A Comprehensive Evidence-Based Approach to Assessment and Treatment of Persons with Disorders of Consciousness: A Training Seminar for Rehabilitation Professionals

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

Department of Physical Medicine & Rehabilitation
Harvard Medical School

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

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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Course Objectives

Upon completion of the course, participants will be able to:

1. Describe 3 neurophysiologic features of syndromes associated with severe alterations in consciousness post traumatic brain injury.
2. Identify 2 requirements of operational strategies to support a comprehensive rehabilitation program for patients with disorders of consciousness.
3. List the 6 components of the Coma Recovery Scale-Revised used for assessment of persons with disorders or consciousness post brain injury.
4. Verbalize 4 of the Specialized Metrics considered in the administration guidelines for the Disorders of Consciousness COMPrehensive ASSessment battery (DOC COMPASS©), as discussed by the speaker.
5. Generate 3 examples of the clinical data compiled through the use of the DOC COMPASS© to evaluate treatment effectiveness for persons with disorders of consciousness.

Disorders of Consciousness 2016: The State of the Science

Department of Physical Medicine & Rehabilitation
Harvard Medical School

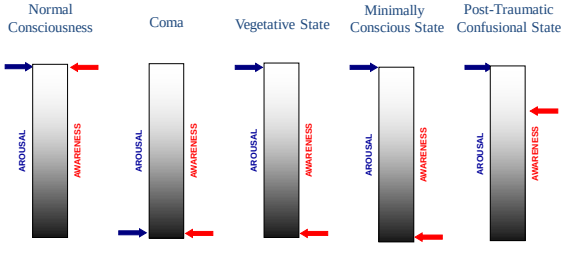
Spaulding Rehabilitation Hospital
Massachusetts General Hospital
Brigham & Women's Hospital

DoC State of the Science: Outline

- The problem of consciousness
- Assessment
  - Behavioral
  - Functional neuroimaging
- Prognosis and outcome
- Treatment

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).*

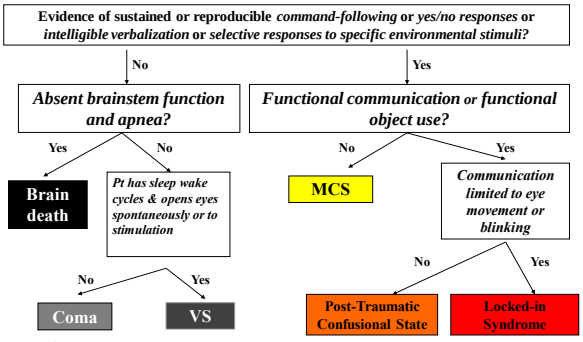
The Problem of Consciousness

"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

Behavior = Gold standard

Behavioral Algorithm for Differential Diagnosis



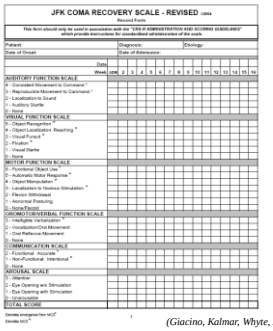
(Adapted from Ashwal, et al, Sem in Ped Neurol, 2002)

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)
WHIM	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)
MMM	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)
RLSIS	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./t/Death (class III)

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

Coma Recovery Scale- Revised



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

Coma Recovery Scale- Revised: Psychometric Characteristics

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

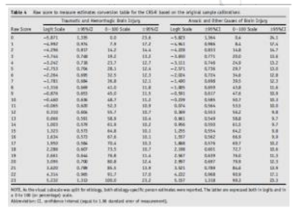
Table 10: Frequency of Agreement Between CRS-R– and DRS-Derived Diagnoses (N=80)

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

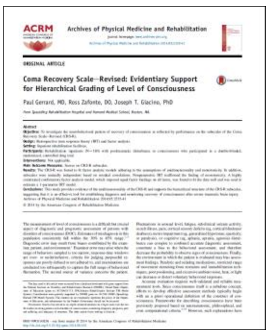
Coma Recovery Scale- Revised: Scaling Properties *(LaPorta, et al., Arch Phys Med Rehabil, 2010*

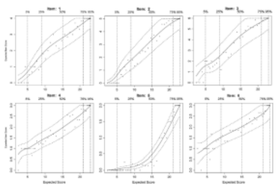
Table 4 - Item parameters and fit statistics for the CRS-R (N=258, analysis no. 4).

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



Coma Recovery Scale- Revised: Construct Validity





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

Coma Recovery Scale- Revised: Diagnostic Sensitivity/Specificity

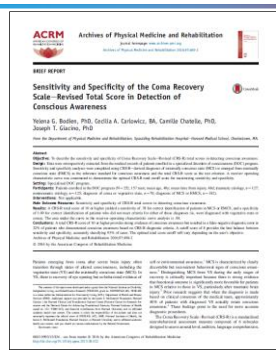


Table 1 Sensitivity, specificity, and accuracy rates for detection of conscious awareness at CRS-R TS cutoffs between 7 and 11

	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)*

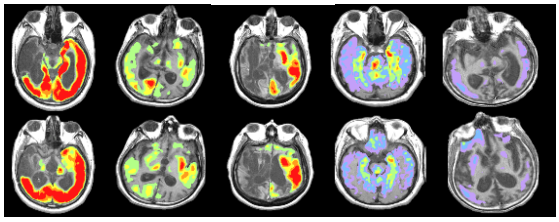
↓

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

Functional Neuroimaging Applications in DOC

Neurophysiologic heterogeneity in VS

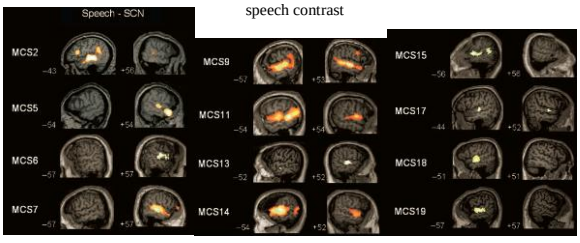
65% (*CMRglu)* *31%*



(Schiff et al, Brain, 2002)

Neurophysiologic heterogeneity in MCS

Intelligible-unintelligible speech contrast



Coleman, et al., Brain, 2009

fMRI Studies of VS and MCS

Passive Paradigms

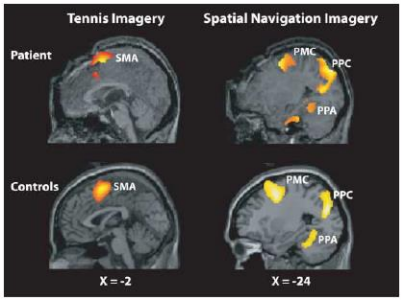
- Language processing
  - Familiar sounds
  - Words
  - Narratives
- Visual processing
  - Shapes
  - Pictures/Scenes
  - Faces

Active Paradigms

- Language comprehension
  - Command-following
    - Word naming/repetition
    - Movement
    - Spatial navigation
    - Pictures
- Communication
  - Yes/no imaging proxies

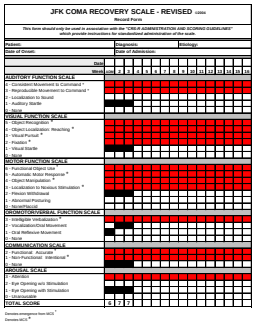
(Owen & Coleman, Nat Rev Neurosci, 2009; Giacino, Hirsch, Schiff, Laureys, Arch PM&R, 2006; Laureys, Owen, Schiff, Lancet, 2004)

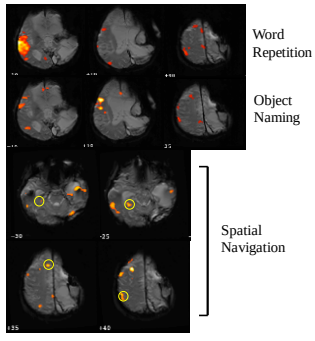
Detecting Awareness in the Vegetative State



(Owen, et al, Science, 2006)

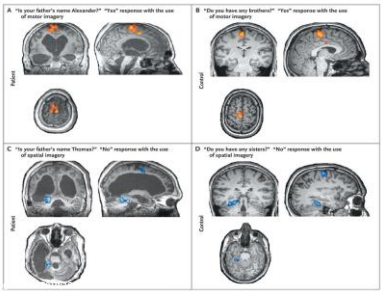
Discordant behavioral and neurophysiologic evidence of conscious awareness in an 18 y/o male s/p severe TBI *(Rodriguez-Moreno, Schiff, Giacino et al, Neurol, 2010)*





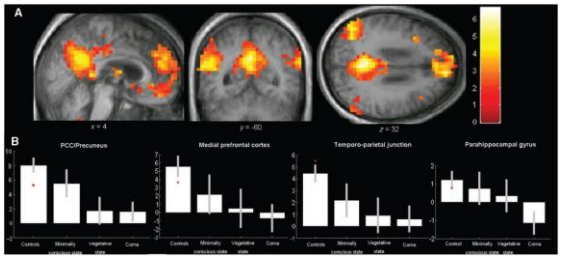
Active fMRI Communication Paradigm

- *29 y/o male*
- *MVA (GCS =5)*
- *R frontal SDH/crani*
- *Remained in VS for 3.5 yrs*
- *Admitted to Liege for workup at 5yrs*
- *CRS-R/SMART found reproducible LE command-following but no behavioral evidence of communication*
- ***fMRI communication paradigm showed 5/6 accurate yes/no responses***



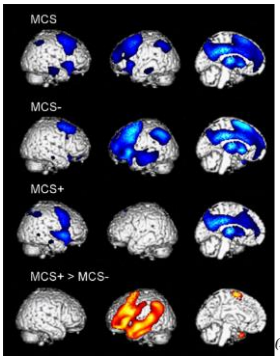
(Monti, et al., NEJM, 2012)

Resting State Networks:
DMN Connectivity in DoC



(Vanhaudenhuyse, et al. Brain 2010)

"MCS+ (plus)" v. "MCS- (minus)"

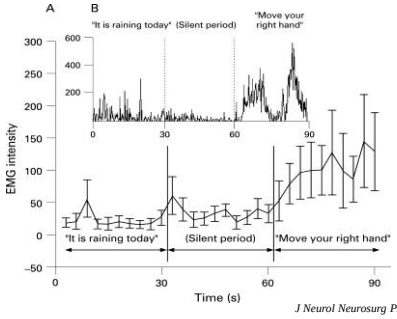


(Bruno, et al., J Neurol, 2012)

Electrophysiologic Approaches

Can electromyography objectively detect voluntary movement in in disorders of consciousness?

Bekinschtein TA, Coleman MR, Niklison J 3rd, Pickard JD, Manes FF.

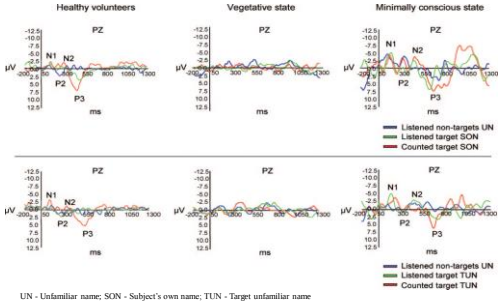


J Neurol Neurosurg Psychiatry, 2008

Voluntary brain processing in disorders of consciousness

Schnakers C, Perrin F, Schabus M, Majerus S, Ledoux D, Damas P, Boly M, Vanhaudenhuyse A, Bruno MA, Moonen G, Laureys S.

Neurology® 2008;71:1614-1620

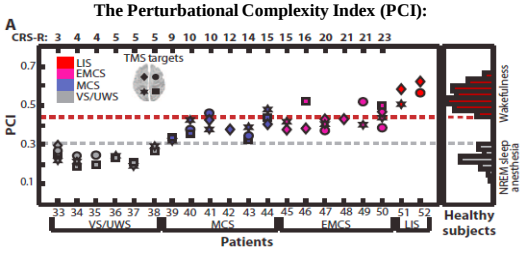


UN - Unfamiliar name; SON - Subject's own name; TUN - Target unfamiliar name

A Theoretically Based Index of Consciousness Independent of Sensory Processing and Behavior

Adenauer G. Casali,[1]*† Olivia Gosseries,[2]* Mario Rosanova,[1] Mélanie Boly,[2†] Simone Sarasso,[1] Karina R. Casali,[1,3] Silvia Casarotto,[1] Marie-Aurélie Bruno,[2] Steven Laureys,[2] Giulio Tononi,[4] Marcello Massimini[1,5]§ Science Trans Medicine, 2013

The Perturbational Complexity Index (PCI):



Prognosis and Outcome

Current Guidelines for Predicting Outcome Following Severe Acquired Brain Injury

The Multi-Society Task Force Report on Medical Aspects of the Persistent Vegetative State

(Multi-Society Task Force on PVS, N Engl J Med 1994;330: 1572-79)

"Recovery of consciousness after 12 months is unlikely in adults and children who have had traumatic injuries…Data were available on 434 patients in VS at one month after a severe head injury…Recovery after 12 months was reported in only 7 of the 434 patients."

Prognostic Guideline for the Vegetative State

Criteria for Permanence

- After *12 months* following traumatic brain injury in adults and children
- After *3 months* following non-traumatic brain injury in adults and children

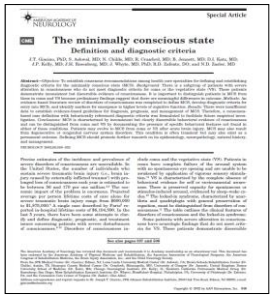
(American Academy of Neurology, Neurol1995;45:1015-1018)

The Minimally Conscious State: Definition and Diagnostic Criteria

(Giacino, et al., Neurol 2002;58:349-53)

"The natural history and long-term outcome of MCS have not yet been adequately investigated…Although it is not known how many patients will emerge from MCS after 12 months after injury, most patients in MCS for this length of time remain severely disabled…"

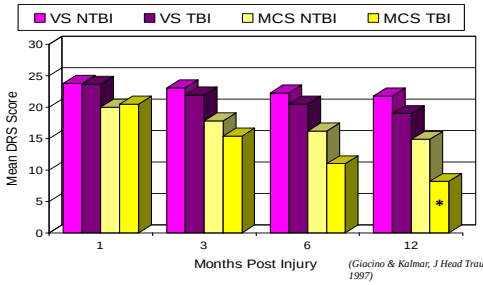
- *No prognostic guidelines established to date*



When is MCS permanent?

Outcome from VS and MCS at 1 Year

VS = 54; MCS = 49; Mixed etiology; Mean time post-injury = 9 wks

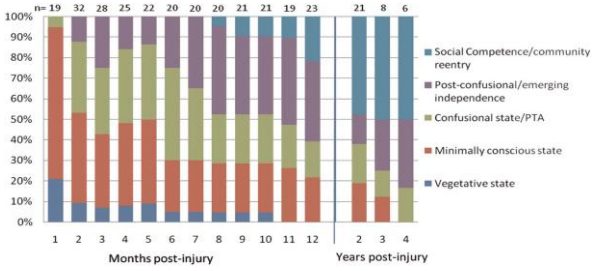


(Giacino & Kalmar, J Head Trauma Rehabil, 1997)

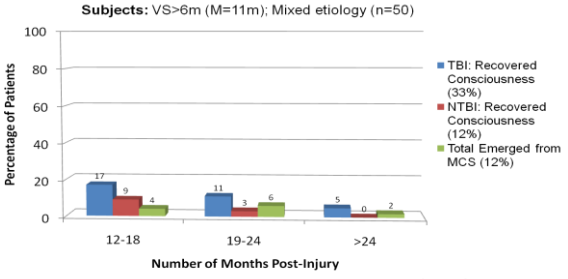
Outcome from VS and MCS: 1-4 years

(Katz, et al., Prog Brain Res, 2009)

- 36 patients admitted to rehab in VS or MCS after TBI or non-TBI
- Mean time post injury= 35d
- Followed weekly on CRS-R



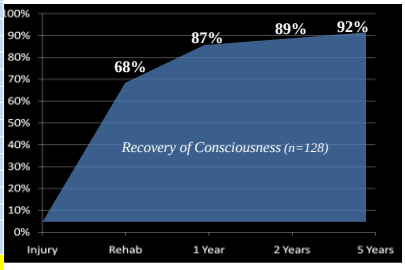
Late Recovery from Vegetative State



(Estraneo, et al, Neurol, 2010)

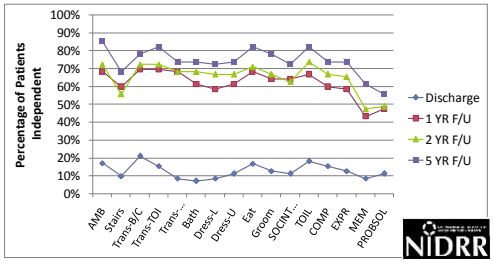
NIDRR	At Least 1 F-U: Overall Sample N=337
Age (quartiles)	20/27/41
Male	72%
Race	
White	67%
Black	23%
Hispanic	7%
Other	3%
Education	
<12 years	29%
≥ 12 years	46%
Missing	25%
Cause of Injury	
N Motor (%)	66%
ED GCS	7/9/10
Rehab Admit GCS	3/8/8
Acute LOS	21/31/42
Rehab LOS	29/46/71

Longitudinal Outcome of Patients with Disorders of Consciousness in the TBI Model Systems

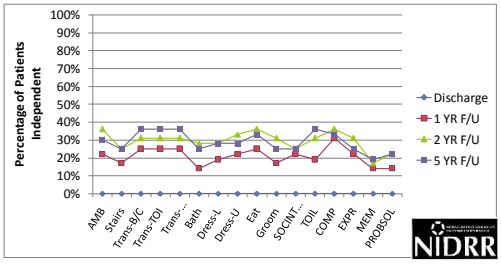


(Nakase-Richardson, Whyte, Giacino, et al, J Neurotrauma, 2011)

Functional Recovery Over 5 Years in Patients who Recovered Command-Following During Inpatient Rehab *(Whyte, Nakase-Richardson, Giacino, et al, APM&R, 2013)*



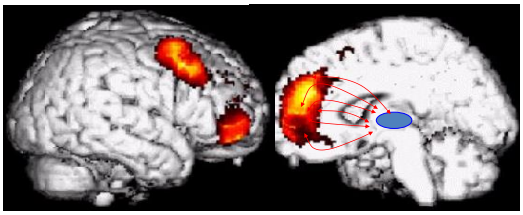
Functional Recovery Over 5 Years in Patients who Failed to Recover Command-Following During Inpatient Rehab *(Whyte, Nakase-Richardson, Giacino, et al, APM&R, 2013)*



Treatment Interventions:

Neuromodulation

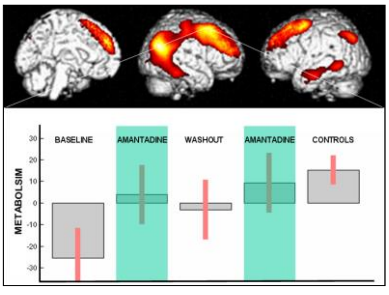
Thalamo-cortical connectivity and consciousness



Intralaminar nuclei "reconnections" in spontaneous recovery from "vegetative" unresponsive state

Laureys et al, *Lancet* 2000

Amantadine



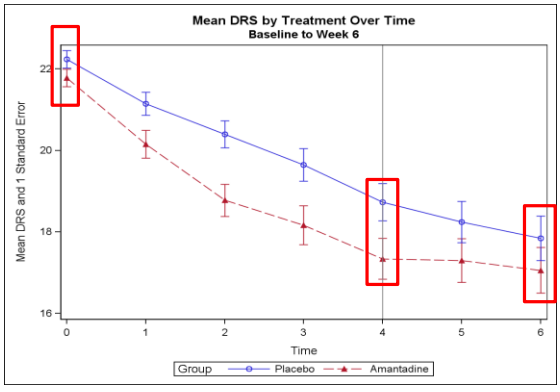
Amantadine-induced facilitation of dopaminergic activity promotes enhanced neurotransmission in the dopamine-dependent nigrostriatal, mesolimbic, and frontostriatal circuits that are responsible for mediating arousal, drive, and attentional functions

(Schnakers et al J Neurol Neurosurg Psychiatry 2008; Giacino et al NEJM 2012)

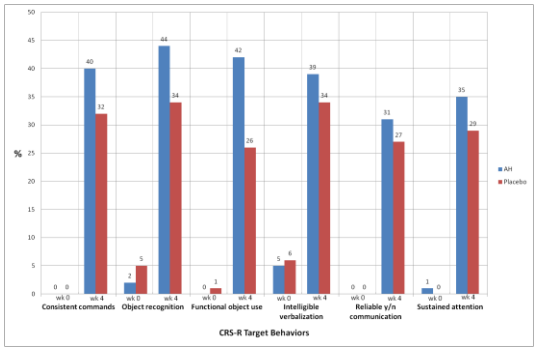
A Multicenter Randomized Controlled Trial of the Effectiveness of Amantadine Hydrochloride in Promoting Recovery of Function Following Severe TBI

- Primary Aims:
  - Determine whether AH, given in a dose of 200 – 400 mg/day improves functional recovery from post-traumatic VS and MCS (4-16 wks post-injury).
  - Determine whether AH-related gains in function persist following drug discontinuation

NIDRR Award # H133A031713)
(Giacino, Whyte, Bagiella, et al., NEJM, 2012)



Amantadine Trial Results: Behavioral Recovery (CRS-R)



Discussion: Mechanism of Effect

- Improved dopamine availability may:
  - Restore tonic arousal, motor initiation, cognitive persistence and other behaviors mediated by dopamine-dependent fronto-striatal circuits
  - Preserve dysfunctional but viable neuronal populations in meso-limbic and frontal systems involved in attention and drive.

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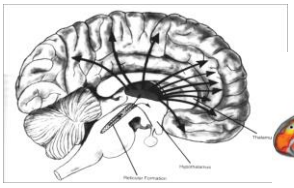
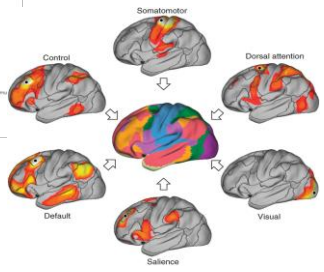
Relationship of lesion burden to outcome in regions of interest: Resting state and reticulo-thalamic networks

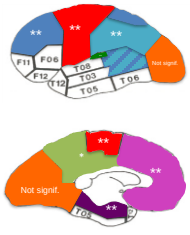




(Katz, et al., in preparation)

Relationship of lesion burden to outcome in cortical networks

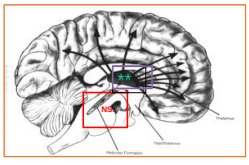
(**DRS/CRS-R significant; *DRS significant)



DRS and CRS-R		DRS only	NS
**Executive n=173 DRS: p=.0041 CRS-R: p=.0037	**Sensorimotor n=173 DRS: p=.0016 CRS-R: p=.0205	*Precuneus/P. Cingulate n=173 DRS: p=.0169 CRS-R: p=.0710	Visual n=173 DRS: Not signif. CRS-R: Not signif.
**Lateral temporo-parietal n=173 DRS: p=.0017 CRS-R: p=.0027	**Auditory n=173 DRS: p=.0151 CRS-R: p=.0144		
**Medial Prefrontal n=173 DRS: p=.0020 CRS-R: p=.0061			
**Parahippocampal n=173 DRS: p=.0056 CRS-R: p=.0091			

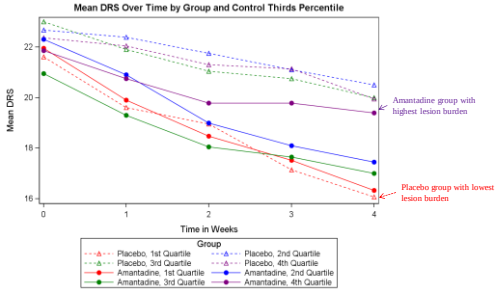
Relationship of lesion burden to outcome in subcortical and brain stem structures

(**DRS/CRS-R significant; *DRS significant)



**DRS and CRS-R	NS
**Thalamus n=176 DRS: p=.0001 CRS-R: p=.0043	Pons/midbrain n=176 DRS: Not signig. CRS-R: Not signif.
**Putamen n=176 DRS: p=.0011 CRS-R: p=.0034	
**Caudate n=176 DRS: p=.0107 CRS-R: p=.0105	

DRS over 4 weeks in amantadine and placebo groups with progressive levels of cortical lesion burden (1st-4th quartiles)

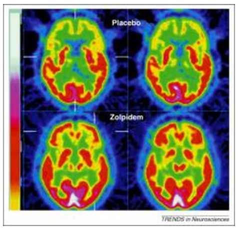


Conclusions

- Higher lesion burden on routine CT imaging is associated with worse recovery in patients with traumatic DoC.
- Some ROIs appear to have a more significant impact on recovery than others, but the specific regions contributing to unfavorable outcome remains uncertain.
- Lesion burden did not significantly limit the response to amantadine treatment, however, a decrease in rate of recovery was observed in the amantadine-treated group with highest lesion burden.

Zolpidem

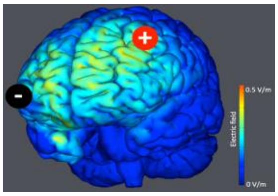
Marked anterior forebrain hypometabolism is noted bilaterally in frontal/prefrontal cortex, thalami and striatum. Following zolpidem administration broad increases of metabolic rates are observed in these regions.



(Brefel-Courbon, et al., AnnNeurol, 2007)

Thalamo-cortical connectivity and consciousness: Transcranial direct current stimulation (tDCS)

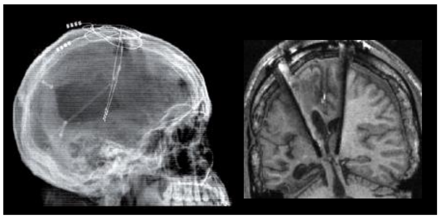
tDCS may increase of neuronal excitability via facilitation of resting membrane action potential, spontaneous neuronal firing rates, synaptic strength and cerebral blood flow/metabolism through NMDA, calcium uptake or dopaminergic modulation.



(Thibaut et al, Neurology 2014)

Central thalamic deep brain stimulation

Central lateral nucleus co-activates with anterior cingulate and SMA, nodes in the mesial frontal circuit that mediate response preparedness, motor intention and drive functions.



Schiff , Giacino, et al, *Nature* 2007

Central Thalamic Deep Brain Stimulation for Treatment of Chronic Post-Traumatic Minimally Conscious State

nature Vol 448|2 August 2007|doi:10.1038/nature06041

LETTERS

Behavioural improvements with thalamic stimulation after severe traumatic brain injury

N. D. Schiff[1], J. T. Giacino[2,3], K. Kalmar[2], J. D. Victor[1], K. Baker[4], M. Gerber[2], B. Fritz[2], B. Eisenberg[2], J. O'Connor[2], E. J. Kobylarz[1], S. Farris[4], A. Machado[4], C. McCagg[2], F. Plum[1], J. J. Fins[5] & A. R. Rezai[4]

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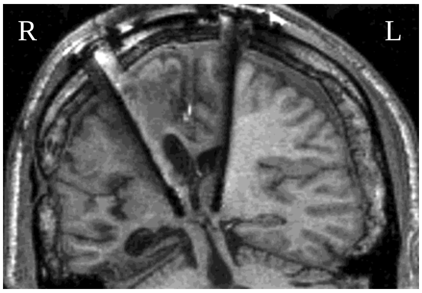
Rationale for DBS in MCS

- Hallmark of MCS: Response inconsistency/impersistence
- Primary aim: To determine whether thalamic DBS can promote behavioral responsiveness and improve functional outcome in patients diagnosed with chronic MCS

Patient 1: Electrode placement



Design

- Double-blinded alternating crossover design

Condition	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
ON	X		X		X	
OFF		X		X		X

Primary Outcome Measure: Coma Recovery Scale- Revised

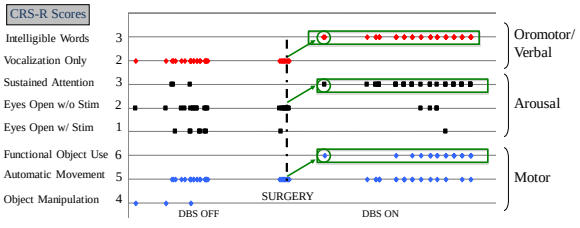
Frequency of best score on Arousal, Motor, and Communication subscales of CRS-R

(Giacino, et al, Arch Phys Med Rehabil, 1991, 2004)

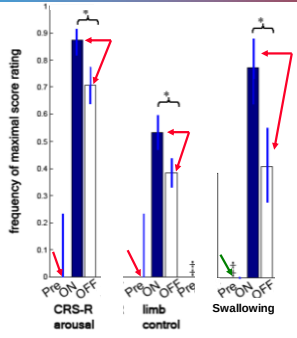
Patient 1

- 33 y/o RH male
  - Blunt head trauma following assault resulting in b/l SDH (R>L)
  - 2 yrs inpatient rehab + 4 yrs nursing home
- Clinical status on re-admission (6.5 yrs post-injury):
  - Diagnosis: MCS
  - Inconsistent command-following
  - Rare single-word verbalization
  - Unable to communicate reliably or use common objects
  - Total care required, Unable to communicate with family/staff

Patient 1: Results



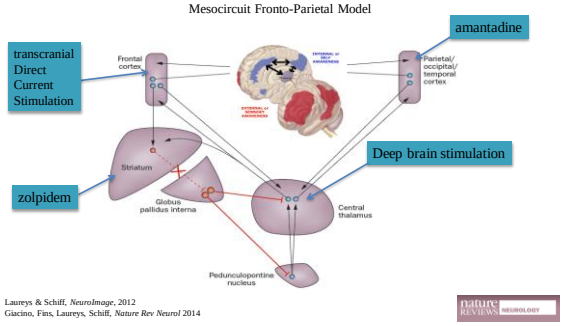
Behavioral Performance: Pre-DBS v. DBS On v. DBS Off



Conclusions

- DBS modulates specific cognitive and behavioral functions (arousal, functional limb movement, swallowing) via central thalamic upregulation of mesial frontal circuit (anterior cingulate and SMA).

Paradigms (re)framed by neuroimaging



Laureys & Schiff, *NeuroImage*, 2012
Giacino, Fins, Laureys, Schiff, *Nature Rev Neurol* 2014

nature REVIEWS NEUROLOGY

Summary

- Disorders of consciousness exist along a dynamic continuum of residual cognitive function.
- Diagnostic error remains high among patients with Dock.
- 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.
- Recent outcome studies suggest that individuals who sustain severe brain injury experience more substantial and longer periods of recovery than previously thought.
- Preliminary results support use of targeted neuromodulatory interventions aimed at facilitating recovery of specific cognitive and behavioral functions.