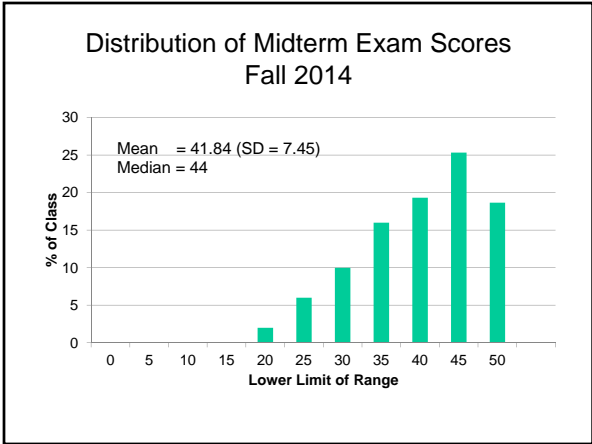


Coma and Anesthesia
Fall 2014

1

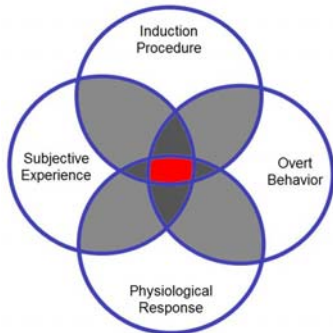
- Midterm Exam Feedback**
- Initial Scoring: $M = 32.26$ ($SD = 9.37$)
 - No “Bad” Items
 - Two Items “Iffy”: #s 9, 10
 - M Score > 1 SD Below Mean
 - Rescored Full Credit for All Students
 - Rescore: $M = 37.12$, $SD = 7.80$
 - Adjust Average Score: Add 5 Points
 - Final Score: $M = 41.84$, $SD = 7.45$
- 2



Defining Altered States of Consciousness by Converging Operations



Stoyva & Kamiya (1966)
after Garner, Hake, & Eriksen (1956); Campbell & Fiske (1959)



4

Clinical Disruptions of Consciousness

- Concussion
 - Temporary Disturbance of Consciousness
 - Results from Closed-Head Injury
- Coma
 - Chronic Loss of Consciousness
 - Failure to Arouse to Vigorous/Painful Stimuli
- Stupor
 - Chronic Loss of Consciousness
 - Responds to Vigorous/Painful Stimulation

5

“The Ding”

Yarnell & Lynch (1973)

- College Football Players (18 Games)
 - Mild Concussion vs. Broken Limbs
 - Memory Tests
 - Recall Examination on Field
 - Recall Impact, Play in Progress
- No Loss of Consciousness
 - Immediate Disorientation
 - Loss of Memory Within Minutes
 - Sometimes Lucid Interval Before Amnesia

6

Coma
Jennett & Plum (1972)

- Loss of Consciousness
 - No Communication
 - No Response to Stimulation
 - Auditory
 - Visual
 - Somatosensory Reflexes
 - No Signs of Emotion
- Vegetative Function OK
- Eyes Closed
 - But No Sleep Cycles

7

Glasgow Coma Scale
Teasdale & Jennett (1974)

<p><u>Best Eye Response</u></p> <p>1 - No eye opening 2 - Eye opening to pain 3 - Eye opening to verbal command 4 - Eyes open spontaneously</p>	<p><u>Best Verbal Response</u></p> <p>1 - No verbal response 2 - Incomprehensible sounds 3 - Inappropriate words 4 - Confused 5 - Oriented</p>
---	--

<u>Best Motor Response</u>	
1 - No motor response	2 - Extension to pain
3 - Flexion to pain	4 - Withdrawal from pain
5 - Localising Pain	6 - Obeys commands

Range of Scores: 3 - 15
 < 8, Severe 9-12, Moderate >12, Mild

8

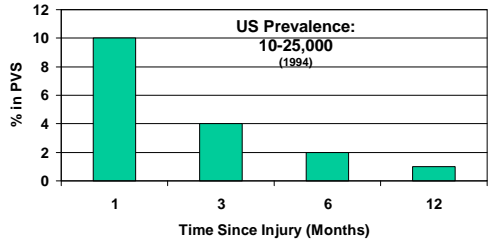
Vegetative State
Jennett & Plum (1972)

- Follows Coma (usually within 1 month)
- Wakefulness without Consciousness
 - No Communication
 - Partial Response to Stimulation
 - Auditory, Visual Startle
 - Sometimes Brief Orientation
 - Withdrawal to Noxious Somatosensory Stimulus
 - Few Signs of Emotion
 - Sometimes Reflexive Crying, Smiling
- Eyes Open
 - Sleep Cycles

9

Incidence of PVS in Severe Head Injury

Braakman et al. (1988)



10

Anatomy of Coma and Vegetative State

- **Coma:** Posterior Brain Stem

- Reticular Formation
 - Periaqueductal Gray
 - Parabrachial Nucleus

- **PVS:** Diencephalon

- Thalamus
- RF Intact
 - Continues to Generate the Sleep-Wake Cycle



11

Reticular Activating System Rediscovered?

Damasio, *The Feeling of What Happens* (1999)

- Moruzzi & Magoun (1949)

- Lesions, Stimulation in Cats
 - Anterior Lesions – Hypersomnia
 - Posterior Lesions - Insomnia
- “Desynchronized” EEG
 - Sign of Cortical Activation



- RAS Extends into Thalamus

12

A "Proto-Self"?

Damasio, *The Feeling of What Happens* (1999)



- Two Types of Self-Consciousness
 - Core Self
 - On-line Conscious Awareness
 - Distinguishes Self from Nonself
 - Autobiographical Self
 - Narrative Personal History
- Unconscious Proto-Self
 - Associated with RF
 - Monitors Physical Condition of the Organism
 - Anything More than Homeostatic Regulation?

13

Locked-In Syndrome

- Full Consciousness
 - Anarthria, Aphonia
 - Loss of Articulate Speech, Vocalization
 - Quadriplegia
 - Paralysis of Limbs
 - Preserved Auditory, Visual Function
 - Startle, Orienting
 - Localization, Fixation, Pursuit
 - Preserved Communication
 - Blinking, Vertical Eye Movements
 - Preserved Emotion

14

"Locked-In" Syndrome

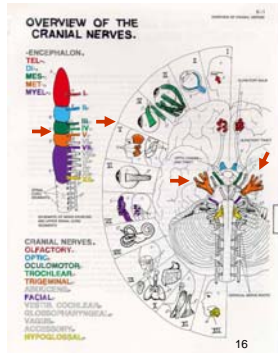
- Follows Coma
- Largely Immobile
- Limited Responsiveness
 - Vertical Eye Movements
 - Blinking
- Anterior Brain Stem
 - Pons
 - Excludes Reticular Formation



15

How Do You Get “Locked In”?

- Most Motor Pathways Pass Through Anterior Brainstem
- Damage At or Below Trigeminal Nerve (V)
- Spares
 - Afferent Nerves
 - Olfactory Nerve (I)
 - Optic Nerve (II)
 - Efferent Nerves
 - Oculomotor Nerve (III)
 - Trochlear Nerve (IV)



Management and Rehabilitation of the Persistent Vegetative State

- “Persistent” Can Become “Permanent”
 - Should the Qualifiers be Dropped?
- Recovery vs. “Post-Vegetative State”
 - Differentiated Response to Environment
 - Internal (Bowel, Bladder discomfort)
 - External (Pain)
- Physical Therapy
- Electrical Stimulation of Brainstem
- Cognitive Stimulation

17

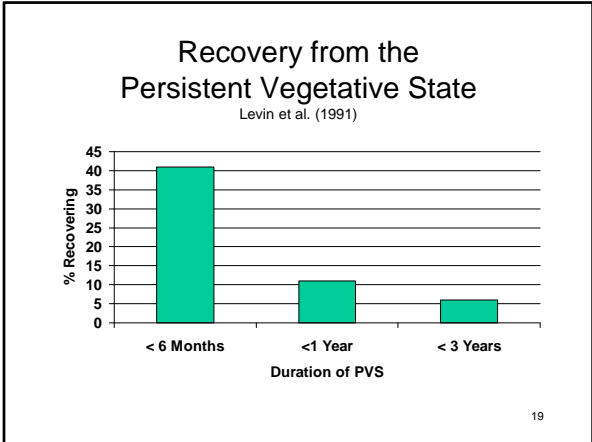
Recovery from Coma, PVS

West County Times, 04/07/03

- Tustin, Ca. Woman
- In “Coma” for 1 year
 - 1 Day After Giving Birth
 - 10 Minutes After Brain-Tumor Surgery
- Recovery after 1 Year
 - Turned Toward Mother, “Smiled”
 - Can Now Lift Arms, Hold Child
 - Cannot Walk, Talk, or Smile
 - Communicates by Rolling Eyes


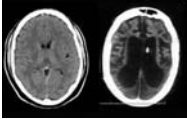


18



Terri Schiavo (1963-2005)

- 1990
 - Respiratory/Cardiac Arrest
- 1998
 - Husband Petition to Remove Tube
 - Parents Appealed
 - State, Federal Involvement
- 2002 CT Scan
- 2005 Autopsy

20

Minimally Conscious State

Giacino et a. (2002)

- Partial, Inconsistent Consciousness
 - Communication Inconsistent but Intelligible
 - Contingent Vocalization
 - Spontaneous Verbalization, Gesture
 - Partial Response to Stimulation
 - Auditory Localization
 - Inconsistent Command Following
 - Sustained Visual Fixation
 - Inconsistent Sustained Pursuit
 - Localizes Noxious Stimuli
 - Automatic Movements
 - Reaches for Objects, Accommodates to Shape
 - Contingent Smiling, Crying

21

Brain Activity in Minimally Conscious State

Schiff et al. (2005)

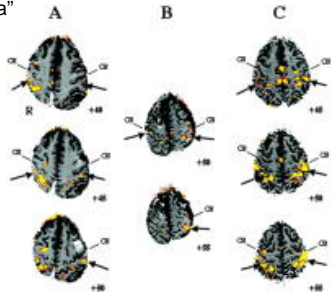
- 2 Patients in MCS
 - 1 with Damage to Left Temporal Lobe
- Passive Stimulation
 - Light Touch of Hands
 - Auditory Narratives of Familiar Events
 - Familiar Voice
 - Auditory Passages Without Semantic Content
 - Reversed Speech

22

Response to Somatosensory Stimulation

Schiff et al. (2005)

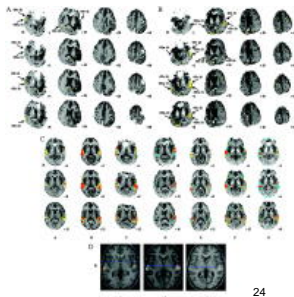
- Primary Somatosensory Area
 - “Anatomic Hand Area”



Response to Verbal Stimulation

Schiff et al. (2005)

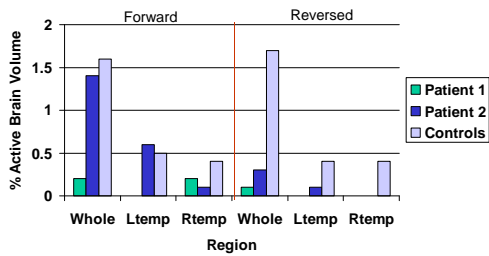
- Activation of Language Centers
 - Recognition of Speech
 - Discrimination of Nonspeech



- Speech vs. Nonspeech
 - Pt. 1, Damaged Wernicke's area
 - Pt. #2, "Reduced Engagement"

Brain Activity to Speech Stimulation

Schiff et al. (2005)

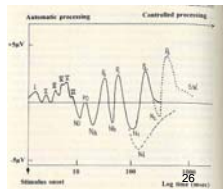


25

ERP Responses to Patients' Own Names

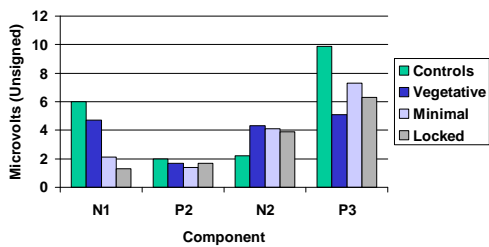
Perrin et al. (2006)

- "Cognitive" Event-Related Potentials
 - N1, P2, N2
 - P3: Orienting Response to Unexpected Stimulus
- Own First Name vs. Other First Name
- Patients
 - Persistent Vegetative State
 - Minimally Conscious State
 - Locked-In Syndrome
 - Age-Matched Controls

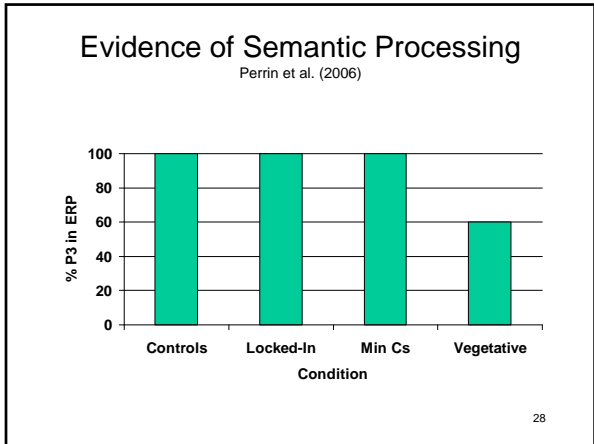


ERP Amplitudes

Perrin et al. (2006)



27



Conclusions and Implications

Perrin et al. (2006)

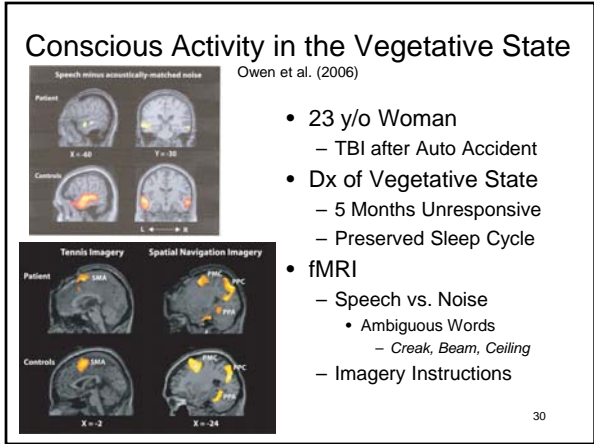
- Ambiguity of P3
 - Does Not Necessarily Entail Conscious Perception
 - Also Occurs in Subliminal Stimulation
 - “Automatic” component of Speech Comprehension?

What Counts as Evidence of Consciousness?

Coma

General Anesthesia

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Voluntary Brain Activity in the Persistent Vegetative State

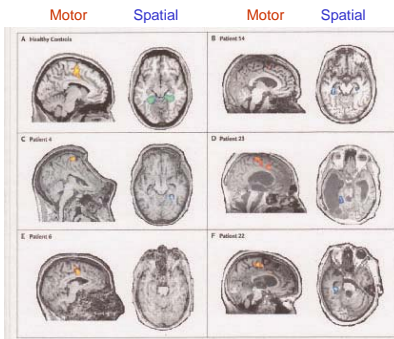
Monti et al. (2010)

- 54 Patients: PVS = 23; MCS = 31
 - 16 Healthy Controls
- Motor and Spatial Imagery Tasks
 - Hitting a Ball on a Tennis Court
 - Walking Familiar Street or House
- fMRI of Regions of Interest
 - Motor: Supplemental Motor Area
 - Spatial: Parahippocampal Gyrus

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fMRI Response to Imagery Tasks

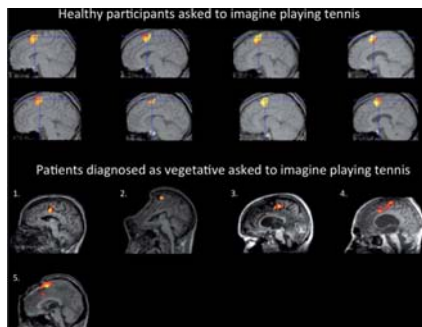
Monti et al. (2010)



32

Imagine Playing Tennis

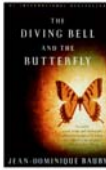
Owen (2013)



33

Useful for Communication?

- Asked Factual Yes-No Questions
 - “Do You Have Any Brothers?”
- Motor/Spatial for Yes/No
 - (Counterbalanced)
- Interrogator Blind to Correct Answers

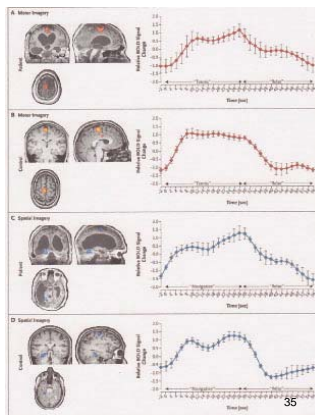


34

Time Course of Activation

Monti et al. (2010)

1 of 5 out of 54
Patients with PVS or MCS



Differential Response to Command

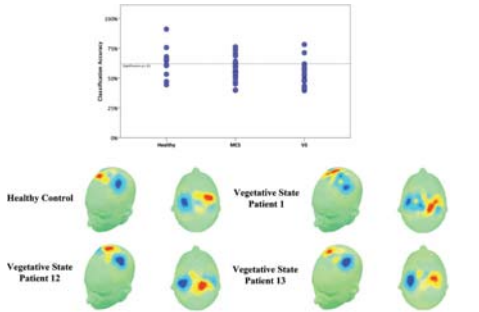
Cruse et al. (2011, 2012); Owen (2013)

- Patients in PVS, MCS
- Respond to Signal
 - Squeeze Right Hand
 - Wiggle Left Toe
- Classify EEG Activity in Premotor Cortex
 - 9/12 Normal Controls (75%)
 - 3/16 PVS (19%)
 - 5/23 MCS (22%)

36

Differential Response to Command

Cruse et al. (2011, 2012); Owen (2013)



37

Imagining for Communication

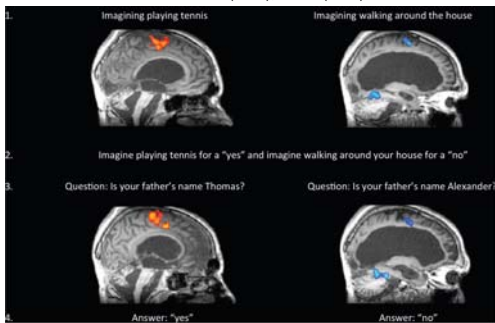
Monti et al. (2010); Owen (2013)

- Patient in PVS for 5 Years
- Imagination Tasks
 - Playing Tennis
 - Moving Around House
- 5 Yes/No Questions Answered Correctly

38

Imagining for Communication

Monti et al. (2010); Owen (2013)



39

Conclusions About PVS and MCS

- Some Evidence of Intentional Activity
 - Specific Response to Instructions
- But Only in Small Minority of Patients
- Doubt Clinical Criteria for MCS
 - PVS > MCS
- Use Technique for Diagnosis
- Use Technique for Communication
 - Medical Decisions
 - Confirm Advance Directives
 - Life Support, Limited Treatment

40

General Anesthesia as “Controlled Coma”

- Sedation
- Loss of Consciousness
 - Analgesia
 - Amnesia
- Immobility
 - Lack of Voluntary Motor Behavior
 - Anesthetic Agents
 - Reflexive Response
 - Muscle Relaxants

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Pain Relief in Pre-19th-Century Surgery

- Tolerate
- Alcohol
- Opiates (Laudanum)
- Bite Board
- Physical Restraint

42

Ether Day

First Demonstration of Ether as an Anesthetic Agent
William Morton, October 16, 1846



Surgeon:
J.C. Warren

Anesthetist:
W.T.G. Morton

Patient:
Gilbert Abbot

Massachusetts
General Hospital

43

Robert Hinckley (1893)

Sedation

Anxiety

Muscle Relaxation

Lack of Response

Balanced Anesthesia

Anesthesia

Awareness

Analgesia

Pain

44

Pre-Anesthetic Procedure

- Pre-Operative Visit
 - Exchange Information
 - Informed Consent
- Sedative Premedication
 - Benzodiazepine
 - Diazepam, Midazolam
 - Barbiturate
 - Thiopental
 - Propofol
- Relieve Preoperative Anxiety
- Facilitate Induction of Anesthesia

45

Inducing Anesthesia

- Rapid Sequence Induction
 - Short-Acting Barbiturate, Propofol
 - Intravenous
- Inhalation (Mask) Induction
 - Nitrous Oxide in Oxygen
- Muscle Relaxant

46

Maintaining Anesthesia

- Connection to Ventilator
 - Artificial Respiration
- Maintenance of General Anesthesia
 - Nitrous Oxide and Oxygen
 - Volatile Agent
 - Isoflurane
 - Intravenous Narcotics
 - Sufentanyl, Propofol

47

Reversing Anesthesia

- Reverse Muscle Relaxation
 - Anticholinesterase Agent
 - Neostigmine
- Restore Normal Breathing
- Intravenous Narcotic Analgesic
 - Morphine
 - Post-Operative Pain

48

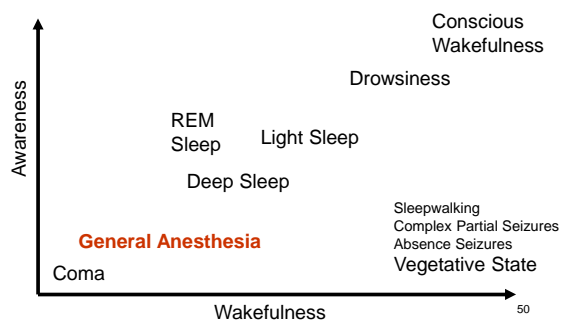
General Anesthesia as “Controlled Coma”

- Sedation
- Loss of Consciousness
 - Analgesia
 - Amnesia
- Immobility
 - Lack of Voluntary Motor Behavior
 - Anesthetic Agents
 - Reflexive Response
 - Muscle Relaxants

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Two Continua of Consciousness

After Laureys (2005)



50

Mechanisms of General Anesthesia

- Originally, Purely “Empirical” Treatment
- Informal Theories
 - Alter Membrane Dynamics
 - Inhibit Action Potentials
 - Interfere Axonal Transmission
 - Interfere with Synaptic Transmission
 - Neurotransmitter Release
 - Neurotransmitter Uptake

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Single-Process Theories of General Anesthesia

- Dissolve in Lipid Bilayers of Neurons
 - Fat cells
 - Form Plasma Membrane of Neuronal Cell
 - Expansion of Cell Membranes
 - Close Ion Channels
- Bind Directly to Proteins in Neuron
 - Stabilize Shape
 - Alters Suitability for “Lock and Key” Mechanism
 - Interferes with Synaptic Transmission
 - Mostly on Post-Synaptic Side

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Dual-Process Theory of General Anesthesia

- Inhibit Excitatory Neurotransmitters
 - N-methyl-D-aspartate (NMDA) receptors
- Potentiate Inhibitory Neurotransmitters
 - Gamma-Aminobutyric Acid (GABA) receptors

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Pharmacological Mechanisms

- Halogenated Ethers
 - Alters Lipid Membrane
 - Alters Action of Sodium Pump
 - “Depolarization”
- Narcotics
 - Interfere with Postsynaptic Uptake
 - “Lock and Key”

54

Clinical Assessment of Consciousness

- Lack of Response
 - Verbal Command
 - “Surgical Stimulation”
- No awareness of pain during procedure
- No memory of surgical events

55

Loss of Consciousness

- <<1% Report Surgical Awareness
 - 0.2% of General Surgical Cases
 - 0.4-1.8% of Malpractice Claims
 - Post-Traumatic Stress Disorder
- “Light Planes” of Anesthesia
 - Caesarian Section
 - Trauma Surgery
 - Cardiopulmonary Bypass Surgery
 - Neurosurgery

56

Minimum Alveolar Concentration Potency of Inhaled Anesthetic

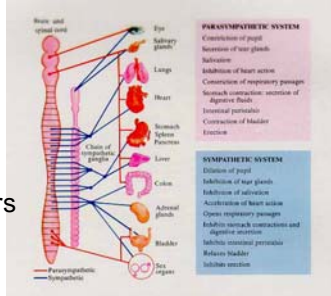
- MAC
 - Prevents Movement to Stimulation
 - In 50% of Subjects
- MAC-Aware
 - Eliminates Awareness of Stimulation
 - In 50% of Subjects
- Analogy to Sensory Thresholds
- Standard of Care = 1.3 MAC

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PRST Score

Autonomic Nervous System Index of Consciousness

- Blood *P*ressure
- Heart *R*ate
- Sweating
- Secretion of *T*ears



58

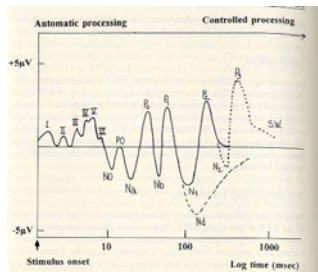
Central Nervous System Indices of Consciousness

- Event-Related (Evoked) Potential
- EEG Power Spectrum
- Bispectral Index

59

Event-Related (Evoked) Potential

- Stimulus
 - Auditory
 - Visual
 - Somatosensory
- Components
 - Early (Brainstem)
 - Middle (Subcortical)
 - Late (Cortical)
- Auditory "AEP Index"
 - Abolish late components
 - Delay Midlatency Components



60

EEG Power Spectrum

- EEG Bands
 - Delta (0.5-4 Hz)
 - Theta (5-7 Hz)
 - Alpha (8-12 Hz)
 - Beta (18-30 Hz)
 - Gamma (30-50 Hz)

Median $f < 2-3$ Hz
Spectral Edge $f < 8-12$ H

Wikipedia: Hugo Gambardella, Dec 7, 2005

Bispectral Analysis (BIS)

Aspect Medical Systems (Sigl et al., 1994; Kelly, 2007)

- BIS Algorithm
 - High-Frequency Activation (14-30 Hz)
 - Low-Frequency Synchronization
 - Periods of “Nearly Suppressed” EEG
 - Presence of “Flat Line” EEG
- Bispectral Index
 - Awake = 100
 - 50% reduction in recall = 86
 - 95% reduction in recall = 64
 - Anesthetized < 60

McSleepy, the Anesthesia Robot

Hemmerling et al. (2008)

- Automated Delivery of Anesthesia
- Consciousness
 - Bispectral Index
- Muscle Relaxation
 - EMG Variant
- Pain (Proxies)
 - Heart Rate
 - Blood Pressure
- Met DaVinci, the Surgical Robot, in 2010
 - Performed Trans-Atlantic Prostatectomy in Italy

Explicit vs. Implicit Memory Following General Anesthesia

Kihlstrom, Schacter, Cork, et al. (1990)

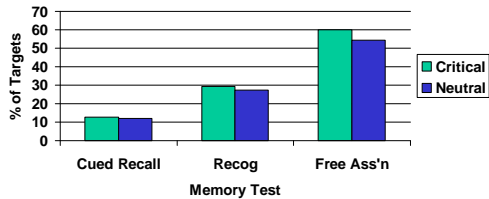
- Elective Surgery
- Isoflurane
 - No Nitrous Oxide
 - No Benzodiazepines
- Paired-Associates
 - *Ocean-Water, Butter-Knife*
 - *M* Time = 50 min, *M* Repetitions = 67
- Memory Tests
 - In Recovery Room; After 14 days

64

Explicit and Implicit Memory Following General Anesthesia

Kihlstrom, Schacter, Cork, et al. (1990)

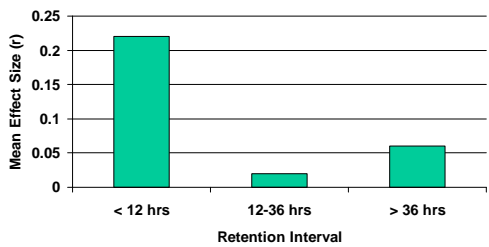
Immediate Test



65

Implicit Memory Following General Anesthesia

Merikle & Daneman (1996)



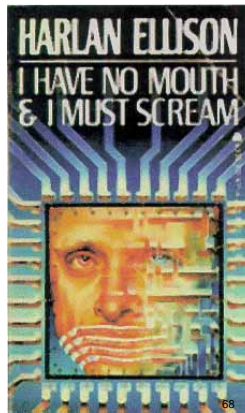
66

Nature of Explicit Memory Deficits in Surgical Anesthesia

- Loss of Consciousness
- Loss of Memory
 - Anterograde Amnesia?
 - Retrograde Amnesia
- Is the Patient Aware, and Then Forgets?

67

Is the Anesthetized Patient Aware During Surgery but Unable to Respond?



1967

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Isolated Forearm Technique

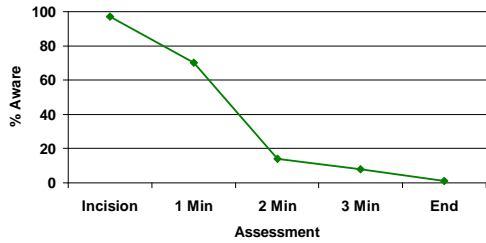
Tunstall (1977)

- Balanced Anesthesia
 - Induction
 - Muscle Relaxant
 - Maintenance
- Forearm Ischemia
 - Prevents Muscle Relaxant from Circulating to One Arm

69

Awareness During Caesarian Section

King et al. (1993)



70

24 New Studies, 1993-2006

Deeprase & Andrade (2006)



- Assessment of Awareness
 - Isolated Forearm Technique
 - Auditory Evoked Potentials
 - Processed EEG
 - Bispectral Index
 - Spectral Edge Frequency
 - Narcotrend
- 44 Tests of Implicit Memory
 - “Mixed” Evidence Favoring Perceptual Priming
 - No Evidence Favoring Semantic Priming

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Priming and Anesthesia

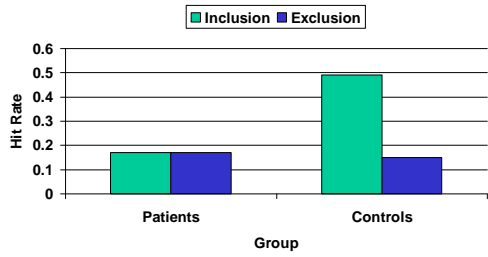
Iselin-Chaves et al. (2005, 2006)

- 48 Patients Receiving Isoflurane or Propofol
 - Unpremedicated
- 40 Words Presented 25 Consecutive Times
- Auditory Word-Stem Completion
 - Within 36 Hours of Surgery
 - Inclusion and Exclusion Instructions
- Anesthesia Monitored by BIS
 - Light = 61-80
 - Adequate = 41-60
 - Deep = 21-40

72

Performance in the Method of Opposition

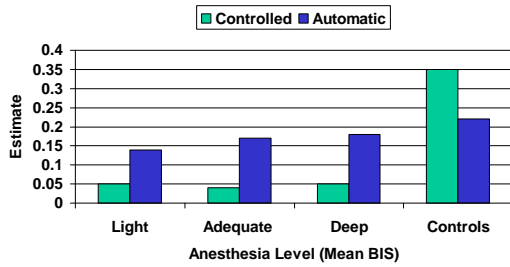
Iselin-Chaves et al. (2005, 2006)



73

Applying the Process-Dissociation Procedure

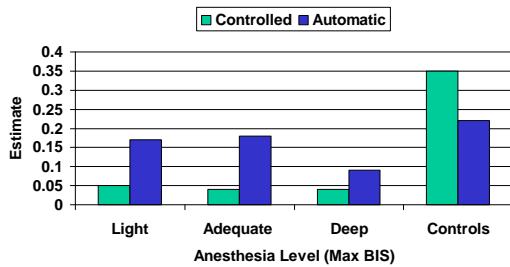
Iselin-Chaves et al. (2005, 2006)



74

Reanalysis for "Maximum" BIS

Iselin-Chaves et al. (2005, 2006)



75

Anesthetic Effects on Memory

- No Explicit Memory for Surgical Events
 - By Clinical Definition of Adequate Anesthesia
- Spared Implicit Memory
 - Perceptual vs. Semantic Priming
 - Not An Artifact of Surgical Awareness
 - Clinically Adequate Anesthesia
 - Confirmed by EEG Monitoring
 - Process-Dissociation Procedure
 - Automatic vs. Controlled Influences
- Implicit Memory as Implicit Perception
 - No Conscious Perception of Primes

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