale- Revised: Psychometric Characteristics

The JFK Coma Recovery Scale–Revised: Measurement Characteristics and Diagnostic Utility

Joseph T. Giacino, PhD, Kathleen Kalmar, PhD, John Whyte, MD, PhD

ABSTRACT. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020-9.

Objective: To determine the measurement properties and diagnostic utility of the JFK Coma Recovery Scale-Revised (CRS-R).

Design: Analysis of interrater and test-retest reliability, internal consistency, concurrent validity, and diagnostic accuracy.

Setting: Acute inpatient brain injury rehabilitation hospital.

Participants: Convenience sample of 80 patients with severe acquired brain injury admitted to an inpatient Coma Intervention Program with a diagnosis of either vegetative state (VS) or minimally conscious state (MCS).

Interventions: Not applicable.

Main Outcome Measures: The CRS-R, the JFK Coma Recovery Scale (CRS), and the Disability Rating Scale (DRS).

Results: Interrater and test-retest reliability were high for CRS-R total scores. Subscale analysis showed moderate to high interrater and test-retest agreement although systematic differences in scoring were noted on the visual and oromotor/verbal subscales. CRS-R total scores correlated significantly with total scores on the CRS and DRS indicating acceptable concurrent validity. The CRS-R was able to distinguish 10 patients in an MCS who were otherwise misclassified as in a VS by the DRS.

Conclusions: The CRS-R can be administered reliably by trained examiners and repeated measurements yield stable estimates of patient status. CRS-R subscale scores demonstrated good agreement across raters and ratings but should be used cautiously because some scores were underrepresented in the current study. The CRS-R appears capable of differentiating patients in an MCS from those in a VS.

Key Words: Coma; Minimally conscious state; Outcome assessment (health care); Persistent vegetative state; Rehabilitation.

SPECIALIZED ASSESSMENT instruments designed for use in patients with disorders of consciousness (including coma,[1] vegetative state [VS],[2] minimally conscious state [MCS][3]) were first introduced in rehabilitation settings in the early 1990s.[4-7] Most were developed by neurorehabilitation specialists who recognized the inherent constraints of the Glasgow Coma Scale[8] (GCS) and Levels of Cognitive Functioning Scale[9] (LCFS) in detecting subtle but potentially meaningful changes in neurobehavioral function. In contrast to the GCS and LCFS, these second-generation tools employ a standardized approach to assessment to ensure adequate interrater reliability.[10] The primary indications for use of standardized measures in this population include diagnostic assessment, outcome prediction, projection of disposition needs, interdisciplinary treatment planning, and monitoring treatment effectiveness.

Description and Purpose of the JFK Coma Recovery Scale

The JFK Coma Recovery Scale (CRS), initially described by Giacino et al in 1991,[6] was developed to more fully characterize and monitor patients functioning at LCFS levels I through IV. The CRS consists of 25 hierarchically arranged items that comprise 6 subscales addressing auditory, visual, motor, oromotor, communication, and arousal processes. Scoring is based on the presence or absence of specific behavioral responses to sensory stimuli administered in a standardized manner. The lowest item on each subscale represents reflexive activity, whereas the highest items represent cognitively mediated behaviors. A previously completed factor analytic study[11] found that individual CRS items tended to cluster together in distinct subgroups. These subgroups were composed of items associated with brainstem, subcortical, and cortical functions, suggesting that the scale is capable of defining different levels of neurobehavioral function. Adequate interrater reliability has been demonstrated for total CRS scores[6] and for each of the 6 individual subscales.[12] Concurrent validity has been established using the GCS and the Disability Rating Scale[13] (DRS).

Clinical and Research Applications

The CRS has been used in clinical and research settings. Giacino and Kalmar[14] used the CRS to estimate the incidence of selected neurobehavioral signs in patients admitted to rehabilitation with a diagnosis of either VS or MCS. Visual tracking and motor agitation were observed significantly more frequently in the MCS group. Among patients in the VS group, 73% (8/11) of those with tracking recovered consciousness within the first 12 months postinjury, as compared with 45% (20/44) of those without tracking. This difference highlights the importance of visual tracking in outcome prediction.

The prognostic utility of the CRS has been investigated in a number of additional studies. Giacino[6] found that CRS change scores obtained over the initial 4 weeks of inpatient rehabilitation correlated more strongly with functional outcome at 1 year than did GCS change scores, after controlling for the influence of injury severity and length of time postinjury. In a second study[14] exploring the influence of diagnosis on functional outcome, level of functional disability on the DRS was significantly lower at 12 months postinjury in patients diagnosed with MCS on admission to rehabilitation (mean time postinjury, 9wk), relative to those in VS. This difference was most pronounced for patients with traumatic brain injury (TBI)

From the JFK Johnson Rehabilitation Institute and New Jersey Neuroscience Institute, JFK Medical Center, Edison, NJ (Giacino, Kalmar); and Moss Rehabilitation Research Institute, Albert Einstein Healthcare Network, and Thomas Jefferson University, Philadelphia, PA (Whyte).

Supported in part by the Irving I. and Felicia F. Rubin Family Brain Injury Research Grant.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

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0003-9993/04/8512-8510$30.00/0
doi:10.1016/j.apmr.2004.02.033

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

CRS-R Subscale	Cohen κ	95% CI	P	Rater Agreement
Auditory	0.63	±.35	.00	85%
Visual	0.90	±.19	.00	95%
Motor	1.00	±.00	.00	100%
Oromotor/verbal	0.23	±.51	.17	70%
Communication	0.89	±.22	.00	95%

Table 7: Frequency of Test-Retest Agreement in Diagnosis (n=20)

		Rater A2			
		VS	MCS	MCS+	Total
Rater A1	VS	5	0	0	5
	MCS	1	11	1	13
	MCS+	0	0	2	2
	Total	6	11	3	20

Table 10: Frequency of Agreement Between CRS-R– and DRS-Derived Diagnoses (N=80)

		DRS		
		MCS	VS	Total
CRS-R	MCS	51	10	61
	VS	0	19	19
	Total	51	29	80

Coma Recovery Scale- Revised: Scaling Properties*(LaPorta, et al., Arch Phys Med Rehabil, 2010*

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Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2013;94:527-35

ORIGINAL ARTICLE

Can We Scientifically and Reliably Measure the Level of Consciousness in Vegetative and Minimally Conscious States? Rasch Analysis of the Coma Recovery Scale-Revised

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Abstract

Objectives: (1) To appraise, by the means of Rasch analysis, the internal validity and reliability of the Coma Recovery Scale-Revised (CRS-R) in a sample of patients with disorder of consciousness (DOC); and (2) to provide information about the comparability of CRS-R scores across persons with DOC across different settings and groups, including different etiologies.

Design: Multicenter observational prospective study.

Setting: Two rehabilitation wards, 1 intermediate care facility, and 2 nursing homes in Italy.

Participants: Consecutively admitted patients (N=129) for which assessments at 2 different time points were available, giving a total sample of 258 observations.

Interventions: Not applicable.

Main Outcome Measure: CRS-R.

Results: After controlling for any possible dependency between persons' measures collected at different time points, and for uniform differential item functioning by etiology showed by the visual subscale, Rasch analysis demonstrated adequate satisfaction of all the model's requirements, including adequate ordering of scoring categories, unidimensionality, local independence, invariance ($\chi^2_{21}=27.798$, $P=.146$), and absence of differential item functioning across patients' sex, age, time, and setting. The reliability (person separation index=.896) was adequate for individual person measurement. We devised a practical raw score to measure conversion tables based on the CRS-R calibrations.

Conclusions: The CRS-R is a psychometrically sound and robust measurement tool. The linear measures of ability derived from the CRS-R total scores do satisfy all the principles of scientific measurement and are sufficiently reliable for high stakes assessments, such as the diagnosis of the level of consciousness in individual patients. Future studies are needed to directly explore the capabilities of the CRS-R measures to reduce the risk of vegetative state misdiagnosis.

Archives of Physical Medicine and Rehabilitation 2013;94:527-35

Presented to the Congress of the European Society of Physical and Rehabilitation Medicine, May 23–27, 2010, Venice, Italy, and the Congress of the European Federation for Research in Rehabilitation, May 26–28, 2011, Riva del Garda, Italy.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

The Coma Recovery Scale-Revised (CRS-R) was proposed by Giacino et al[1] as a bedside standardized neurobehavioral assessment tool incorporating the current diagnostic criteria for vegetative state (VS), minimally conscious state (MCS), and emergence from the MCS.[2] It consists of 29 hierarchically organized items grouped into 6 subscales addressing auditory, visual, motor, oromotor/verbal,

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http://dx.doi.org/10.1016/j.apmr.2012.09.035

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

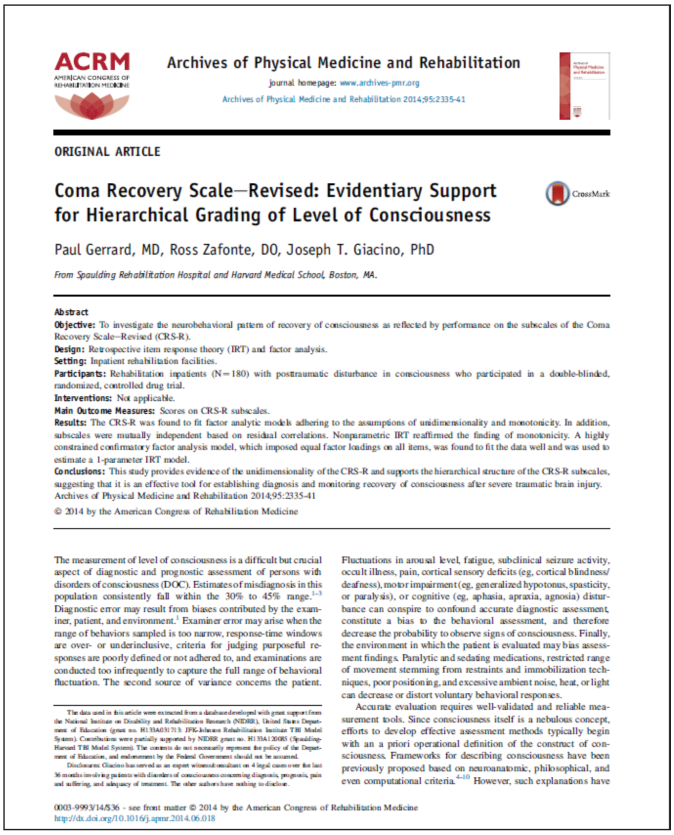
CRS-R subscales	Location	SE	Fit residual	χ^2	P*
CRS6 - Arousal	-1.914	.124	-0.036	4.898	.179
CRS3 - Motor	-0.205	.082	0.641	3.492	.322
CRS2b - Visual (TBI-Haemorrhage)	-0.097	.100	-0.207	1.692	.639
CRS1 - Auditory	-0.064	.102	-1.057	4.954	.175
CRS4 - Oro-motor	0.027	.117	0.903	4.657	.199
CRS2a - Visual (Anoxic - Ischaemic)	0.164	.171	-0.964	4.093	.252
CRS5 - Communication	2.186	.177	-0.984	4.013	.260

Table 4 Raw score to measure estimates conversion table for the CRS-R based on the original sample calibrations

	Traumatic and Hemorrhagic Brain Injury				Anoxic and Other Causes of Brain Injury			
Raw Score	Logit Scale	±95%CI	0–100 Scale	±95%CI	Logit Scale	±95%CI	0–100 Scale	±95%CI
0	−5.871	1.335	0.0	23.6	−5.823	1.364	0.4	24.1
1	−4.992	0.974	7.9	17.2	−4.941	0.986	8.4	17.4
2	−4.296	0.817	14.2	14.4	−4.228	0.833	14.8	14.7
3	−3.744	0.748	19.2	13.2	−3.650	0.771	20.0	13.6
4	−3.242	0.718	23.7	12.7	−3.111	0.746	24.9	13.2
5	−2.753	0.704	28.1	12.4	−2.571	0.736	29.7	13.0
6	−2.264	0.695	32.5	12.3	−2.024	0.724	34.6	12.8
7	−1.781	0.684	36.8	12.1	−1.490	0.698	39.5	12.3
8	−1.316	0.669	41.0	11.8	−1.005	0.659	43.8	11.6
9	−0.876	0.653	45.0	11.5	−0.591	0.617	47.6	10.9
10	−0.460	0.636	48.7	11.2	−0.239	0.585	50.7	10.3
11	−0.065	0.620	52.3	10.9	0.074	0.564	53.5	10.0
12	0.310	0.604	55.7	10.7	0.369	0.553	56.2	9.8
13	0.666	0.591	58.9	10.4	0.661	0.549	58.8	9.7
14	1.003	0.579	61.9	10.2	0.956	0.550	61.5	9.7
15	1.323	0.573	64.8	10.1	1.255	0.554	64.2	9.8
16	1.634	0.573	67.6	10.1	1.557	0.562	66.9	9.9
17	1.950	0.584	70.4	10.3	1.868	0.576	69.7	10.2
18	2.286	0.607	73.5	10.7	2.198	0.601	72.7	10.6
19	2.661	0.644	76.8	11.4	2.567	0.639	76.0	11.3
20	3.095	0.700	80.8	12.4	2.997	0.697	79.9	12.3
21	3.620	0.789	85.5	13.9	3.521	0.789	84.6	13.9
22	4.314	0.965	91.7	17.0	4.222	0.968	90.9	17.1
23	5.232	1.313	100.0	23.2	5.157	1.318	99.3	23.3

NOTE. As the visual subscale was split for etiology, both etiology-specific person estimates were reported. The latter are expressed both in logits and in a 0 to 100 (or percentage) scale.
Abbreviation: CI, confidence interval (equal to 1.96 standard error of measurement).

Coma Recovery Scale- Revised: Construct Validity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Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2014;95:2335-41

ORIGINAL ARTICLE

Coma Recovery Scale—Revised: Evidentiary Support for Hierarchical Grading of Level of Consciousness

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Abstract

Objective: To investigate the neurobehavioral pattern of recovery of consciousness as reflected by performance on the subscales of the Coma Recovery Scale—Revised (CRS-R).

Design: Retrospective item response theory (IRT) and factor analysis.

Setting: Inpatient rehabilitation facilities.

Participants: Rehabilitation inpatients (N=180) with posttraumatic disturbance in consciousness who participated in a double-blinded, randomized, controlled drug trial.

Interventions: Not applicable.

Main Outcome Measures: Scores on CRS-R subscales.

Results: The CRS-R was found to fit factor analytic models adhering to the assumptions of unidimensionality and monotonicity. In addition, subscales were mutually independent based on residual correlations. Nonparametric IRT reaffirmed the finding of monotonicity. A highly constrained confirmatory factor analysis model, which imposed equal factor loadings on all items, was found to fit the data well and was used to estimate a 1-parameter IRT model.

Conclusions: This study provides evidence of the unidimensionality of the CRS-R and supports the hierarchical structure of the CRS-R subscales, suggesting that it is an effective tool for establishing diagnosis and monitoring recovery of consciousness after severe traumatic brain injury.

Archives of Physical Medicine and Rehabilitation 2014;95:2335-41

The measurement of level of consciousness is a difficult but crucial aspect of diagnostic and prognostic assessment of persons with disorders of consciousness (DOC). Estimates of misdiagnosis in this population consistently fall within the 30% to 45% range.[1-3] Diagnostic error may result from biases contributed by the examiner, patient, and environment.[1] Examiner error may arise when the range of behaviors sampled is too narrow, response-time windows are over- or underinclusive, criteria for judging purposeful responses are poorly defined or not adhered to, and examinations are conducted too infrequently to capture the full range of behavioral fluctuation. The second source of variance concerns the patient. Fluctuations in arousal level, fatigue, subclinical seizure activity, occult illness, pain, cortical sensory deficits (eg, cortical blindness/deafness), motor impairment (eg, generalized hypotonus, spasticity, or paralysis), or cognitive (eg, aphasia, apraxia, agnosia) disturbance can conspire to confound accurate diagnostic assessment, constitute a bias to the behavioral assessment, and therefore decrease the probability to observe signs of consciousness. Finally, the environment in which the patient is evaluated may bias assessment findings. Paralytic and sedating medications, restricted range of movement stemming from restraints and immobilization techniques, poor positioning, and excessive ambient noise, heat, or light can decrease or distort voluntary behavioral responses.

Accurate evaluation requires well-validated and reliable measurement tools. Since consciousness itself is a nebulous concept, efforts to develop effective assessment methods typically begin with an a priori operational definition of the construct of consciousness. Frameworks for describing consciousness have been previously proposed based on neuroanatomic, philosophical, and even computational criteria.[4-10] However, such explanations have

The data used in this article were extracted from a database developed with grant support from the National Institute on Disability and Rehabilitation Research (NIDRR), United States Department of Education (grant no. H133A031713: JFK-Johnson Rehabilitation Institute TBI Model System). Contributions were partially supported by NIDRR grant no. H133A120085 (Spaulding-Harvard TBI Model System). The contents do not necessarily represent the policy of the Department of Education, and endorsement by the Federal Government should not be assumed.

Disclosures: Giacino has served as an expert witness/consultant on 4 legal cases over the last 36 months involving patients with disorders of consciousness concerning diagnosis, prognosis, pain and suffering, and adequacy of treatment. The other authors have nothing to disclose.

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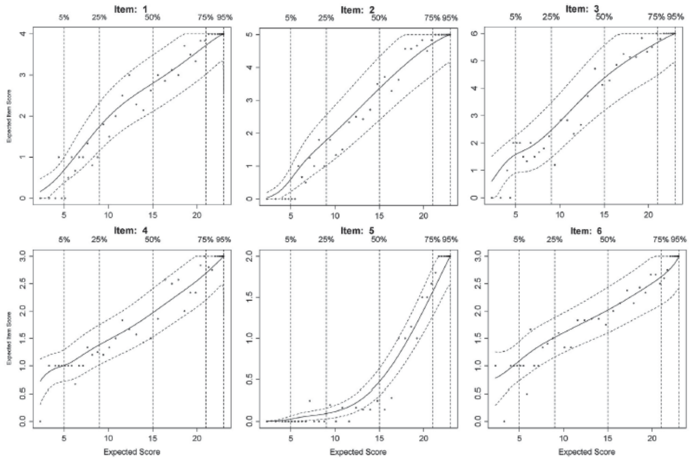
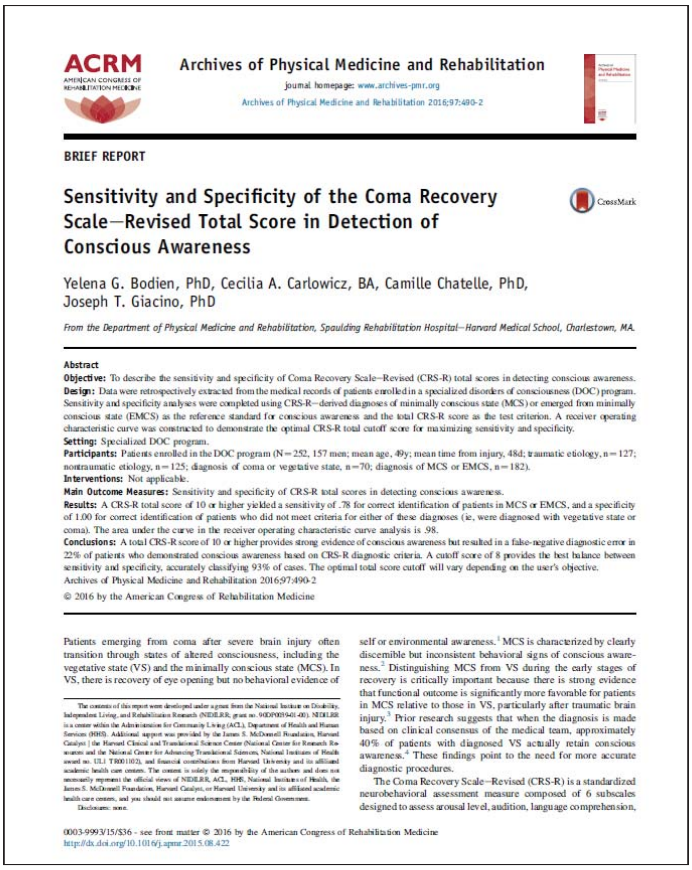
http://dx.doi.org/10.1016/j.apmr.2014.06.018



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

Coma Recovery Scale- Revised: Diagnostic Sensitivity/Specificity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Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2016;97:490-2

BRIEF REPORT

Sensitivity and Specificity of the Coma Recovery Scale—Revised Total Score in Detection of Conscious Awareness

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Abstract

Objective: To describe the sensitivity and specificity of Coma Recovery Scale—Revised (CRS-R) total scores in detecting conscious awareness.

Design: Data were retrospectively extracted from the medical records of patients enrolled in a specialized disorders of consciousness (DOC) program. Sensitivity and specificity analyses were completed using CRS-R—derived diagnoses of minimally conscious state (MCS) or emerged from minimally conscious state (EMCS) as the reference standard for conscious awareness and the total CRS-R score as the test criterion. A receiver operating characteristic curve was constructed to demonstrate the optimal CRS-R total cutoff score for maximizing sensitivity and specificity.

Setting: Specialized DOC program.

Participants: Patients enrolled in the DOC program (N=252, 157 men; mean age, 49y; mean time from injury, 48d; traumatic etiology, n=127; nontraumatic etiology, n=125; diagnosis of coma or vegetative state, n=70; diagnosis of MCS or EMCS, n=182).

Interventions: Not applicable.

Main Outcome Measures: Sensitivity and specificity of CRS-R total scores in detecting conscious awareness.

Results: A CRS-R total score of 10 or higher yielded a sensitivity of .78 for correct identification of patients in MCS or EMCS, and a specificity of 1.00 for correct identification of patients who did not meet criteria for either of these diagnoses (ie, were diagnosed with vegetative state or coma). The area under the curve in the receiver operating characteristic curve analysis is .98.

Conclusions: A total CRS-R score of 10 or higher provides strong evidence of conscious awareness but resulted in a false-negative diagnostic error in 22% of patients who demonstrated conscious awareness based on CRS-R diagnostic criteria. A cutoff score of 8 provides the best balance between sensitivity and specificity, accurately classifying 93% of cases. The optimal total score cutoff will vary depending on the user's objective.

Archives of Physical Medicine and Rehabilitation 2016;97:490-2

Patients emerging from coma after severe brain injury often transition through states of altered consciousness, including the vegetative state (VS) and the minimally conscious state (MCS). In VS, there is recovery of eye opening but no behavioral evidence of self or environmental awareness.[1] MCS is characterized by clearly discernible but inconsistent behavioral signs of conscious awareness.[2] Distinguishing MCS from VS during the early stages of recovery is critically important because there is strong evidence that functional outcome is significantly more favorable for patients in MCS relative to those in VS, particularly after traumatic brain injury.[3] Prior research suggests that when the diagnosis is made based on clinical consensus of the medical team, approximately 40% of patients with diagnosed VS actually retain conscious awareness.[4] These findings point to the need for more accurate diagnostic procedures.

The Coma Recovery Scale—Revised (CRS-R) is a standardized neurobehavioral assessment measure composed of 6 subscales designed to assess arousal level, audition, language comprehension,

The contents of this report were developed under a grant from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR; grant no. 90DP0039-01-00). NIDILRR is a center within the Administration for Community Living (ACL), Department of Health and Human Services (HHS). Additional support was provided by the James S. McDonnell Foundation, Harvard Catalyst | the Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health award no. UL1 TR001102), and financial contributions from Harvard University and its affiliated academic health care centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIDILRR, ACL, HHS, National Institutes of Health, the James S. McDonnell Foundation, Harvard Catalyst, or Harvard University and its affiliated academic health care centers, and you should not assume endorsement by the Federal Government.

Disclosures: none.

0003-9993/15/$36 - see front matter © 2016 by the American Congress of Rehabilitation Medicine
http://dx.doi.org/10.1016/j.apmr.2015.08.422

Table 1 Sensitivity, specificity, and accuracy rates for detection of conscious awareness at CRS-R TS cutoffs between 7 and 11

	CRS-R TS Cutoff				
Parameter	7	8	9	10	11
Sensitivity	.97	.93	.88	0.78	0.73
Specificity	.80	.963	.97	1	1
Accuracy	.921	.937	.905	0.841	0.802

(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)

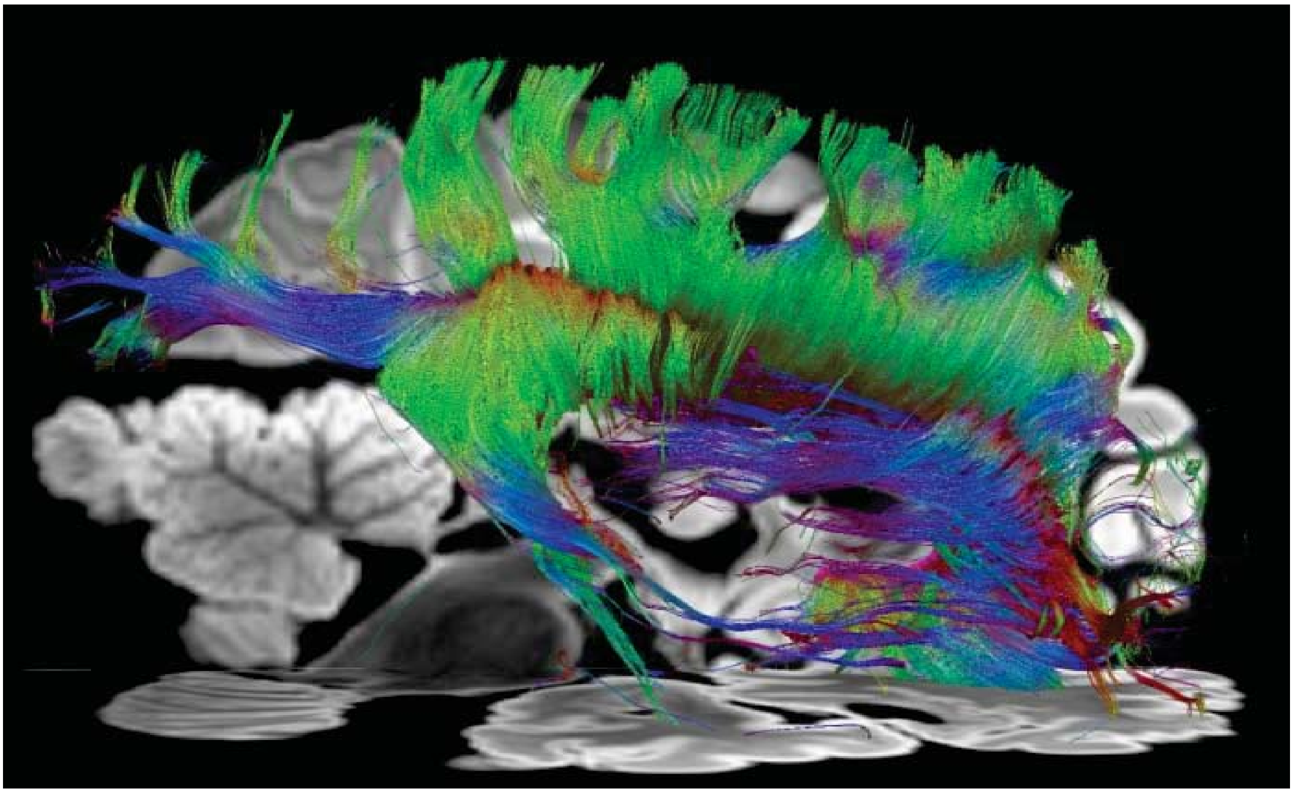
Incidence of diagnostic error

- 37% *(Childs et al, Neurol, 1993)*
- 43% *(Andrews et al, BMJ, 1996)*

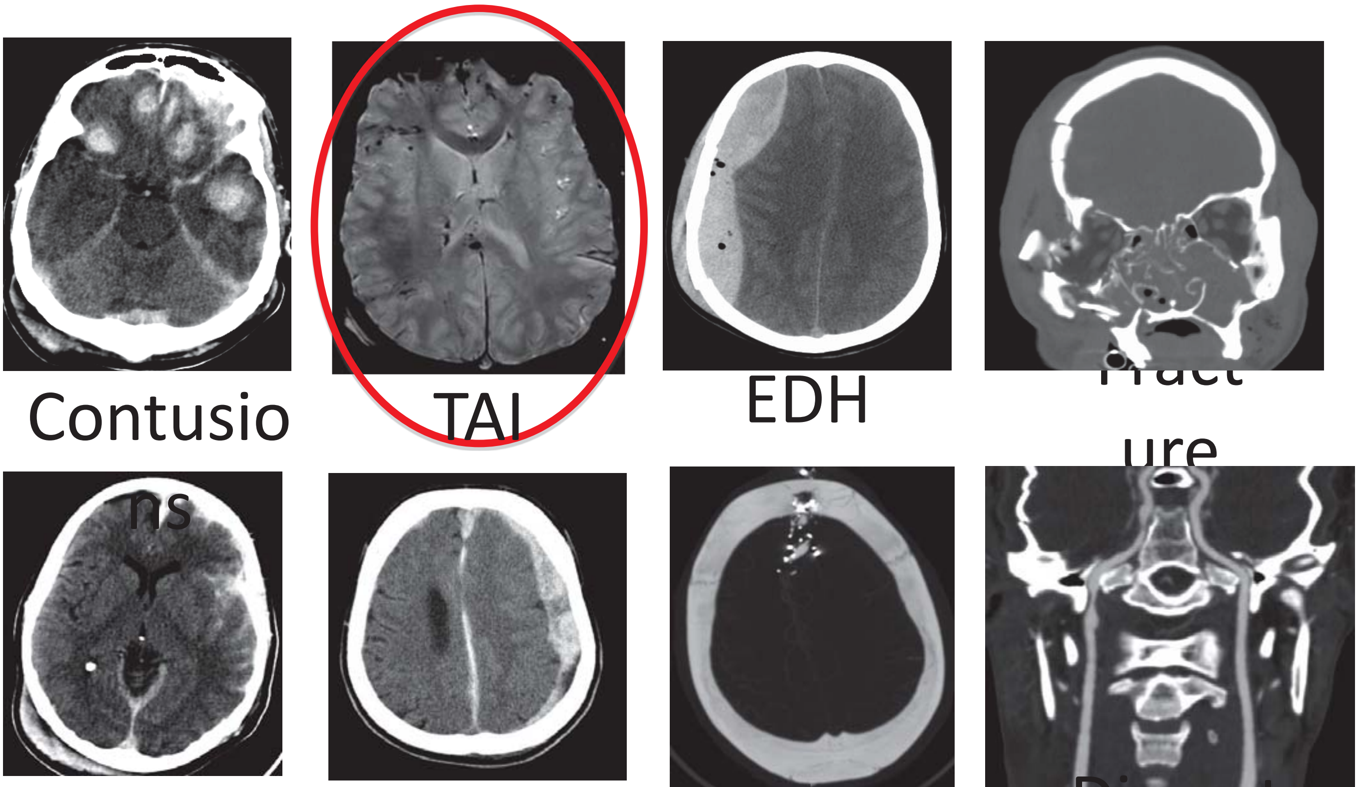
↓

- 41% *(Schnakers et al, Brain Injury, 2008)*

Neuroimaging Approaches to Diagnostic Assessment



The Broad Spectrum of TBI Pathophysiology

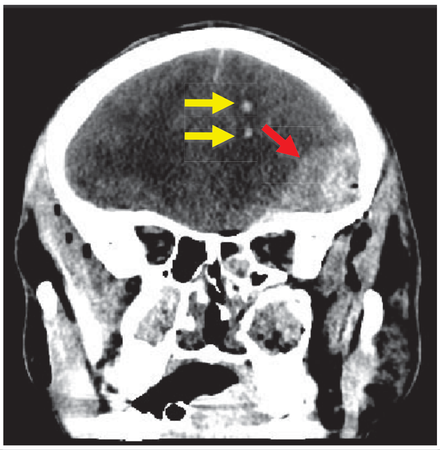


Neuroimaging to Detect Traumatic Axonal Injury

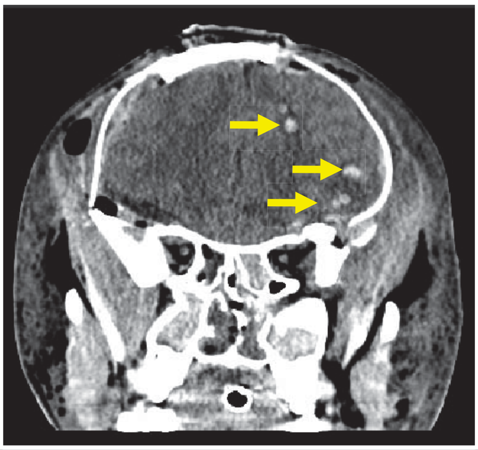
- Conventional MRI
- Advanced imaging techniques
  - Susceptibility-weighted imaging (SWI)
  - Diffusion tensor imaging (DTI)
  - Diffusion tractography
  - Resting state functional MRI (rs-fMRI)
  - Stimulus-based functional MRI (fMRI)
- Limitations, pitfalls and artifacts

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)



Admission
CT

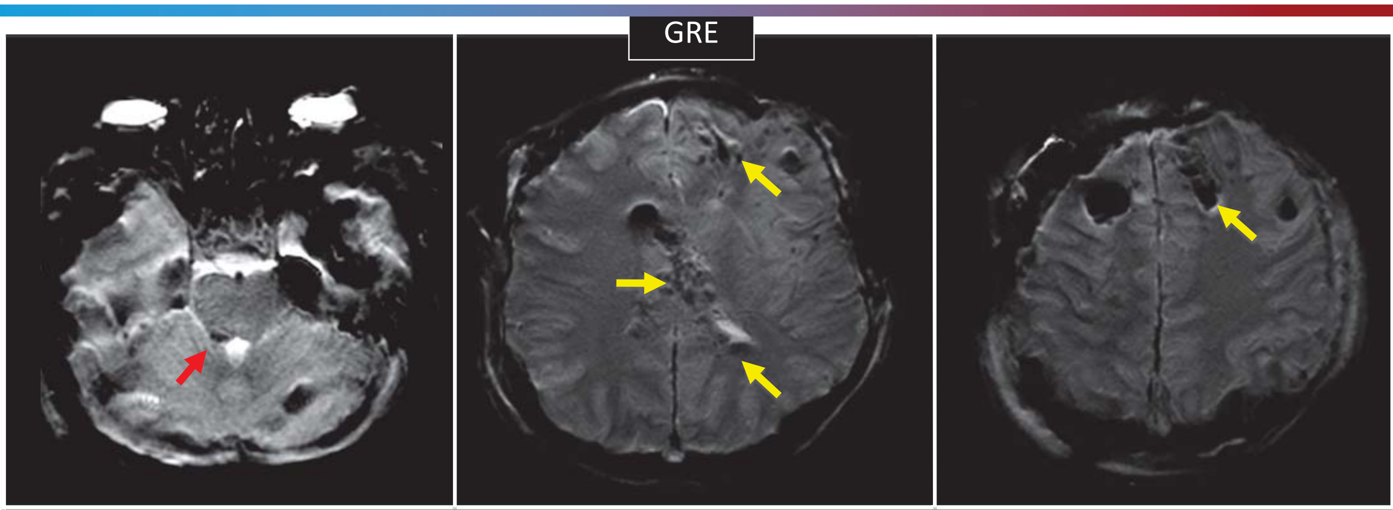


CT s/p Bilateral
Hemicraniectomies

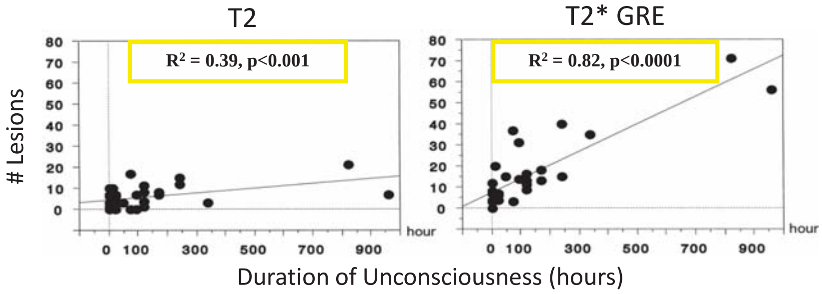
Patient in NeuroICU on
Day 3

Conventional MRI (Day 8)

- T2*-Weighted Gradient-recalled Echo -



Edlow, Giacino et al. Neurocritical Care 2013

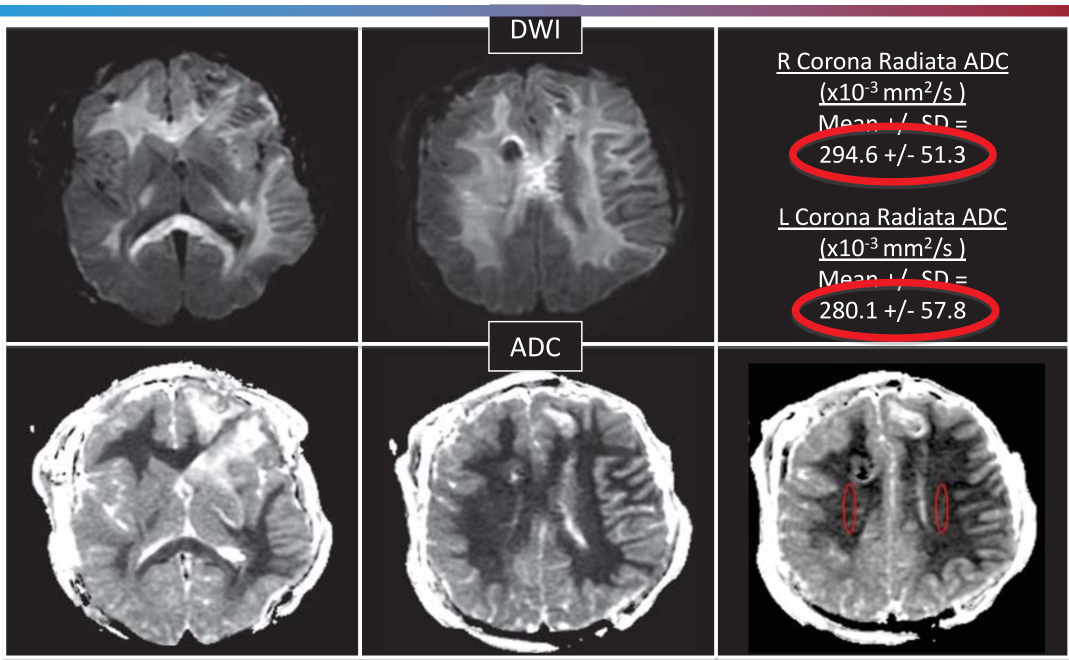


Yanagawa et al. J Trauma 2000;49:272-277.

Variable	*Value*	n	*Proportional OR adjusted for age*	p *Value* $OR_{adjusted}$
Total		48		
Age	Continuous	48		
Pupils	Normal	37		
	Dilation[a]	11	11.7 (2.3–58.9)	0.003
Secondary events[b]	Absent	33		
	Present	14	7.1 (1.8–27.3)	0.004
GCS score	6–8	26		
	3–5	22	2.1 (0.71–6.5)	0.17
Rotterdam CT score[c]			1.8 (1.1–2.9)	0.013
Depth of lesion	Hemispheres	12		
	Central	14	[illegible]	[illegible]
	BSI unilateral	8	7.9 (1.0–62.4)	0.050
	BSI bilateral	14	181.6 (16.5–2000)	<0.001

Skandsen et al. J Neurotrauma 2011;28:691-699.

Diffusion-Weighted Imaging (Day 8)



Edlow, Giacino et al. Neurocritical Care 2013

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

Location	Modified Rankin Scale Score ≤ 3 (*n* = 14)	Modified Rankin Scale Score > 3 (*n* = 66)	*P* Value
Whole brain	830 (740–900)	750 (680–810)	.001
White matter	790 (720–860)	730 (620–780)	.005

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

Unexpected Recovery from Traumatic Coma

Day 254 - Rehabilitation

Day 356 – Home with family

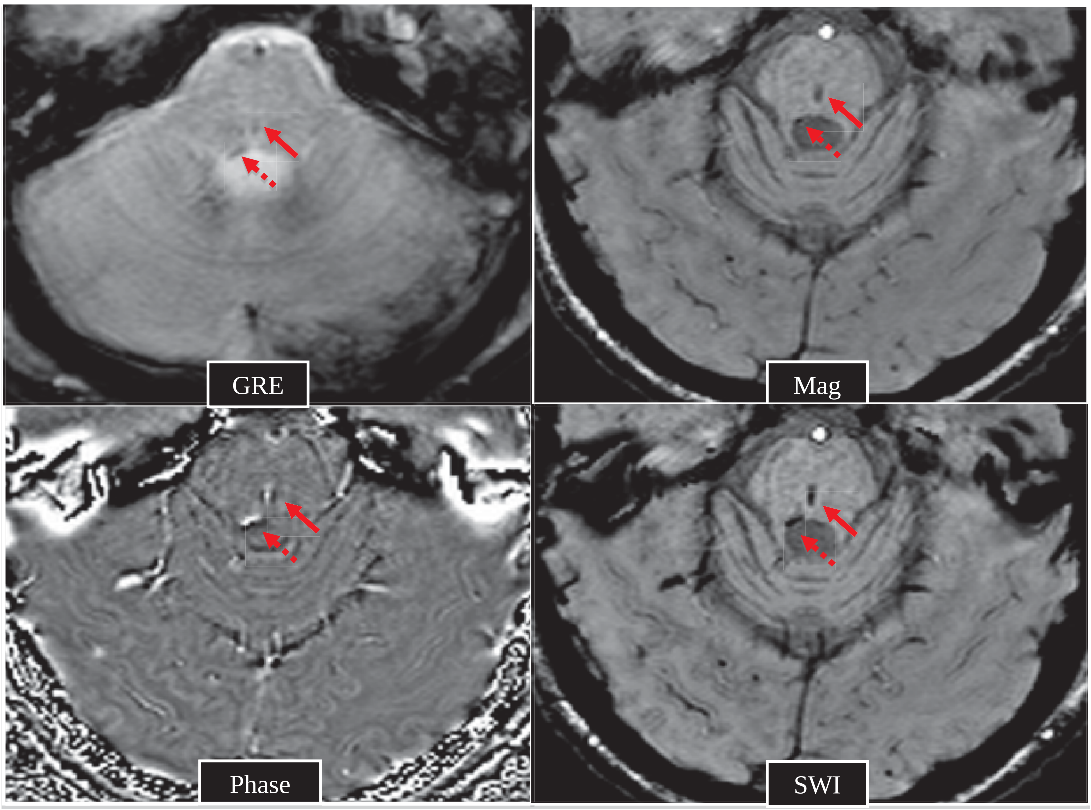
Photos shown with consent from patient and family

Advanced Imaging Techniques

- Susceptibility-weighted Imaging (SWI) -

Can Advanced Imaging Techniques Improve Prognostic Accuracy?

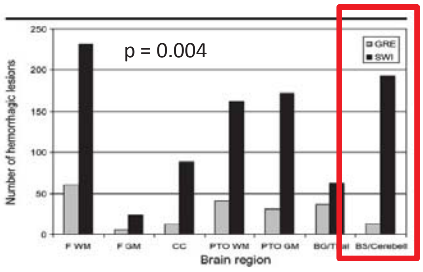
- 23yo F in traumatic coma (GCS 4T) on day 10 post-injury -



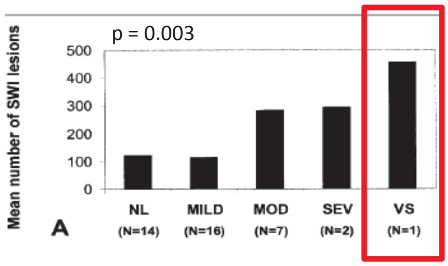
Edlow & Wu. Seminars in Neurology 2012;32:372-398.

Detecting Traumatic Microbleeds

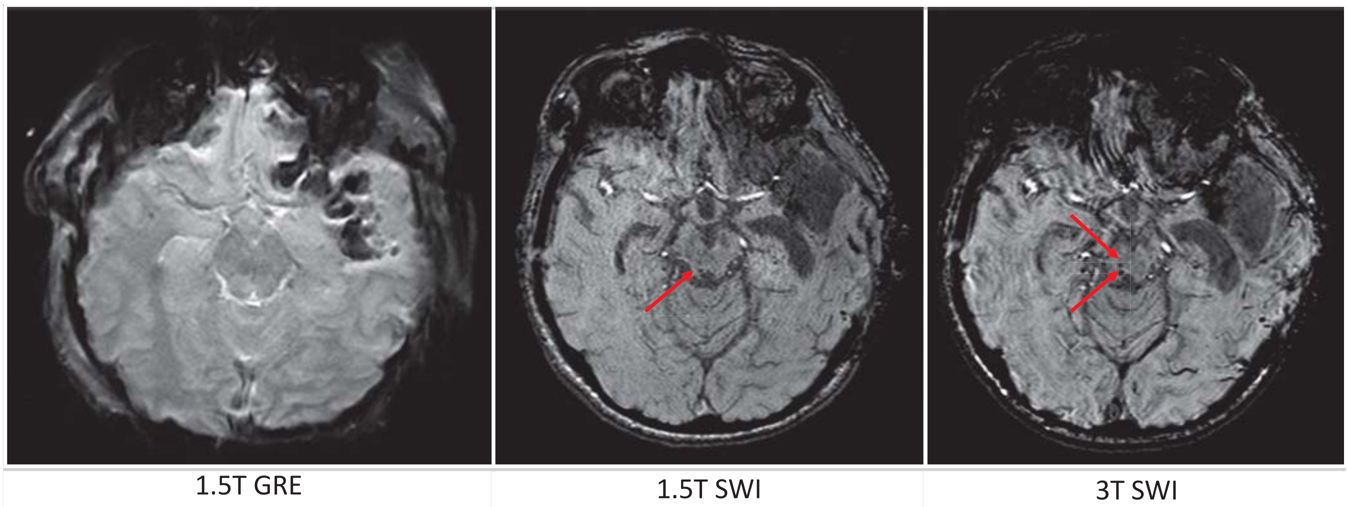
- Sequence Selection & Field Strength -



Tong et al. Radiology 2003;227:332-339.



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



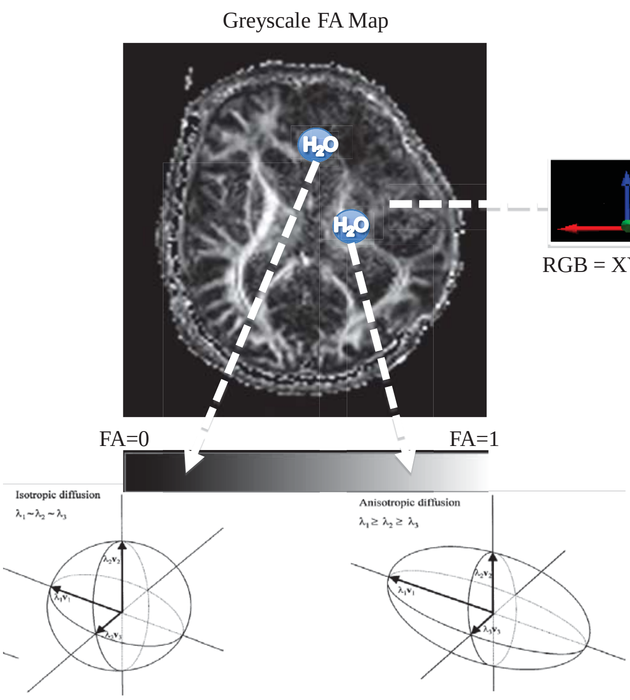
Edlow, Giacino et al. Neurocritical Care 2013; epub ahead of print.

Advanced Imaging Techniques

- Diffusion Tensor Imaging -

Diffusion Tensor Imaging (DTI)

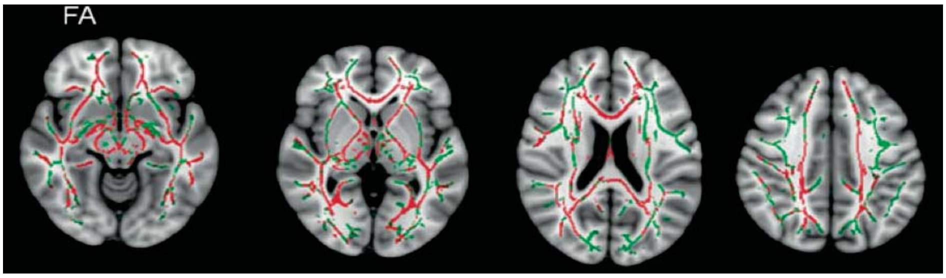
- Fractional Anisotropy (FA) Maps -



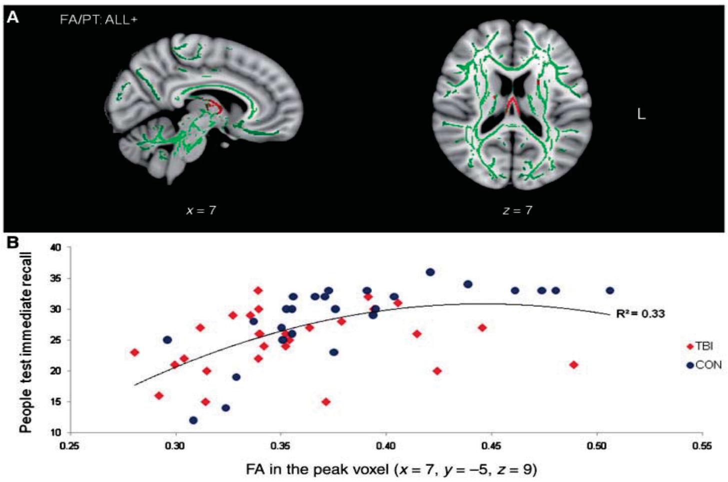
Wiegell et al. Radiology 2000;217:897-903

DTI and Neurocognition in Traumatic DOC

- Tract-based Spatial Statistics -



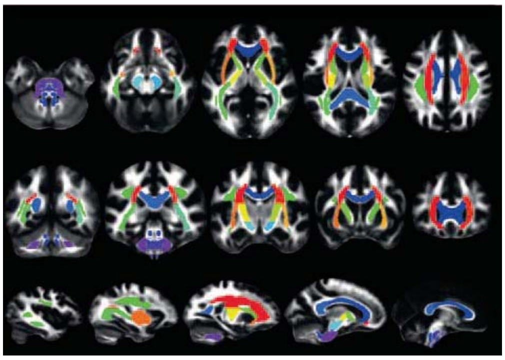
Fractional anisotropy (red): controls > traumatic brain injury



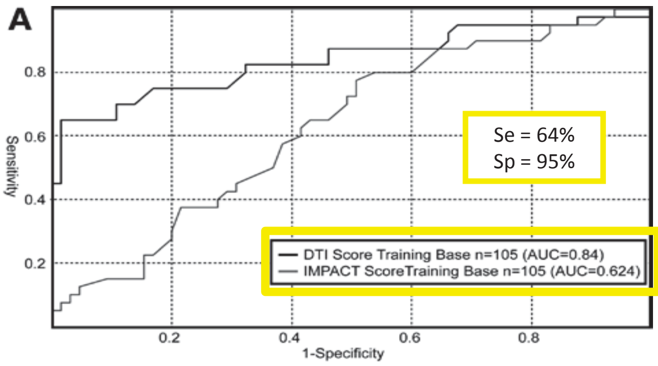
Kinnunen et al. Brain 2011;134:449-463

The DTI IMPACT Score

White Matter ROIs (n= 20)

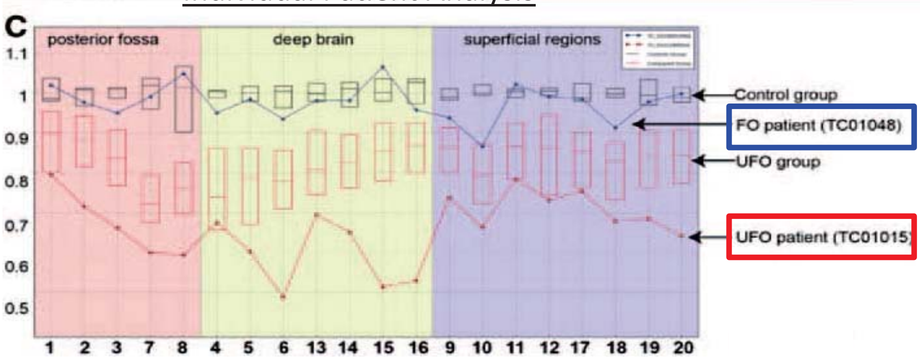


Severe TBI Cohort (n= 105)



Individual Patient Analysis

Normalized FA



White Matter ROI

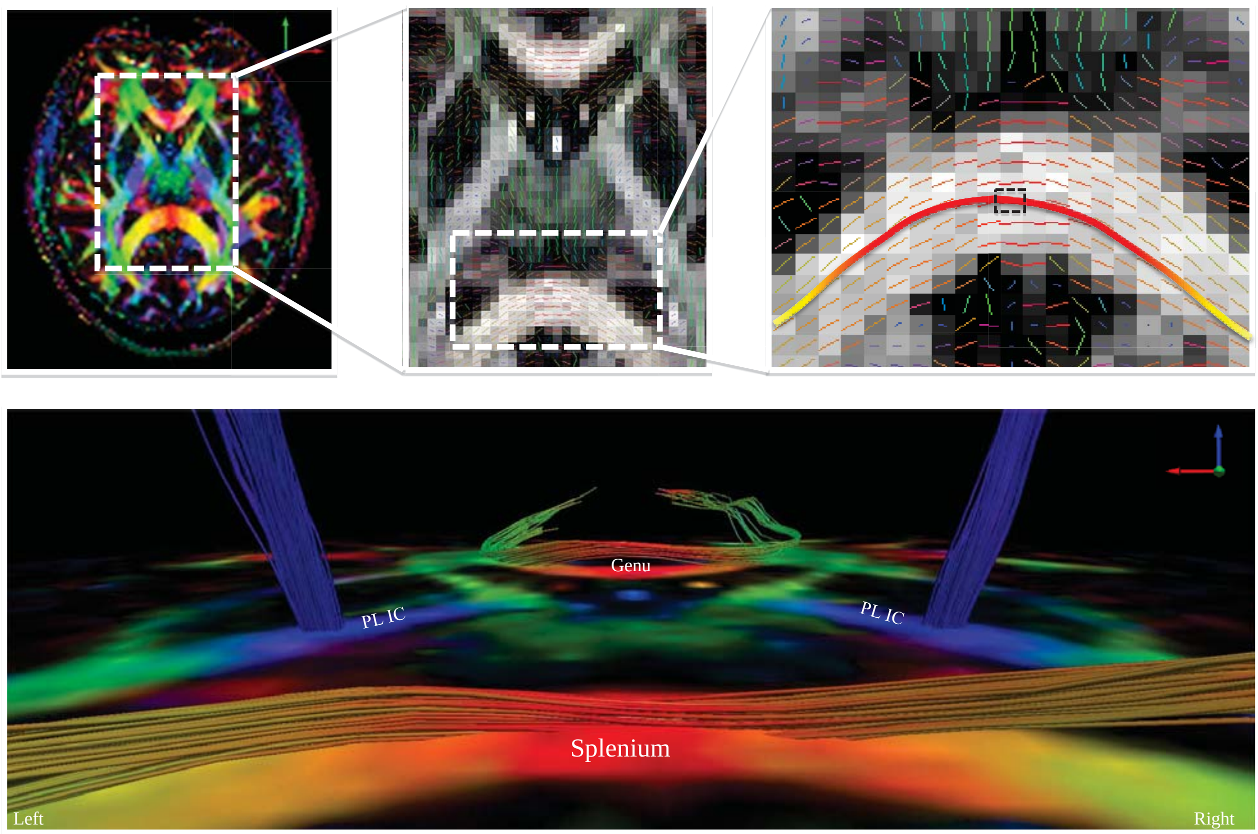
Galanaud et al. Anesthesiol 2012;117:1300-10.

Advanced Imaging Techniques

- Diffusion Tractography -

Diffusion Tensor Tractography

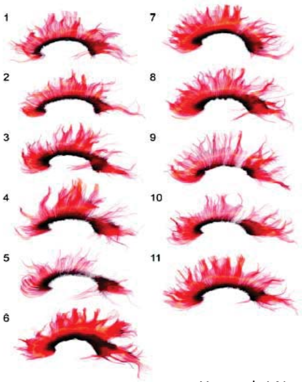
- Background and Principles -

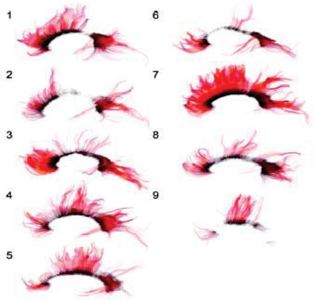


Edlow & Wu. Seminars in Neurology 2012;32:372-398.

Diffusion Tractography in TBI

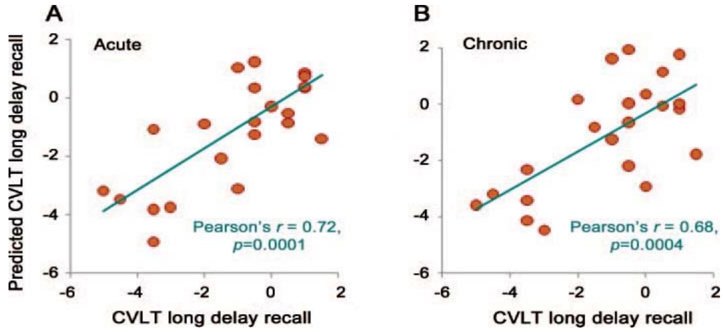
Controls (n=11) | Severe TBI Patients (n=9)





Xu et al. J Neurotrauma 2007; 24: 753.

TBI Patients (n=28, severe=23)



Wang et al. Neurology. 2011; 77:818.

Controls (n=32) | Traumatic VS (n=7)

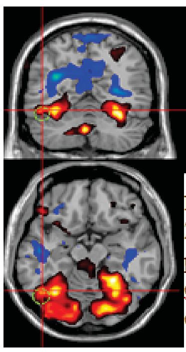
		Controls Median (IQR)	Traumatic brain injury Median (IQR)
Thalamus	FA	0.34 (0.33 to 0.36)	0.32 (0.30 to 0.35)
	ADC	0.66 (0.63 to 0.68)	0.85 (0.83 to 0.88)*
	Axial	0.90 (0.88 to 0.93)	1.12 (1.07 to 1.17)*
	Radial	0.54 (0.52 to 0.56)	0.72 (0.67 to 0.74)*
	Tracts	728 (611 to 825)	212 (137 to 318)*

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

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

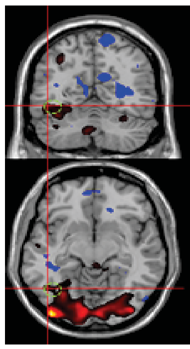
N=20
Healthy
Subjects

Visual Discrimination - YES



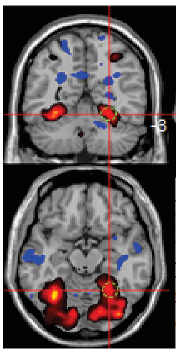
Peak: -45, -60, -15mm
Z-score: 4.18
p-value: <0.0001
corr p-value: 0.003
cluster size: 783mm³

Communication- YES



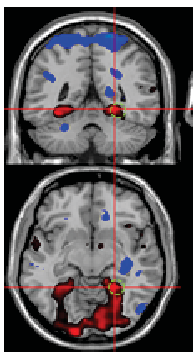
Peak: -45, -60, -9mm
Z-score: 3.27
p-value: <0.001
corr p-value: 0.041
cluster size: 162mm³

Visual Discrimination - Places



Peak: 27, -54, -15mm
Z-score: 4.66
p-value: <0.0001
corr p-value: 0.001
cluster size: 2214mm³

Communication (False) - Places



Peak: 24, -48, -9mm
Z-score: 4.33
p-value: <0.0001
corr p-value: 0.002
cluster size: 1593mm³

NIDRR

fMRI-based detection of covert command-following and communication in a patient with severe traumatic brain injury

		CRS-R (command following)			
		+	+	-	-
fMRI (command following)	+	High Certainty	Moderate Certainty	Low Certainty	Low Certainty
	-	Low Certainty	Low Certainty	Moderate Certainty	High Certainty
		+	-	+	-
		Family Observation (command following)			

Concordance between the CRS-R, fMRI, and Family Beliefs Questionnaire suggests a **high certainty** that the diagnosis/rating of command-following is correct.

		CRS-R (communication)			
		+	+	-	-
fMRI (communication)	+	High Certainty	Moderate Certainty	Low Certainty	Low Certainty
	-	Low Certainty	Low Certainty	Moderate Certainty	High Certainty
		+	-	+	-
		Family Observation (communication)			

Concordance between the CRS-R and fMRI but not the Family Beliefs Questionnaire suggests a **moderate certainty** that the diagnosis/rating of communication is correct

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

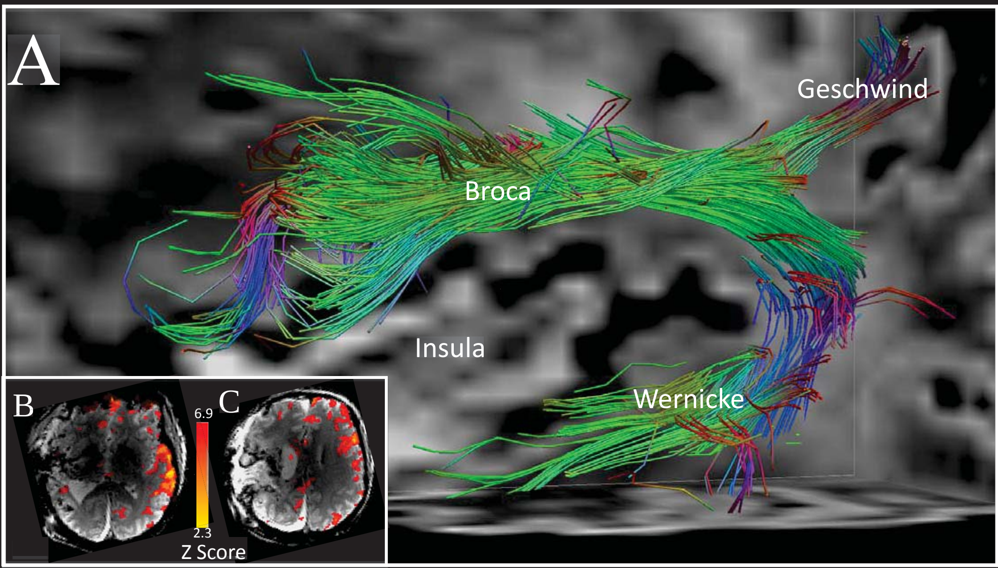
- In communicating prognosis, the clinician should a) tie the prognosis to the strength and consistency of the available data and b) indicate the level of confidence in the prognostic assessment

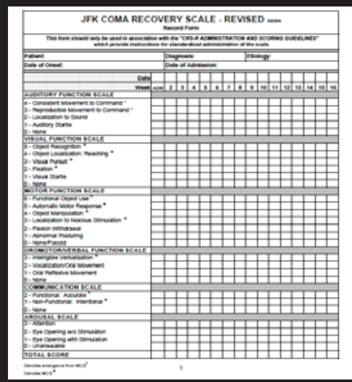
Prognostic Confidence Matrix

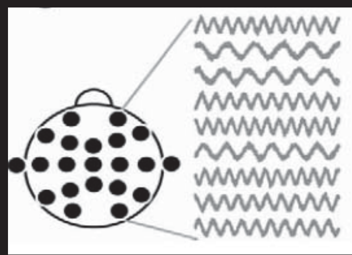
	Clinical +	Clinical -
Imaging +	High	Low
Imaging -	Low	High

Integration of Behavioral, Structural & Functional Data

- Traumatic Coma RESPONSE Study -



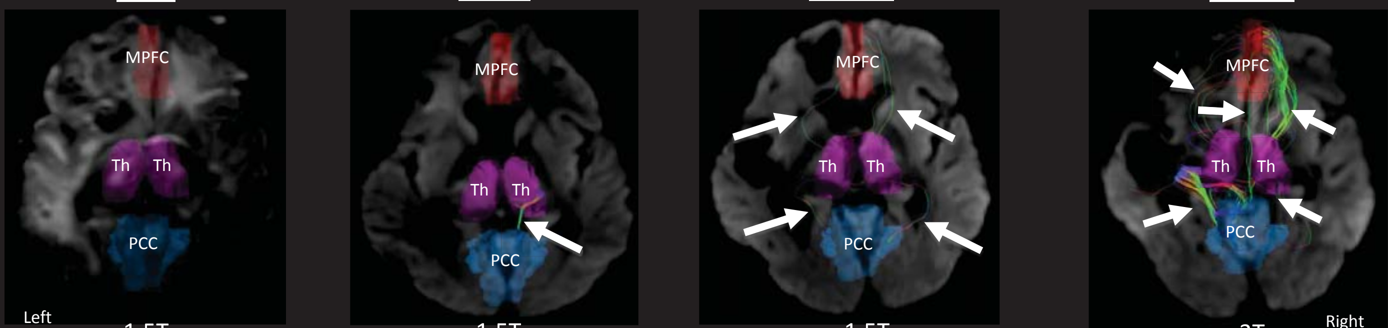




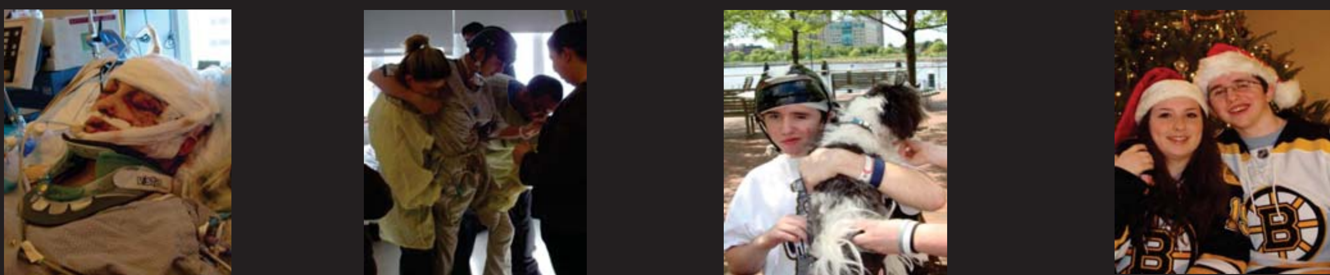
Edlow & Wu. Seminars in Neurology 2012;32:372-398.
Chu-Shore et al. *J Child Neurol* 2011;26:488.
Giacino, et al, Arch PM&R 2004;85:2020-9

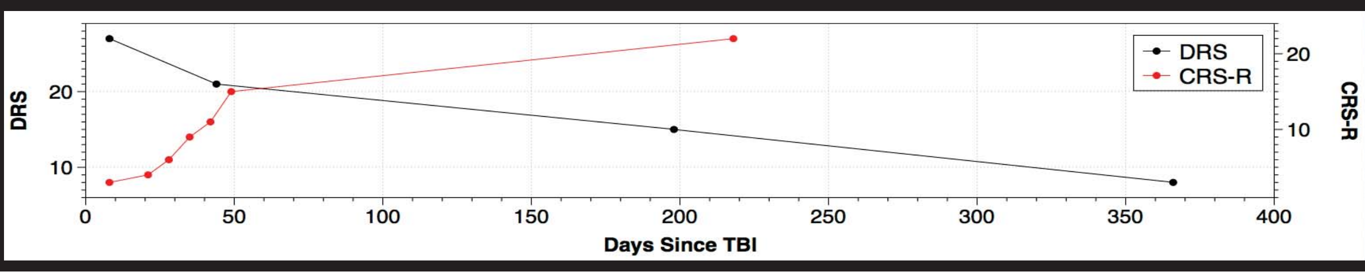
Multimodal Approach: Clinical-Radiologic Correlations

Day 8 | Day 44 | Day 198 | Day 366



1.5T | 1.5T | 1.5T | 3T





Expert Panel on Development of Guidelines for Diagnosis, Prognosis and Treatment of the Vegetative and Minimally Conscious States

An Inter-Organizational Collaboration of the American Academy of Neurology, American Congress of Rehabilitation Medicine and the National Institute on Disability and Rehabilitation Research

Chair: Joseph T. Giacino, PhD
Diagnosis Section Lead: Doug Katz, MD
Prognosis Section Lead: Nicholas Schiff, MD
Treatment Section Lead: John Whyte, MD, PhD
AAN Guideline Development Committee Chair: Gary Gronseth, MD
AAN Guideline Development Committee Liaison: Richard Barbano, MD, PhD
AAN Senior Manager Clinical Practice: Thomas Getchius

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.

Acknowledgements

Spaulding Rehabilitation Hospital:
-Yelena Guller, PhD
-Therese O' Neil-Pirozzi, PhD
- Mel Glenn, MD
- Ron Hirschberg, MD
- Matt Doiron, BA
- Cecilia Carlowicz, BA
- Sabrina Taylor, PhD
- Ross Zafonte, DO

Brigham and Women's Hospital:
- Emily Stern, MD

- Hong Pan, PhD
- Martha Shenton, PhD
- Sylvain Boiux, PhD
- Ben Fuchs, BA
- Courtney Chaley, BA

Athinoula A. Martinos Center for Biomedical Imaging
- Ona Wu, PhD

Cornell-Weill Medical School
- Nicholas Schiff, MD
- Joseph Fins, MD

Boston University Medical School
- Douglas Katz, MD

Moss Rehabilitation Research Institute
- John Whyte, MD, PHD

James A. Haley Veterans Medical Center
- Risa Nakase-Richardson, PhD

Mt. Sinai Medical Center
- Emilia Bagiella, PhD

Massachusetts General Hospital:
Brian Edlow, MD

Department of Physical Medicine & Rehabilitation
Harvard Medical School

Spaulding Rehabilitation Hospital
Massachusetts General Hospital
Brigham & Women's Hospital