Kennedy Krieger Institute

A comprehensive resource for children with disabilities

JOHNS HOPKINS MEDICINE

SCHOOL OF MEDICINE

A New Understanding of Disorders of Consciousness

April 14, 2011

Beth S. Slomine, Ph.D. ABPP

Director of Training and Neuropsychological Rehabilitation Services

Kennedy Krieger Institute

Associate Professor

Johns Hopkins University School of Medicine

Megan E. Kramer, Ph.D.

Postdoctoral Fellow in Neuropsychology

Kennedy Krieger Institute

Johns Hopkins University School of Medicine

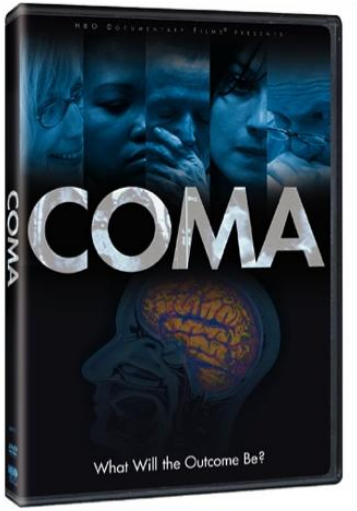
Overview of Presentation

- Terminology
- Neurobiology
- Assessment
  - Behavioral assessment tools
  - Neuroimaging
- Interventions
  - Behavioral interventions
  - Neurostimulant medications
  - Deep brain stimulation
- Predicting outcomes

Terminology

Disorders of Consciousness (DOC)

- Severely altered arousal and/or awareness of self and the environment
  - Coma
  - Vegetative State
  - Minimally Conscious State
- Consensus definitions from Aspen Neurobehavioral Workgroup



Coma

All criteria must be met

- **No spontaneous or induced eye opening**
- No command following
- No intelligible speech
- No purposeful movement
- No discrete defensive capacity to localize noxious stimuli

- Rarely lasts longer than 2-4 weeks after trauma; evolves to vegetative state

Vegetative State

All criteria must be met

- Presence of sleep-wake cycles (periodic eye opening)
- No sustained, reproducible, purposeful, or voluntary behavioral responses to stimuli
- No evidence of language comprehension
- Bowel and bladder incontinence
- Preservation of autonomic functions permits survival with adequate care
- Variable preservation of cranial/spinal reflexes

An individual in a vegetative state may:

- Show spontaneous movement
- Smile
- Shed tears
- Moan, grunt, scream

- BUT, these behaviors are inconsistent, nonpurposeful, and are only coordinated reflexively

New nomenclature: "Vegetative state + etiology + duration"

No longer use "persistent" or "permanent"

Minimally Conscious State (MCS)

- Pursuit eye movement or sustained fixation in direct response to moving or salient stimuli
- Crying, smiling, or laughing in response to emotional but not neutral content
- Vocalization or gestures in direct response to linguistic content of comments or questions
- Reaching for objects with a clear relationship between object location and direction of reach
- Touching or holding objects in a manner that accommodates the size and shape of the object

Emergence from MCS

- Return of reliable and consistent interactive communication OR functional object use
  - Communication may be through verbalization, writing, yes/no signals, or augmentative communication device (6/6 correct responses to situational orientation questions)
  - Functional object use: discrimination and appropriate use of at least 2 common articles (e.g., cup, hairbrush)

NOT Disorders of Consciousness

- Brain Death:
  - Absence of clinical brain function (including brainstem)

- Locked-In Syndrome
  - Full consciousness, loss of all motor control except for vertical eye movements and blinking
  - Results from injury to ventral pontine regions

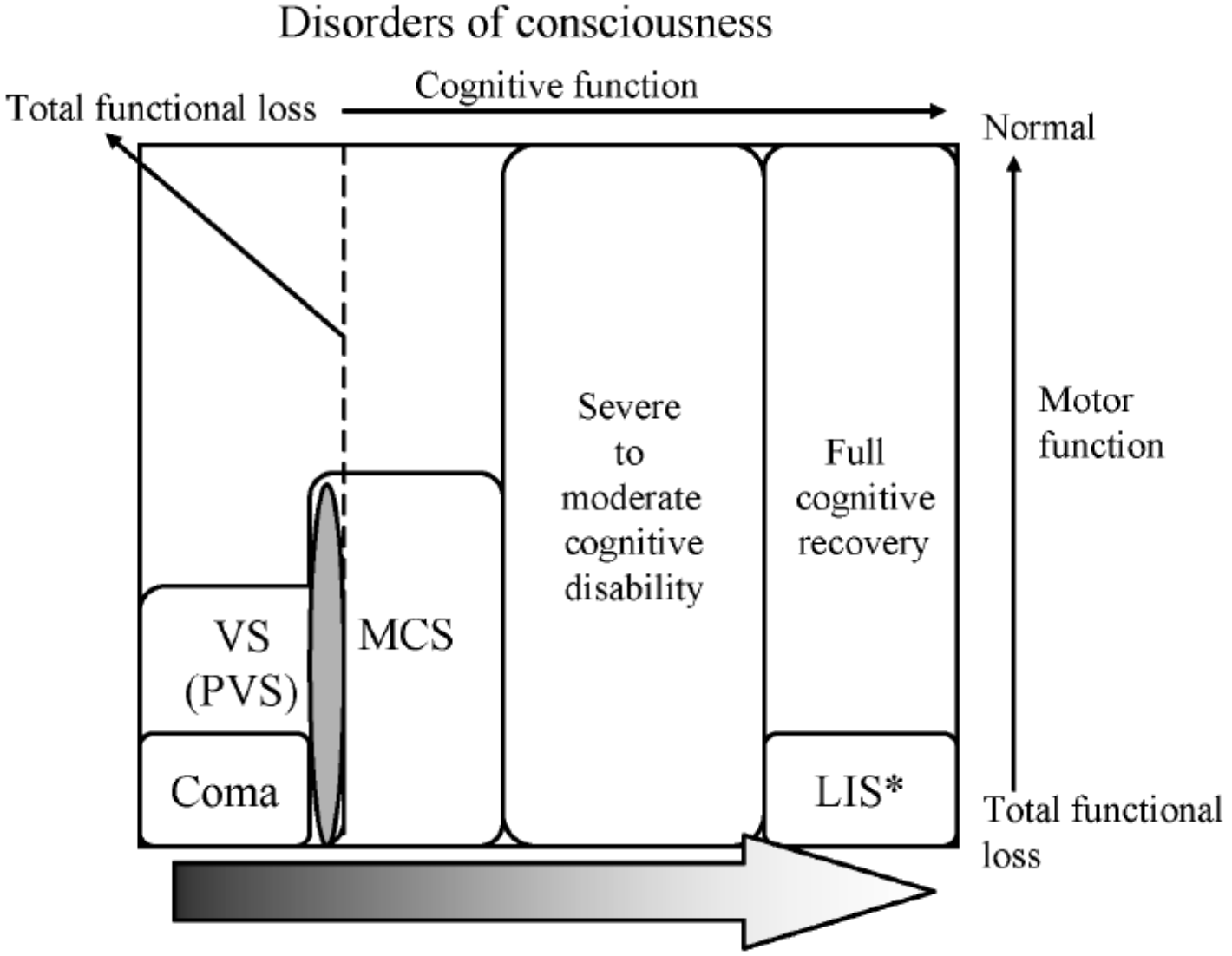
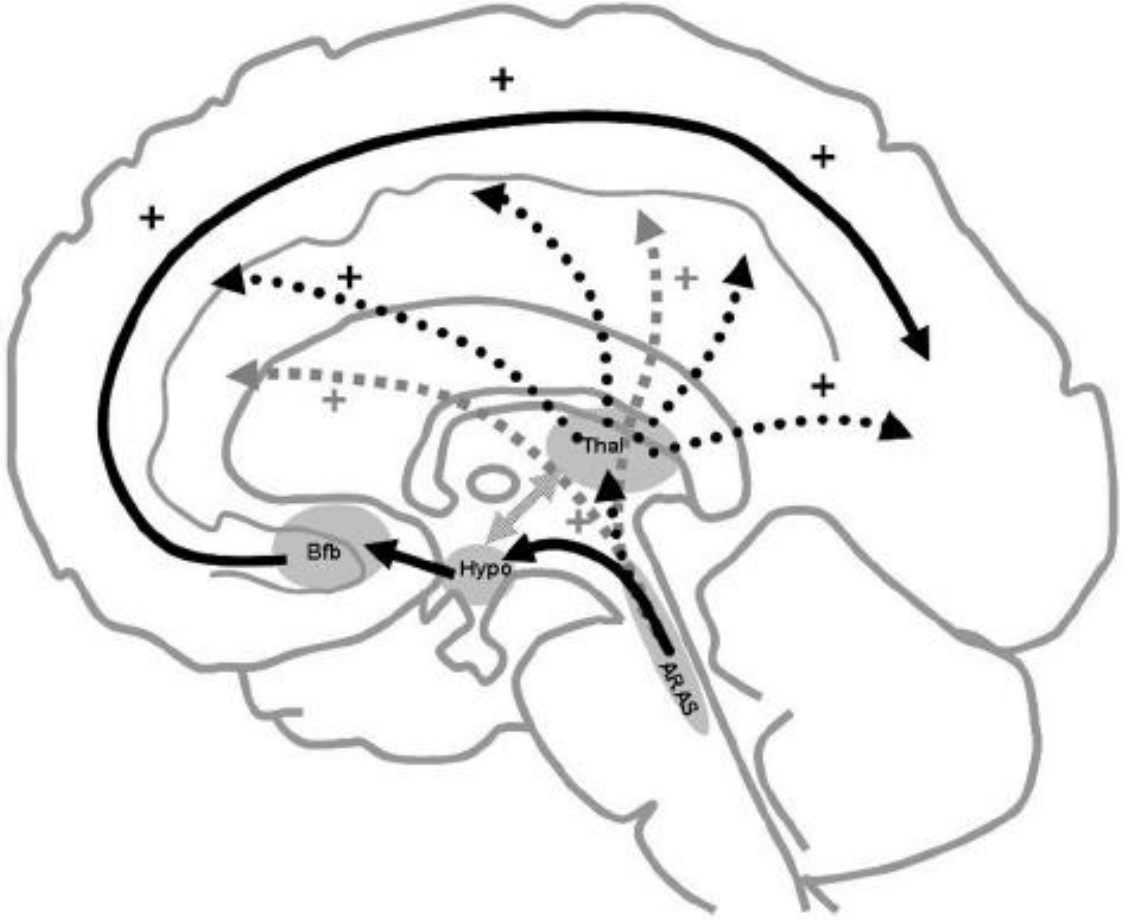


Figure by Nicholas Schiff

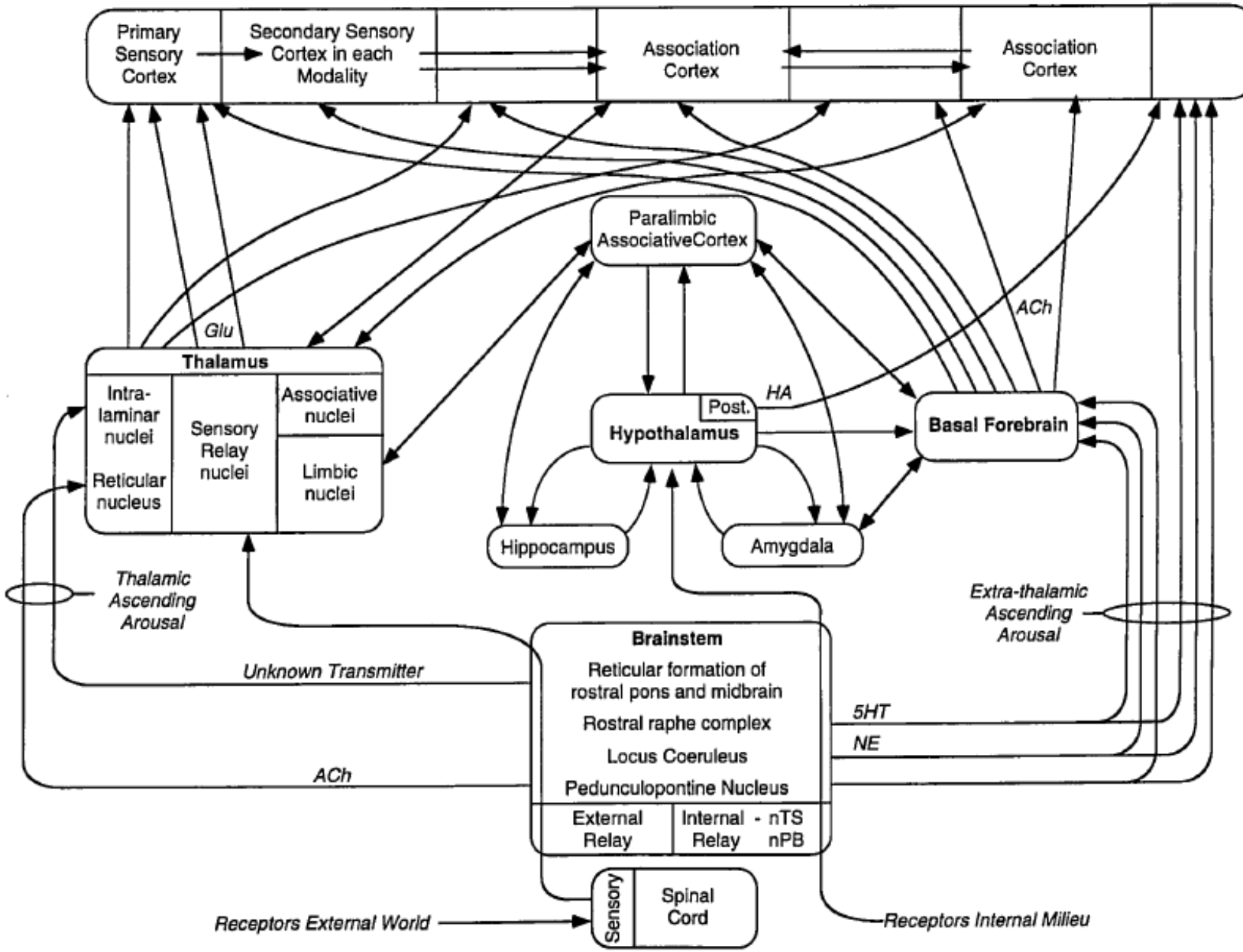
Neurobiology

Anatomic structures subserving awareness and arousal



Bfb: Basal forebrain
Hypo: Hypothalamus
Thal: Thalamus
ARAS: Ascending reticular activating system

Weiss et al., Critical Care, 2007

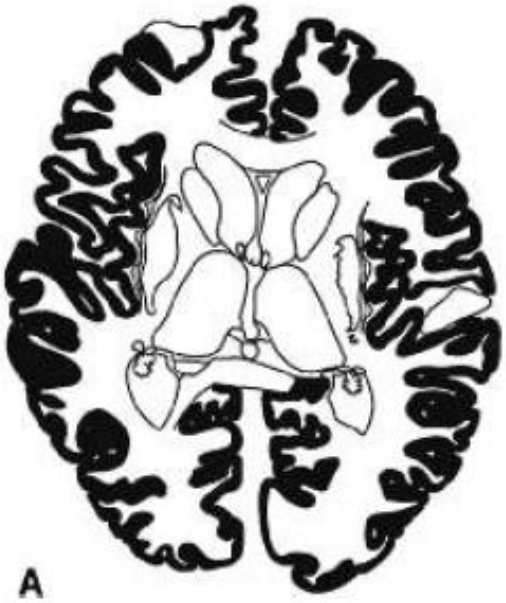


Kinney and Samuels, J Neuropath and Exp Neuro, 1994

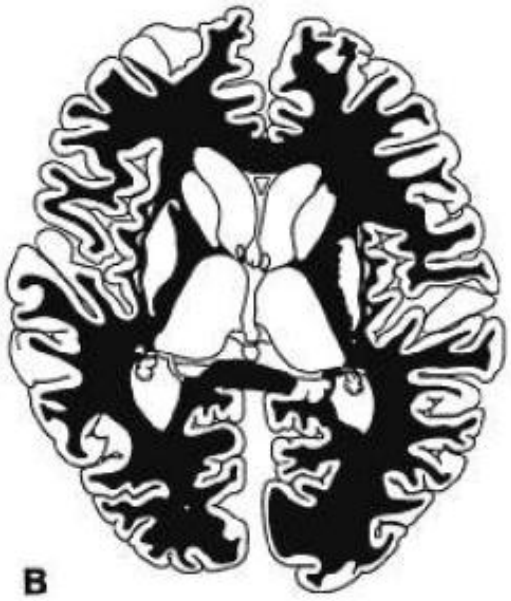
Etiology of Disorders of Consciousness

- Congenital -- developmental processes
- Acquired
  - Degenerative/metabolic neurological diseases
  - Injury
    - Transient, marking a stage in recovery
    - Permanent due to failure to recover from injury

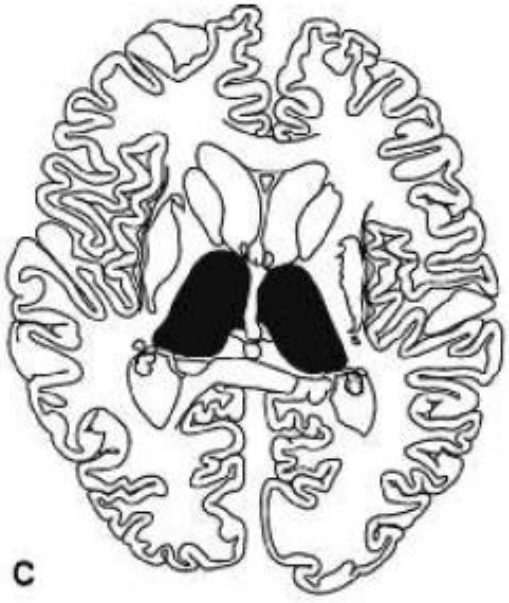
Neuropathology of Vegetative State



Diffuse Cortical Injury



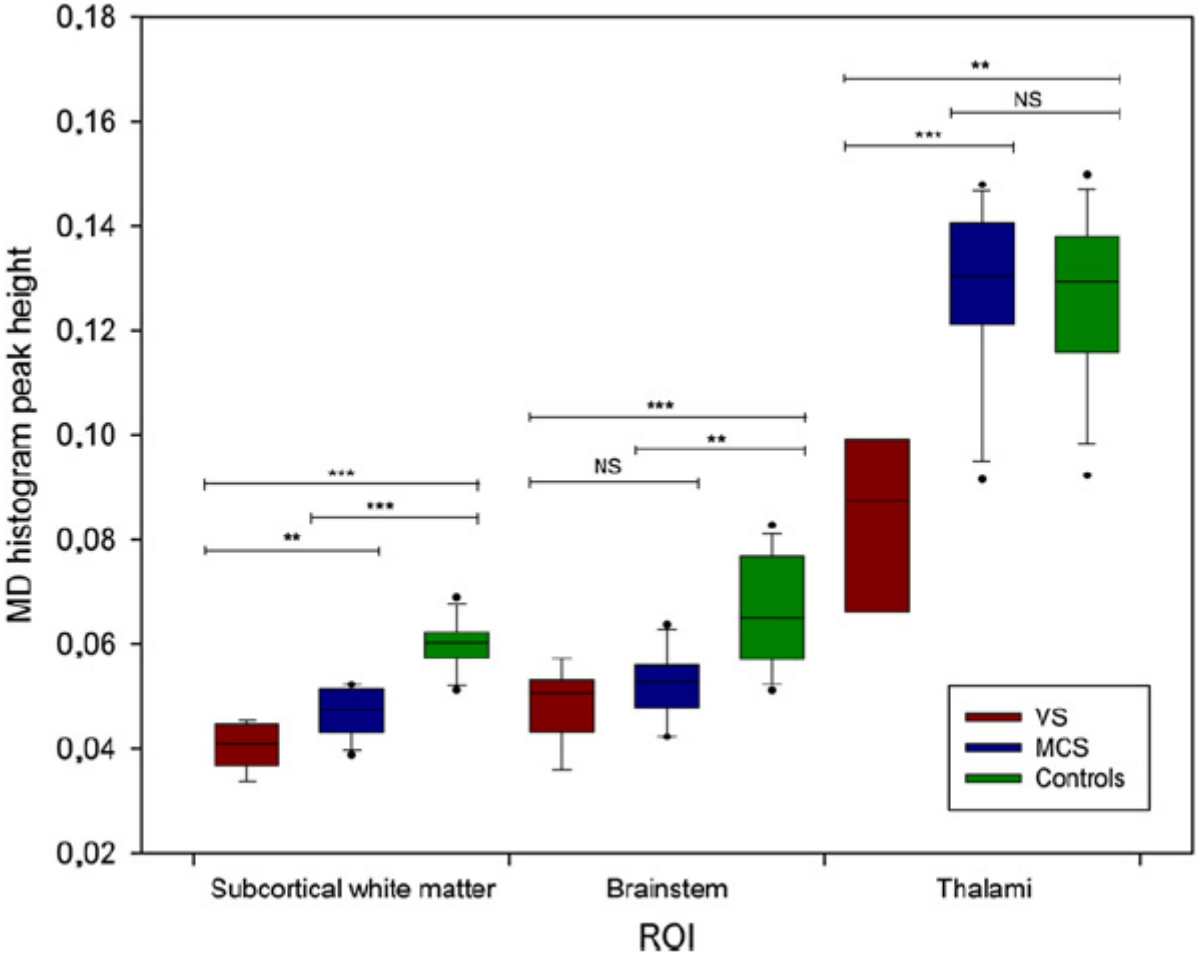
Diffuse Subcortical +/-
Brainstem Injury



Thalamic Injury

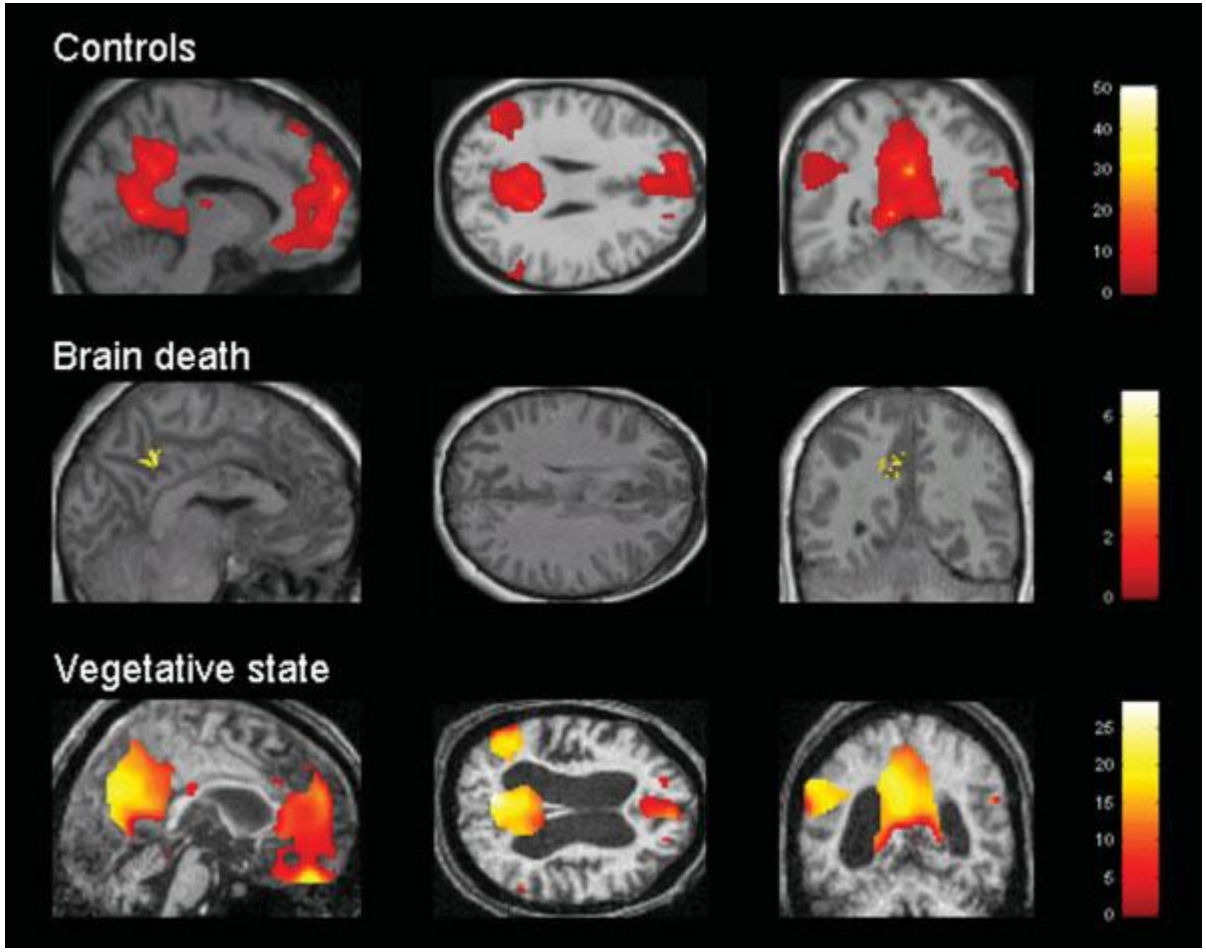
figure from Kinney and Samuels, J Neuropath and Exp Neuro 1994

Reduced anatomic connectivity in DOC



Fernandez-Espejo et al., Neuroimage, 2011

Reduced functional connectivity in DOC



Boly et al, Human Brain Mapping, 2009

Assessment

Why Assess Responsiveness?

- Help team members (medical, therapy, & educational staff) and families understand current level of function
- Provide information for payors – supporting level of care, equipment needs
- Standardize patients by functional ability for research and clinical purposes
- Evaluate response to interventions
- Aid in prognosis and prediction of further recovery

Methods of Assessment

- Standardized clinical evaluation scales
- Individualized quantitative behavioral assessments
- Neuroimaging

Standardized Evaluation Tools

- Review of 37 articles and 13 scales
- Best measure was Coma Recovery Scale – Revised (CRS-R)
  - Good content validity, internal consistency, interrater reliability
- Several scales recommended with moderate reservations
- Coma-Near Coma Scale (CNC) may be used with major reservations
- Several other scales not recommended

Seel et al., Arch Phys Med Rehab, 2010

Standardized Evaluation Tools

JFK Coma Recovery Scale (Revised)

- Auditory Function
- Visual Function
- Motor Function
  - Functional object use*
- Oromotor/Verbal
- Communication
  - Functional communication*
- Arousal

Rappaport Coma / Near Coma Scale

- Command Following
- Vocalization
- Motor responses to
  - Pain
  - Visual stimulation/threat
  - Tactile stimulation
  - Olfactory stimulation
  - Auditory stimulation

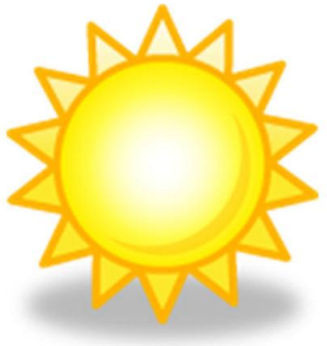
Individualized Assessments

- Target a few behaviors of particular interest
  - Short assessments
  - Can be repeated throughout day by varying staff and family members

- Examples:
  - Arousal: eye opening, response to stimulus
  - Command following versus automatic movements
  - Vision/Hearing: preferential attention to salient stimuli

Recommendations for Assessment

- Choose target behavior carefully
  - Family/therapist input
  - Consider impairments
  - Non-reflexive movements
  - Use broad range of stimuli/responses

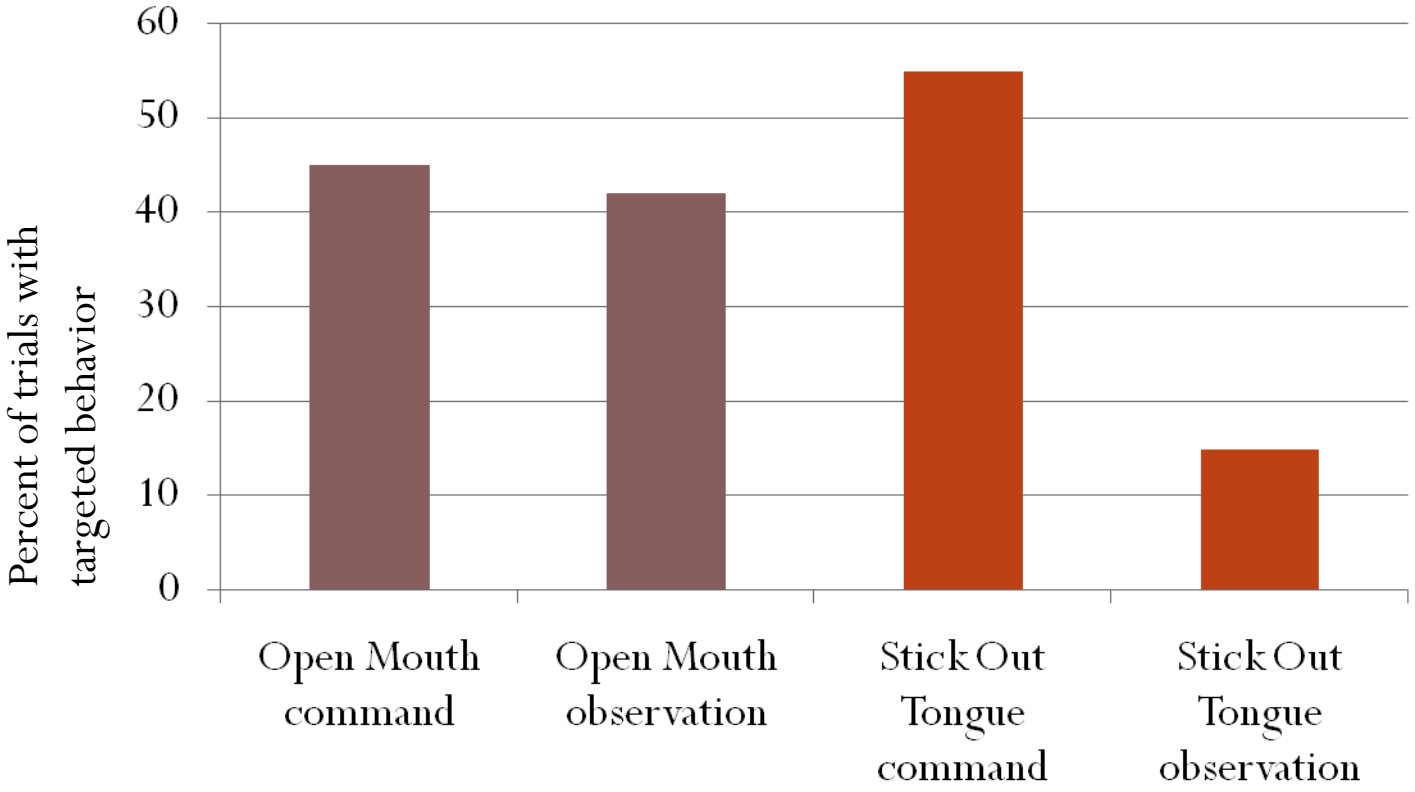


- Optimize patient's arousal/attention
  - Minimize sedating medications
  - Provide sufficient stimulation
  - Choose a distraction-free environment

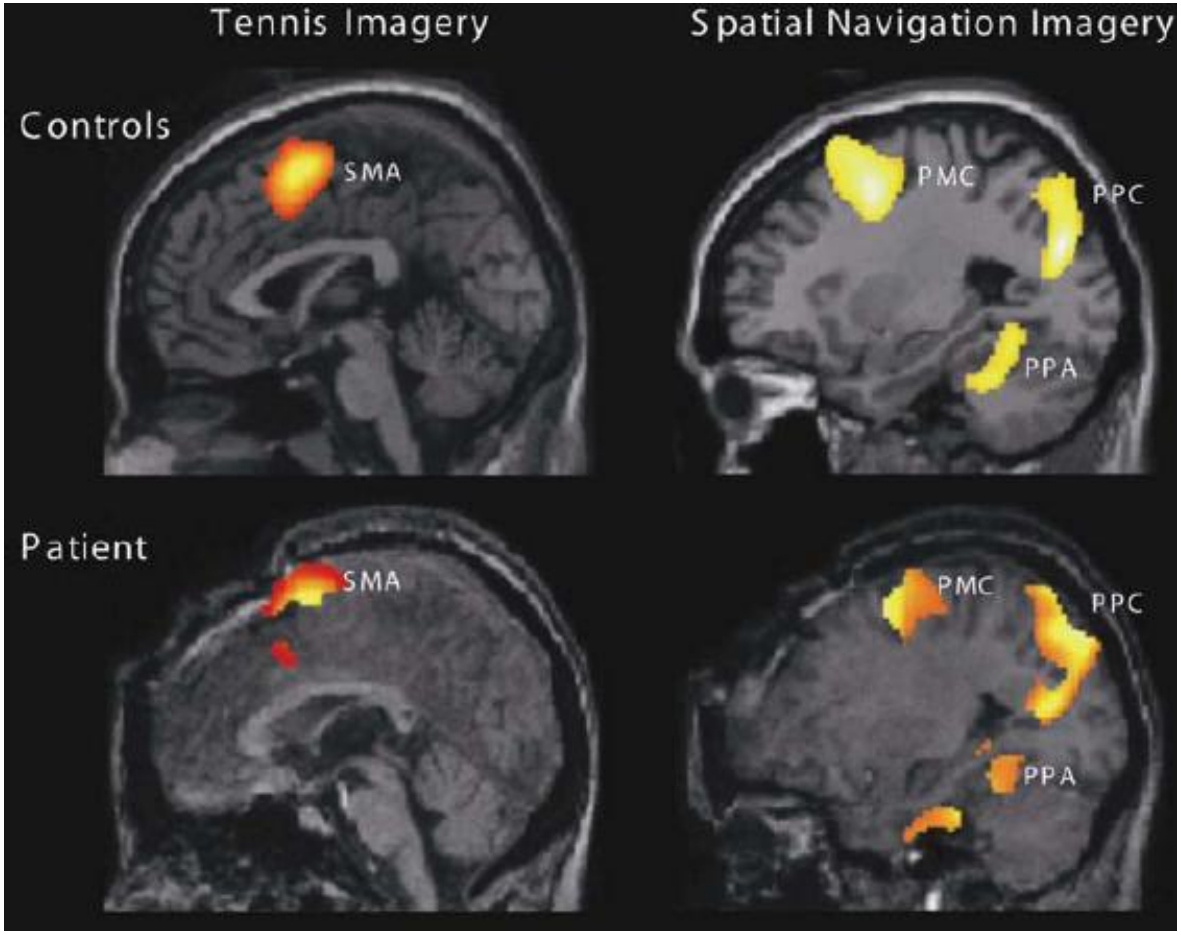
Command Following Protocol

	Opens Mouth	Sticks Out Tongue	No Response
Stick out your tongue			
(No Command)			
Open your mouth			
Stick out your tongue			
Open your mouth			
(No command)			
(No command)			
Open your mouth			
Stick out your tongue			

Command Following Protocol



Imaging as evaluation tool?



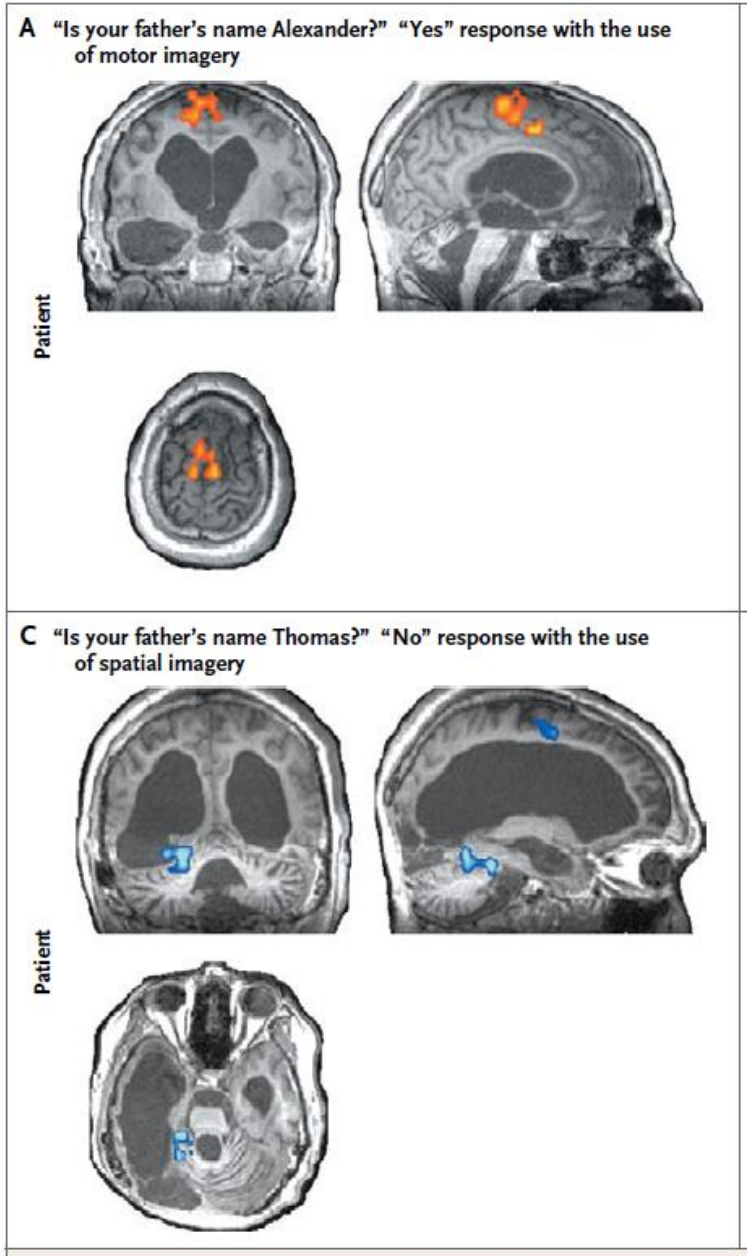
Owen et al., Science, 2006

Neuroimaging – a larger cohort

- 5 of 54 patients in VS or MCS demonstrated "willful modulation of brain behavior"

- One patient with in MCS (but no functional communication) correctly answered 5 of 6 yes/no questions by imagining tennis versus spatial navigation

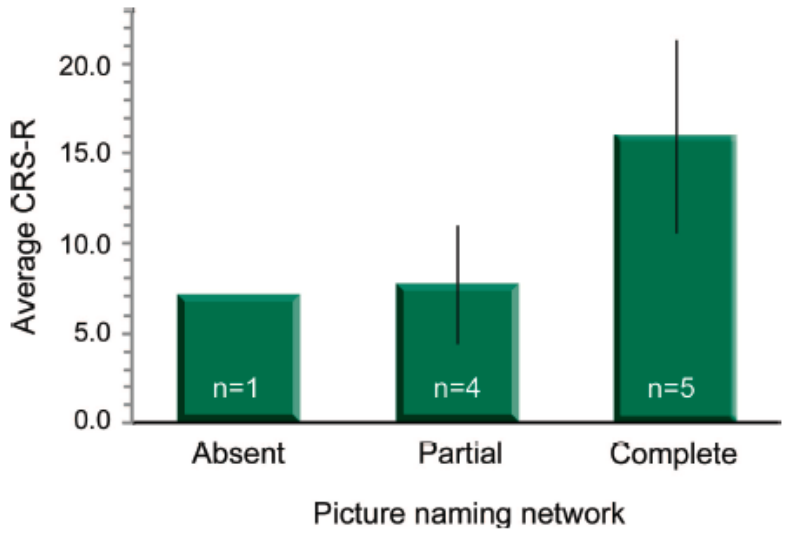
Monti et al., NEJM, 2010



Imaging: network approach

- Observational fMRI study
- Object naming task
- Patients:
  - MCS=5, VS=3, emerged from MCS=1, LIS=1
- Extent of preservation of language network was correlated with Coma Recovery Scale Score

Figure 2 Relationship between Revised Coma Recovery Scale (CRS-R) scores and preservation of the picture-naming network



Patients with disorders of consciousness are grouped according to preservation of the naming network previously observed in healthy volunteers: complete network: patients with activation of all brain areas observed in healthy volunteers (left superior temporal gyrus, left ventral inferior frontal gyrus, left dorsal inferior frontal gyrus, and pre-supplementary motor area); partial network: patients with activation of some brain areas observed in healthy volunteers; and 3) absent network: patients with no activation of any brain areas observed in healthy volunteers. The bars show the average CRS-R score for each group with the corresponding SD.

Rodriguez Moreno et al., Neurology, 2010

Interventions to Optimize Responsiveness

Environmental Interventions

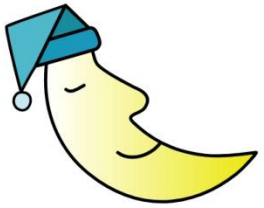
- Optimize stimulation
  - Position upright – wheelchair or stander
  - Lights on during day
  - Multi-sensory stimulation
  - But not too much stimulation
- Optimize sleep
  - Nighttime routine
  - Lights off/noises off at night
  - May need daytime naps/rest breaks

Behavioral Interventions

- Positive reinforcement for desired responses
  - Formal preference assessment often helpful for identifying preferred stimuli
- Shaping purposeful responses for functional use
- Switches

A Structured Medical Approach

- Wean potentially sedating medications
- Optimize night-time sleep
  - Trazodone
  - Melatonin
- Evaluate and optimize hearing and vision
- Await stabilization of active medical issues
- Consider neurostimulant trial(s)



Tracking Sleep

TIME										
600	A	S	S	S	S	S	A	A	A	A
700										
800	S	S	S	S/A	S	S	A	A	A	A
900										
1000	A	S	S	S	S	S	A	A	A	A
1100										
1200	A	A	S	A	A	S	A	A	A	A
1300		S			A					
1400	A	A	S	A	A	A	A	A	A	A
1500	A									
1600	A	S	A	A/S	A	A	A	A	A	A
1700										
1800	A	S	A	A	A	A	A	A	A	A
1900										
2000	A	A	A	A	A	A	S	S	A	A/S
2100										
2200	S	A	S/A	A	S	S	S		A	A
2300								S		
2400	S	S	A	A	A/S	S	A/S	A	S	S
100			S							
200	S	S	A/S	A	S	S	S	A	S	S
300										
400	S	A	S	A	S		S	S	S	S
500	S	A	S	A	S		S	S	S	
	date	date	date	date	date	date	date	date	date	date
	THURS	FRI	SAT	SUN	MON	TUES	WED	THURS	FRI	SAT

	SLEEP	BOTH	AWAKE

Pharmacological Interventions

- Emerging literature
- Typical agents:
  - Dopaminergic agents
  - Gabaergic agents
- Most studies are open-label, observational, and case studies
- Randomized controlled trials of amantadine
  - Adults
  - Children

Brain Injury, April 2011; 25(4): 315–327

informa
healthcare

ORIGINAL ARTICLE

Pharmacological and electrical stimulation in chronic disorders of consciousness: New insights and future directions

LAIS OLIVEIRA[1,2] & FELIPE FREGNI[1,2]

[1]*Laboratory of Neuromodulation, Physical Medicine and Rehabilitation Department, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA and* [2]*Berenson-Allen Center for Noninvasive Brain Stimulation, Neurology Department, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*

(Received 22 October 2009; revised 26 October 2010; accepted 17 January 2011)

Abstract

Background: Chronic disorders of consciousness are costly and challenging conditions to treat. Although recent studies that have tested pharmacological and electrical stimulation for these conditions are promising, the optimal intervention, mechanisms of action and side effects of these experimental therapies are unclear.

Objective: To systematically review the clinical results of treatments for vegetative state (VS) and minimally conscious state (MCS) from the last 10 years.

Methods: MEDLINE, LILACS and SCOPUS were searched as data sources. Because the potential bias when search is limited to databases of peer-reviewed journals, reference lists were examined and experts in the field were contacted for other relevant or unpublished articles (i.e. negative studies). No negative unpublished studies were found. Studies were included related to therapeutic interventions in adult MCS or VS patients at least 3 and 12 months after non-traumatic and traumatic injuries, respectively. Eight studies met the inclusion criteria. The following interventions were reviewed: levodopa, amantadine, zolpidem, baclofen, dorsal column stimulation and deep brain stimulation.

Conclusions: The adverse effects that were associated with these treatments were typically mild. Most of the studies demonstrated considerable improvements with the interventions, but their low strength of evidence limit the generalizability of the findings.

Keywords: *Vegetative state, minimally conscious state, anoxia, traumatic brain injury, therapy, outcome*

Amantadine:
RCT in adults with VS or MCS after TBI

- Recently concluded study
- Double-blind placebo controlled
- Amantadine administered for 4 weeks after admission to acute rehabilitation
- Improved rate of change in DRS during treatment period in amantadine group
- No between-group differences after two week washout period
- No significant adverse effects

Whyte et al., presented at AAPMR 2010

Amantadine: A Pediatric Trial

TABLE 1 Subjects

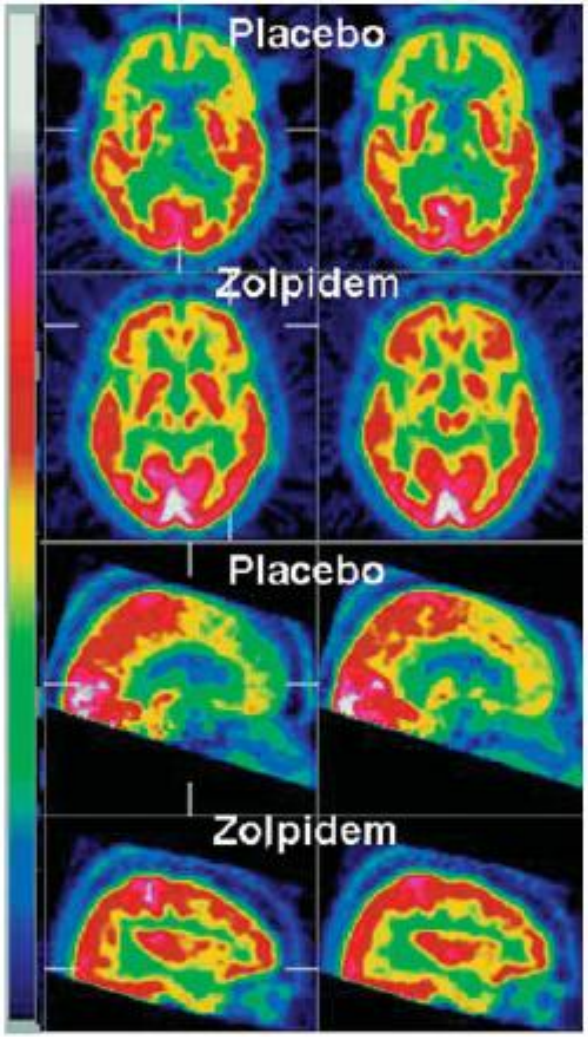
Subject	Age, yrs	Sex	Mechanism of Injury	Initial GCS	Weeks Postinjury When Enrolled	Maximum Dose, Milligram Twice a Day	Level of Consciousness			
							Baseline	End First Arm	W	End Second Arm
1	8	M	Anoxia	3	9	120	VS	VS[a]	VS	VS
2	6	M	Trauma	4	4	83	MCS	MCS	MCS	CS[a]
3[b]	14	M	Trauma	4	10	99	VS	MCS	MCS	N/A
4	13	M	Trauma	4	6	72	VS	VS[a]	VS	VS
5	18	M	Trauma	6	5	149	VS	VS	VS	MCS[a]
6[b]	16	M	Trauma	3	7	175	VS	MCS[a]	VS	MCS[a]
7	14	F	Stroke	4	6	165	MCS	MCS	MCS	CS[a]

[a] Denotes amantadine arm.
[b] Denotes subjects not included in analysis.
W, washout; VS, vegetative state; MCS, minimally conscious state; CS, fully conscious state; GCS, Glassgow Coma Scale.

McMahon et al., AJPMR, 2009
Vargus-Adams, et al., PM&R, 2010

Zolpidem (Ambien)

- Case reports of emergence from chronic VS or MCS in individuals with traumatic or anoxic BI
- Not effective in all individuals
  - (1 in 15, Whyte, AJPMR, 2009)
- Effect typically lasts hours
- Thought to inhibit pathologic tonic outflow to thalamocortical system, thereby resulting in activation
- Limited data in children

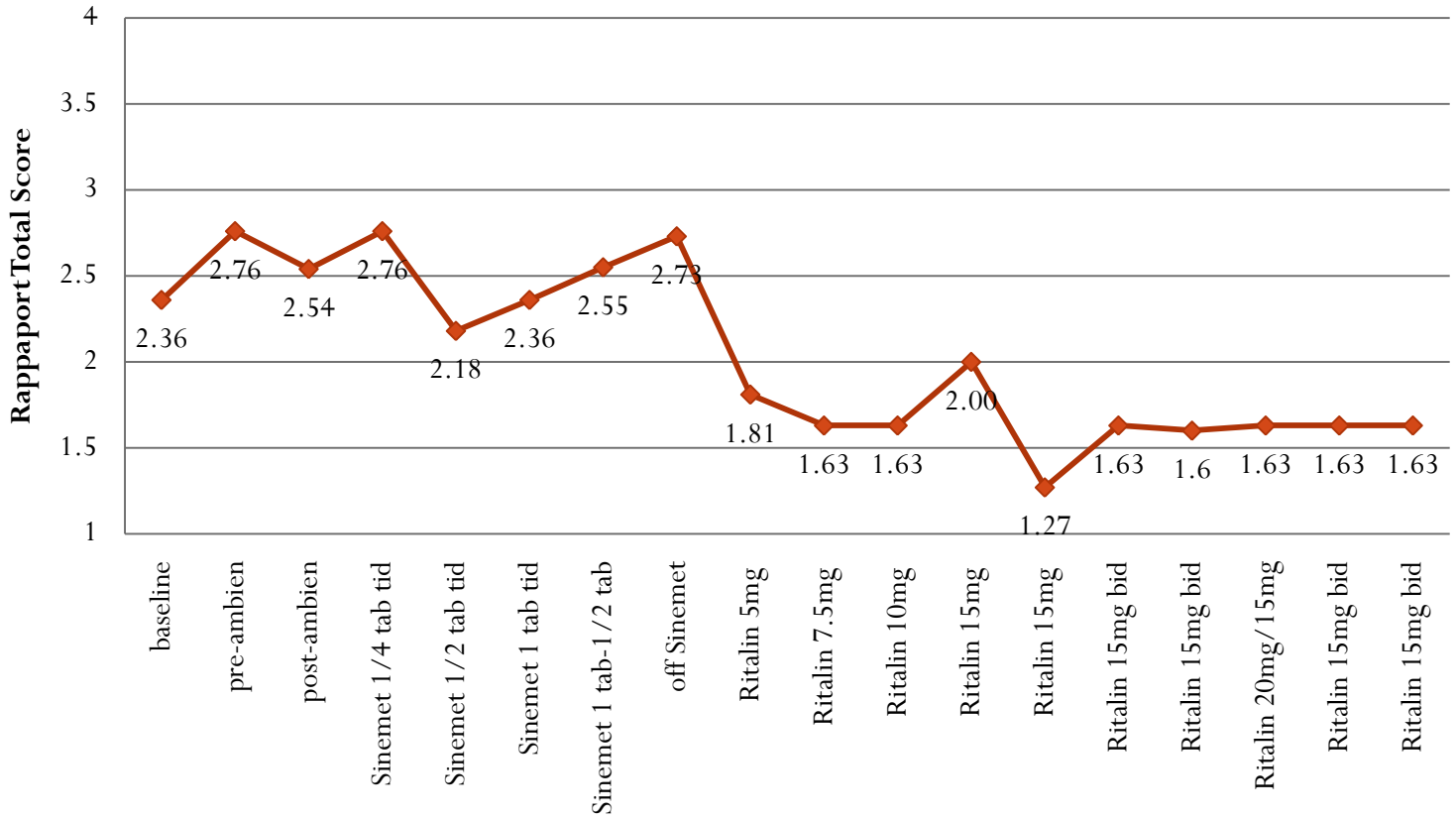


Brefel-Courbon et al., Ann Neurol, 2007

Methylphenidate (Ritalin)

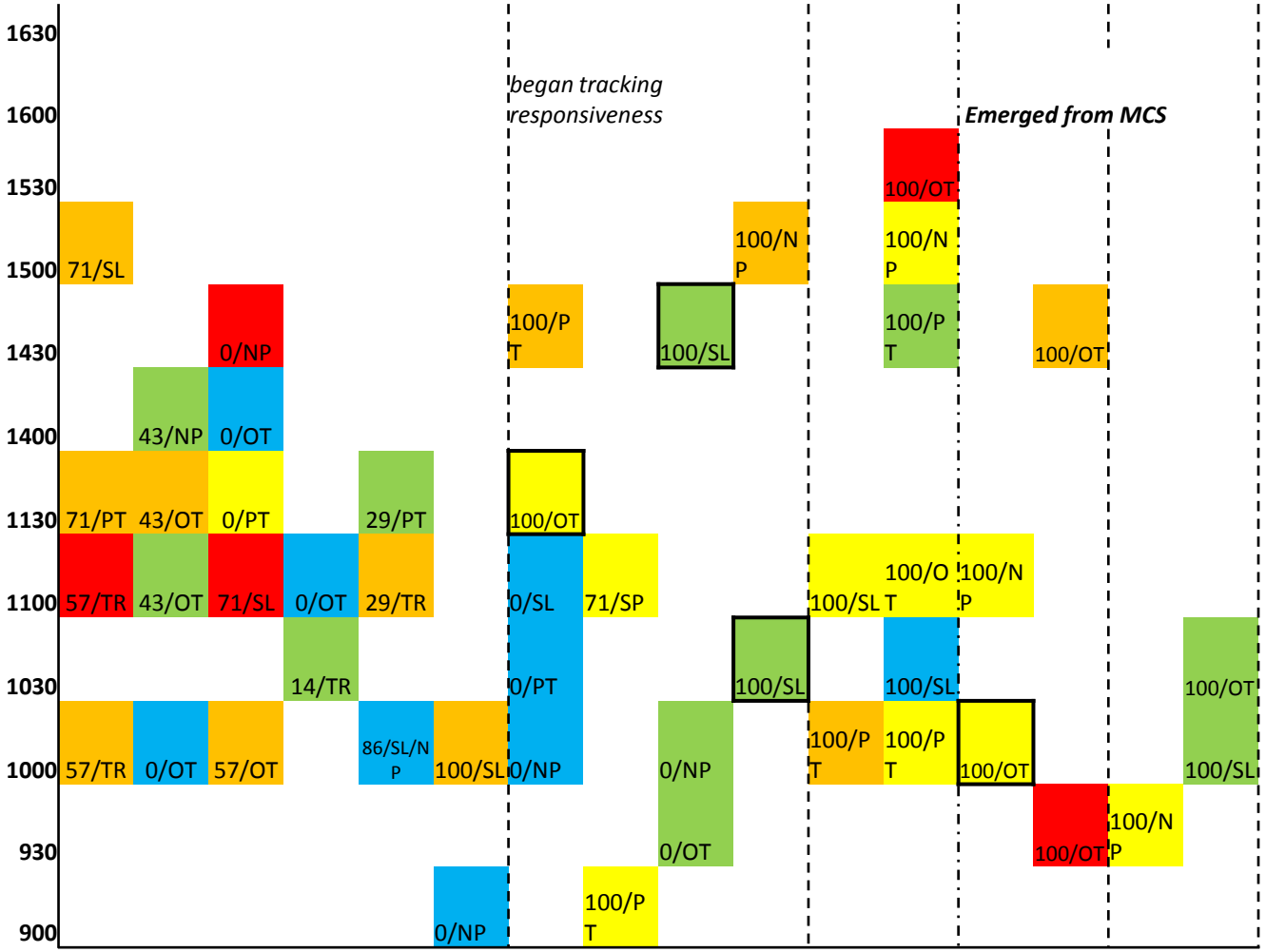
- Increases extracellular dopamine and norepinephrine
- Typically used for attention, processing speed
- Some evidence that rate, but not overall level, of recovery enhanced in moderate TBI (Plenger et al., Archives of PM&R, 1996)
- One report of shorter ICU and hospital stay after adult severe TBI when started on hospital day #2
  (Moein et al., Clinical Neurology & Neurosurgery, 2006)

Tracking Responsiveness by Medication



Pennington et al., Poster presented at 2011 INS Conference

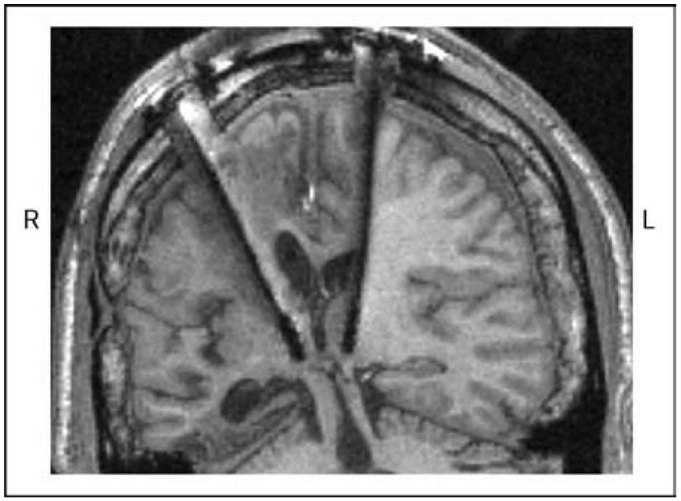
Improving arousal with medication weaning



McCann et al., Poster presented at 2011 INS Conference

Deep Thalamic Stimulation

- Stimulation of thalamus proposed to take the role of arousal regulation normally controlled by frontal lobe
- In MCS, improves regulation of functionally connected but inconsistently active brain networks
- Goal is restoration of reliable communication or response initiation/persistence

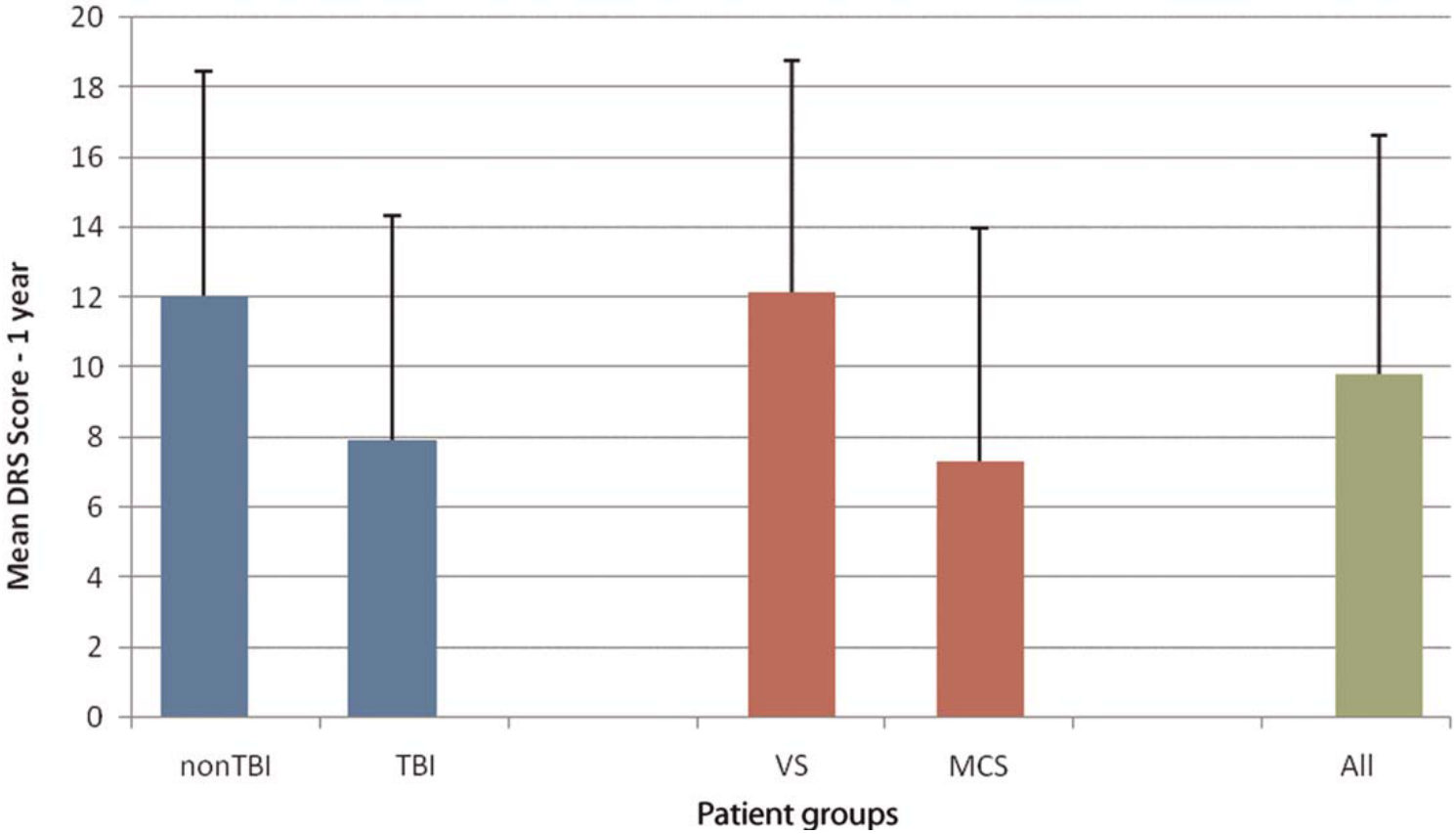


Schiff et al., Nature, 2007

Predicting Outcomes

Predicting Outcome

- Prognosis is better for MCS vs VS at admission to rehab, and for TBI versus non-TBI (Giacino & Kalmar, 1997; Katz et al., 2009)



Katz et al., Progress in Brain Research, 2009

Predicting Outcome

- Minimal signs of consciousness at one month post-injury was associated with emergence from DOC (Whyte et al., 2005)
- Rate of functional change during first two weeks was predictive of disability four months later (Whyte et al., 2005, 2009)
- Patients in VS who transition to MCS within 8 weeks of onset were more likely to continue recovering to higher levels of functioning one year after injury (Katz et al., 2009)
- Of individuals in VS or MCS at 1 year post injury, 0% of VS improved while 33% of MCS improved within 5 years post injury (Luaute et al., 2010)
- Patients with DOC who demonstrated visual tracking had better outcomes than those without (even >230 after admission), with earlier tracking associated with better outcome (Dolce, et al., 2010)

Predicting functional outcome after pediatric TBI: benefit of Time to Follow Commands above and beyond initial GCS score

	Discharge from inpatient rehab (n=120)		3 months after discharge from inpatient rehab (n=34)	
	R^2	B	R^2	β
GCS	.08**	.10	.04	-.07
TFC	.28***	-.52	.29***	-.94
PTA	.00	-.08	.05	-.41
	Overall model R^2=.37		Overall model R^2=.38	

Suskauer et al., JPRM, 2009

Functional outcome at discharge from inpatient rehab for 120 children with TBI

Time to Follow Commands	No assistance needed	Set-up or supervision needed	Physical assist needed
0-2 days (n=41)	41%	37%	22%
3-11 days (n=43)	12%	49%	40%
12-26 days (n=27)	0%	44%	56%
>26 days (n=9)	0%	0%	100%

Suskauer et al., JPRM, 2009

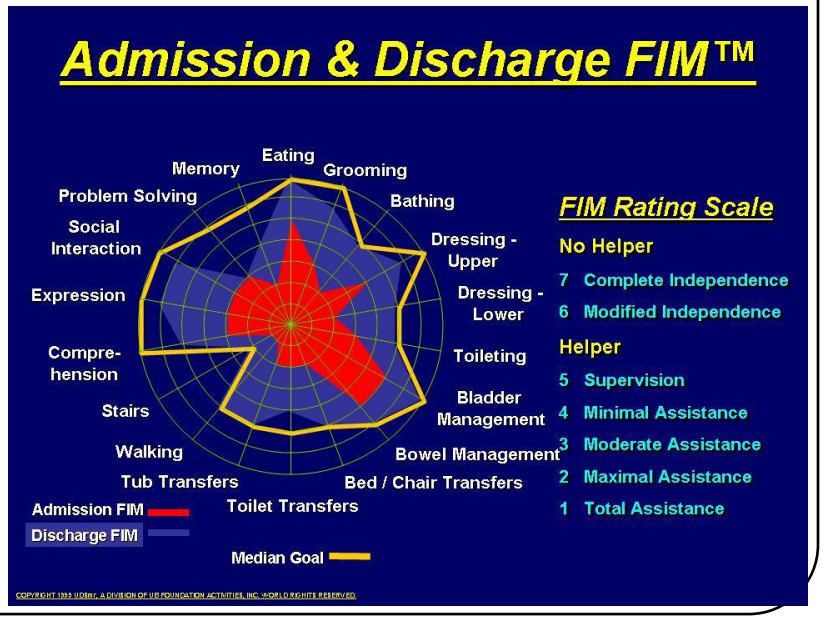
Children with Severe TBI

- Hypotheses:
  - Injury severity would predict functional status at discharge
  - Functional status early in admission would predict status at discharge

- Included only children with lowest level of functioning at admission
  - WeeFIM raw score = 18
- Demographic, injury-related, and rehabilitation variables
  - WeeFIM scores collected at admission, 2-week intervals, discharge

WeeFIM

- Performance based assessment of functional independence in three domains:
  - Mobility, self-care, cognitive abilities
- Each scored from 1 (total assistance) to 7 (independent)
- 18 items; Raw score 18 – 126
- Developmental Quotient (DFQ)
  - Age corrected scores
  - % of age appropriate function

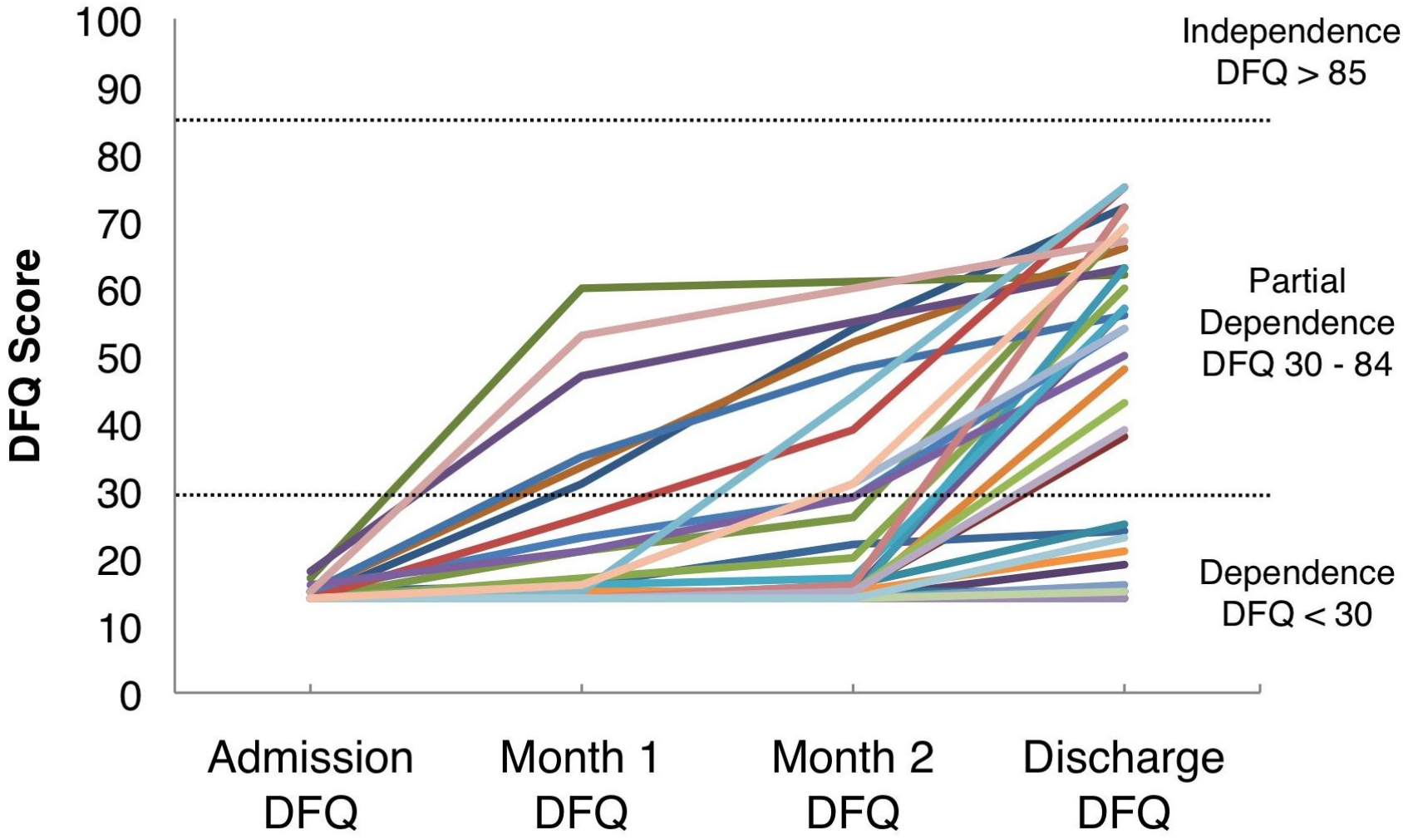


Sample Characteristics

- Demographic
  - N = 35
  - *M* = 11 (3 to 18)
  - 66% Male
  - 77% Caucasian
- Injury/Rehabilitation
  - GCS *M* = 4.3 (3 to 8)
  - Time from injury to rehab
    M = 29 days (5 to 117)
  - Length of rehab stay
    M = 99 days (14 to 255)

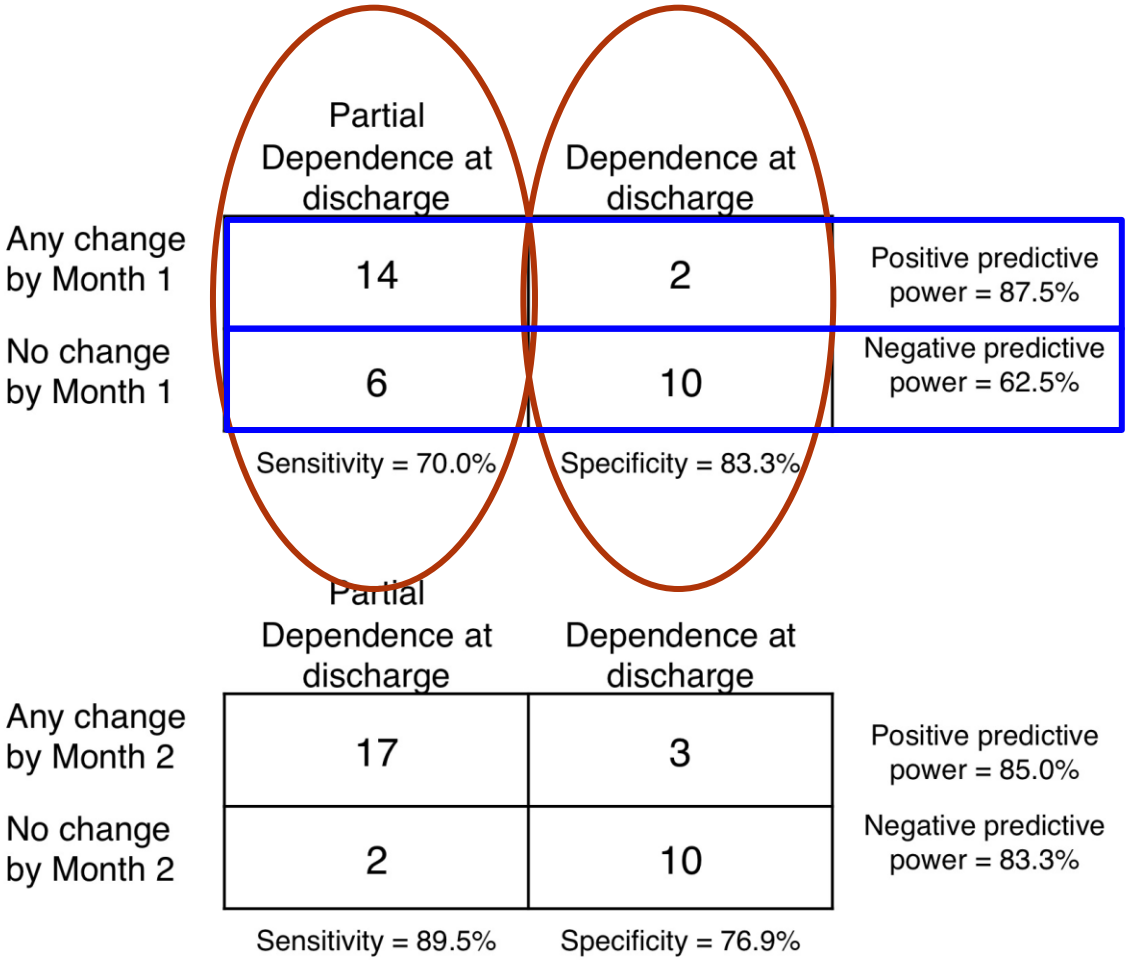
Interval assessment data

- Month 1 data (n=32)
  - *M* = 19 days from admission (range 12 to 27 days)
- Month 2 data (n=32)
  - *M* = 34 days from admission (range 29 to 44 days)

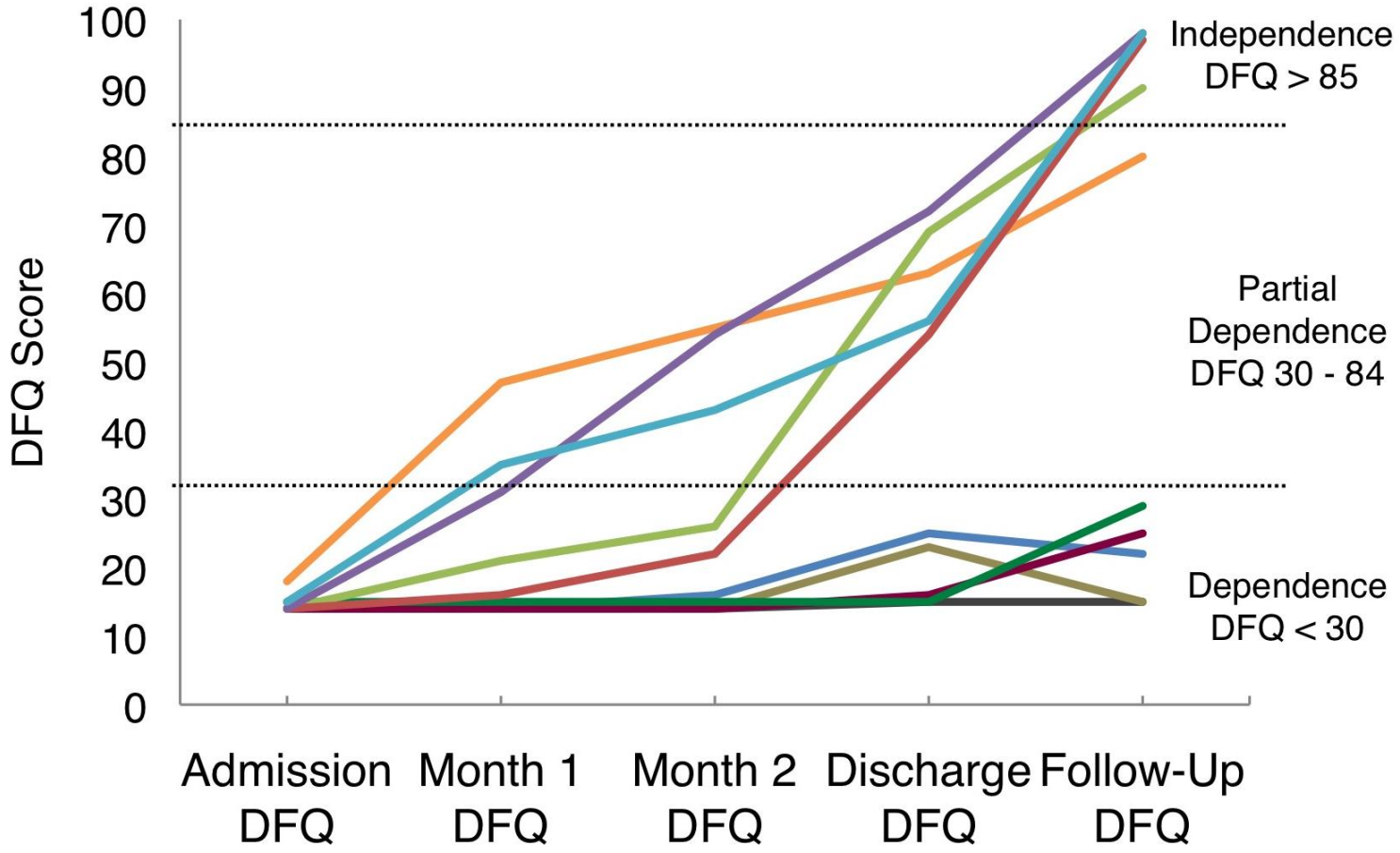


Kramer et al., Submitted

Change or No Change?



3-Month Follow-Up Data



Thank you. Questions?