# Coma and Anesthesia

Fall 2014

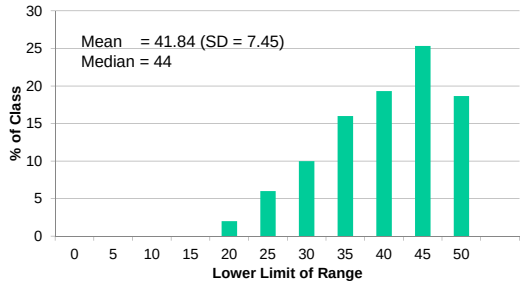
1

## 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

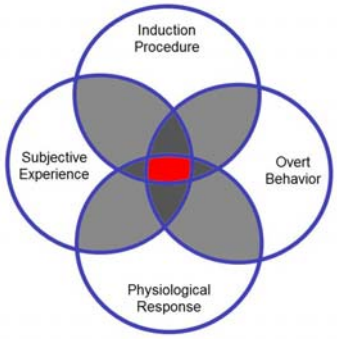
## Distribution of Midterm Exam Scores Fall 2014




## 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)

*Best Eye Response*

1 - No eye opening
2 - Eye opening to pain
3 - Eye opening to verbal command
4 - Eyes open spontaneously

*Best Verbal Response*

1 - No verbal response
2 - Incomprehensible sounds
3 - Inappropriate words
4 - Confused
5 - Oriented

*Best Motor Response*

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

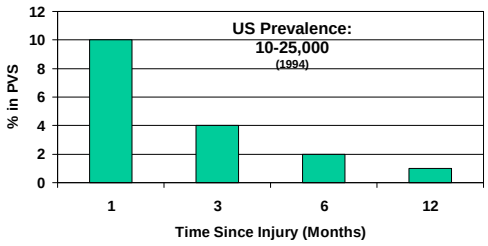
Jennett & Plum (1972)

- 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

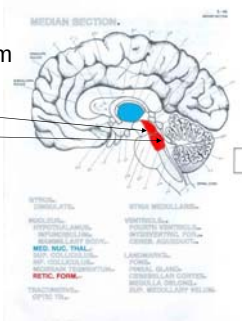
Braakman et al. (1988)




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

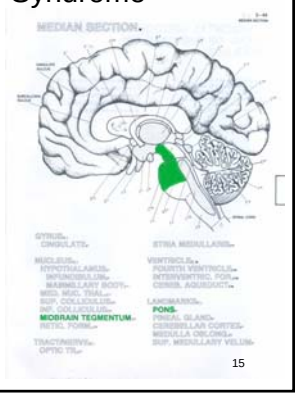
## Locked-In Syndrome

- 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

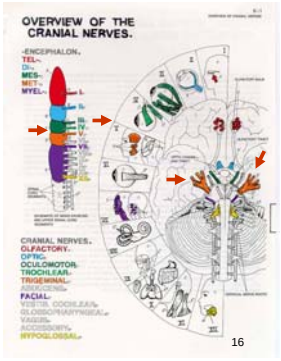
- Follows Coma
- Largely Immobile
- Limited Responsiveness
  - Vertical Eye Movements
  - Blinking
- Anterior Brain Stem
  - Pons
  - Excludes Reticular Formation




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)




16

## 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

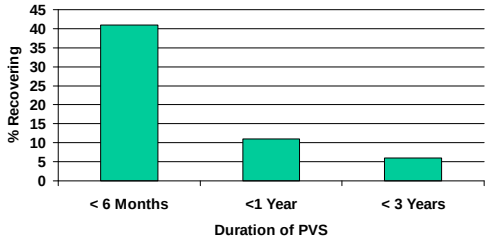
- Tustin, Ca. Woman
- In "Coma" for 1 year
  - 1 Day After Giving Birth
    - 10 Minutes After Brain-Tumor Surgery
- Recovery after 1 Year
  - Turned Toward Mother, "Smiled"
  - Can Now Lift Arms, Hold Child
    - Cannot Walk, Talk, or Smile
  - Communicates by Rolling Eyes


Teen mom rouses from year's coma

18

## Recovery from the Persistent Vegetative State

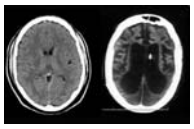
Levin et al. (1991)




19

## 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
      - Inconsisent 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)

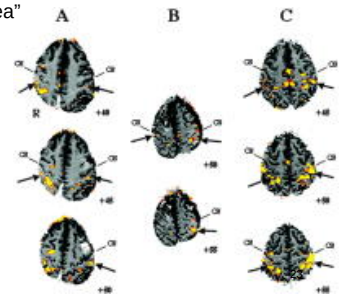
- 2 Patients in MCS
  - 1 with Damage to Left Temporal Lobe
- Passive Stimulation
  - Light Touch of Hands
  - Auditory Narratives of Familiar Events
    - Familiar Voice
  - Auditory Passages Without Semantic Content
    - Reversed Speech

22

## Response to Somatosensory Stimulation

Schiff et al. (2005)

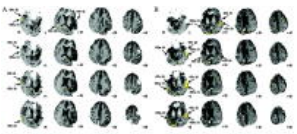
- Primary Somatosensory Area
  - "Anatomic Hand Area"



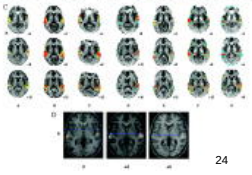

## Response to Verbal Stimulation

Schiff et al. (2005)

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



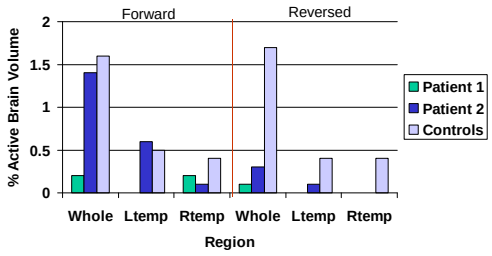
- Speech vs. Nonspeech
  - Pt. 1, Damaged Wernicke's area
  - Pt. #2, "Reduced Engagement"



24

## Brain Activity to Speech Stimulation

Schiff et al. (2005)

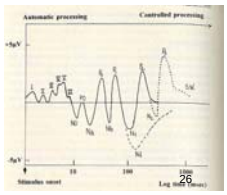



25

## ERP Responses to Patients' Own Names

Perrin et al. (2006)

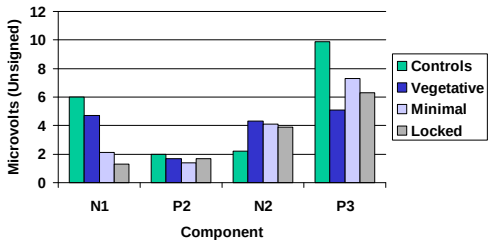
- "Cognitive" Event-Related Potentials
  - N1, P2, N2
  - P3: Orienting Response to Unexpected Stimulus
- Own First Name vs. Other First Name
- Patients
  - Persistent Vegetative State
  - Minimally Conscious State
  - Locked-In Syndrome
  - Age-Matched Controls



26

## ERP Amplitudes

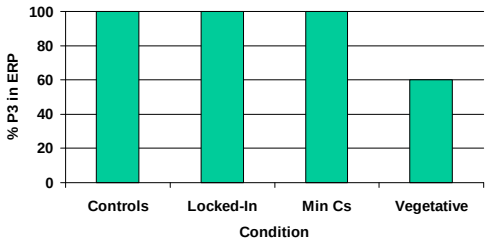
Perrin et al. (2006)




27

## Evidence of Semantic Processing

Perrin et al. (2006)




28

## 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?

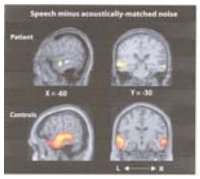
Coma

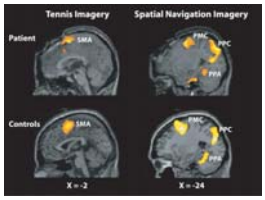
General Anesthesia

29

## Conscious Activity in the Vegetative State

Owen et al. (2006)






- 23 y/o Woman
  - TBI after Auto Accident
- Dx of Vegetative State
  - 5 Months Unresponsive
  - Preserved Sleep Cycle
- fMRI
  - Speech vs. Noise
    - Ambiguous Words
      - *Creak, Beam, Ceiling*
  - Imagery Instructions

30

## Voluntary Brain Activity in the Persistent Vegetative State

Monti et al. (2010)

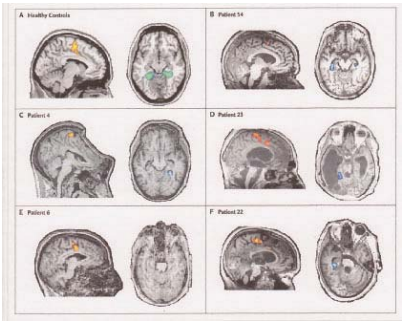
- 54 Patients: PVS = 23; MCS = 31
  - 16 Healthy Controls
- Motor and Spatial Imagery Tasks
  - Hitting a Ball on a Tennis Court
  - Walking Familiar Street or House
- fMRI of Regions of Interest
  - Motor: Supplemental Motor Area
  - Spatial: Parahippocampal Gyrus

31

## fMRI Response to Imagery Tasks

Monti et al. (2010)

Motor Spatial Motor Spatial

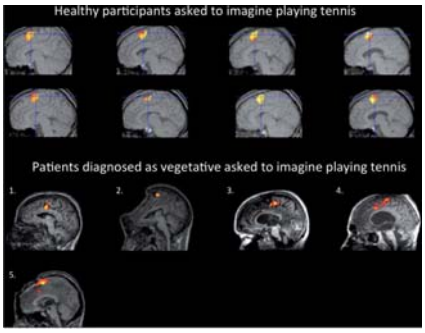


5/54 Patients:
4 PVS (17%)
1 MCS (3%)

32

## Imagine Playing Tennis

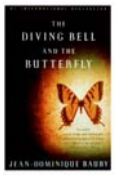
Owen (2013)




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

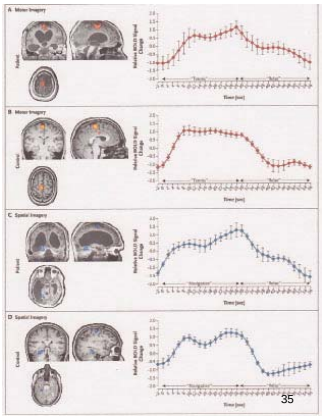



34

## Time Course of Activation

Monti et al. (2010)

1 of 5 out of 54
Patients with PVS or MCS



35

## Differential Response to Command

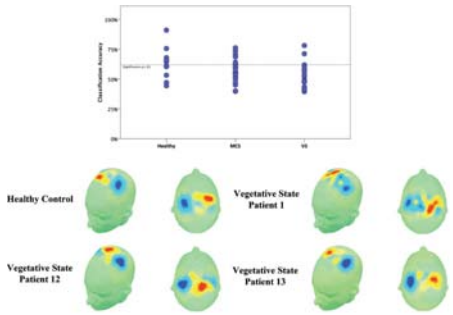
Cruse et al. (2011, 2012); Owen (2013)

- 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

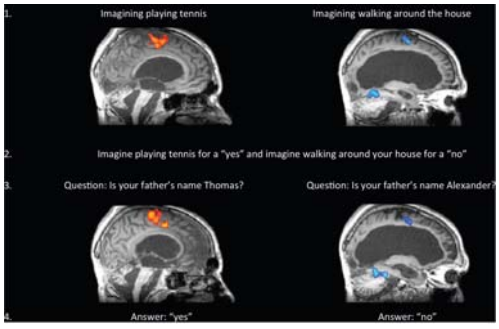
Monti et al. (2010); Owen (2013)

- 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

41

## 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

Robert Hinckley (1893)

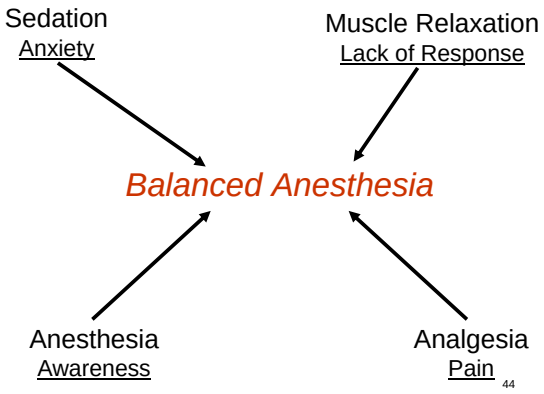
***Surgeon:***
**J.C. Warren**

***Anesthetist:***
**W.T.G. Morton**

***Patient:***
**Gilbert Abbot**

**Massachusetts General Hospital**

43




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

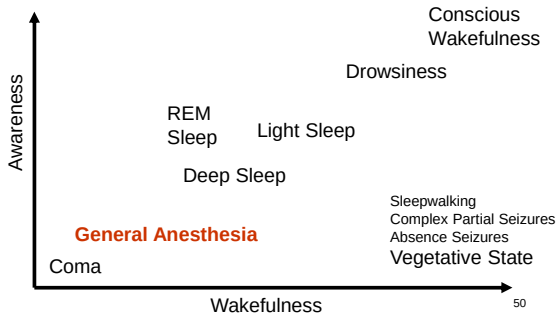
## General Anesthesia as "Controlled Coma"

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

49

## 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

51

## 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

52

## Dual-Process Theory of General Anesthesia

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

53

## 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

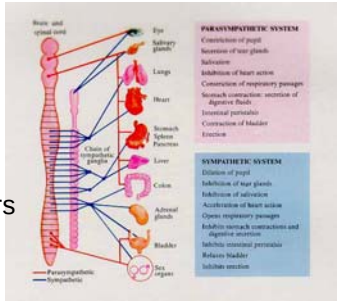
## Minimum Alveolar Concentration
Potency of Inhaled Anesthetic

- 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

57

## PRST Score
Autonomic Nervous System Index of Consciousness

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




58

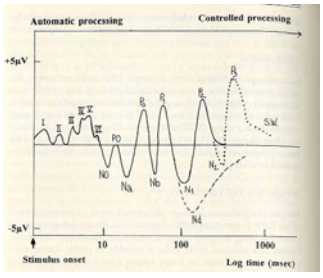
## Central Nervous System Indices of Consciousness

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

59

## Event-Related (Evoked) Potential

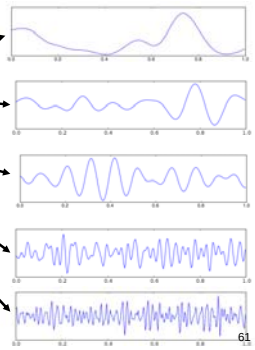
- Stimulus
  - Auditory
  - Visual
  - Somatosensory
- Components
  - Early (Brainstem)
  - Middle (Subcortical)
  - Late (Cortical
- Auditory "AEP Index"
  - Abolish late components
  - Delay Midlatency Components




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)



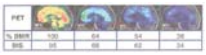
Median *f* < 2-3 Hz

Spectral Edge *f* < 8-12 H

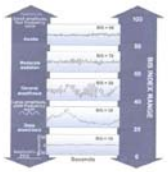
61

## 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



62

## 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

63

## Explicit vs. Implicit Memory Following General Anesthesia

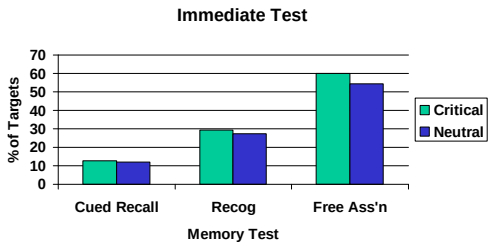
Kihlstrom, Schacter, Cork, et al. (1990)

- 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

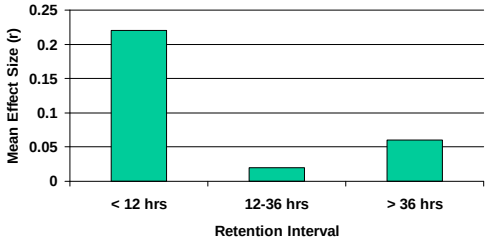
Kihlstrom, Schacter, Cork, et al. (1990)




65

## Implicit Memory Following General Anesthesia

Merikle & Daneman (1996)



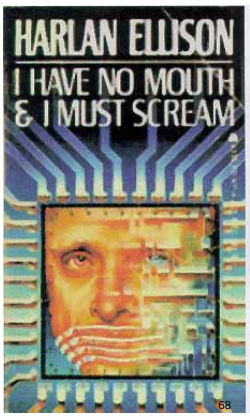

66

## 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

68

## Isolated Forearm Technique

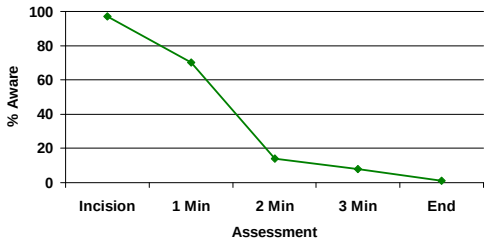
Tunstall (1977)

- 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

Deeprose & 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

71

## Priming and Anesthesia

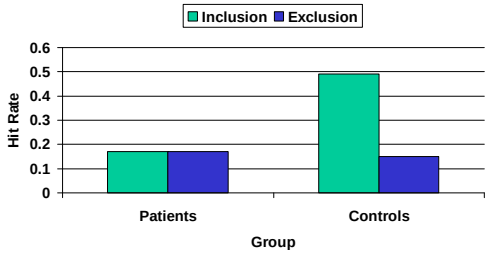
Iselin-Chaves et al. (2005, 2006)

- 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

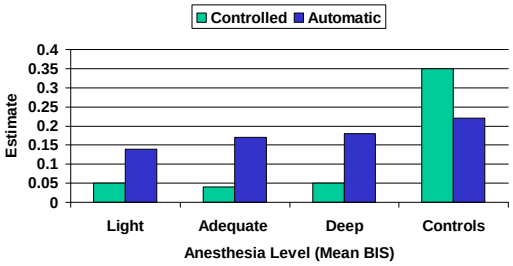
Iselin-Chaves et al. (2005, 2006)




73

## Applying the Process-Dissociation Procedure

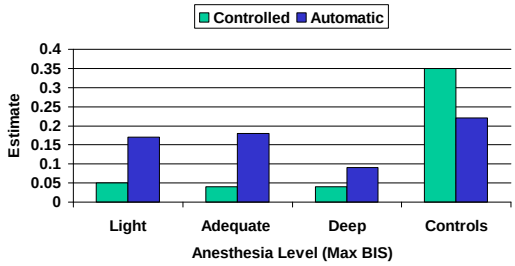
Iselin-Chaves et al. (2005, 2006)




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

76