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: $M = 41.84$, $SD = 7.45$

Distribution of Midterm Exam Scores
Fall 2014

- Mean: 41.84 ($SD = 7.45$)
- Median: 44
Defining Altered States of Consciousness by Converging Operations

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

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

“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
**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

**Glasgow Coma Scale**  
Teasdale & Jennett (1974)

<table>
<thead>
<tr>
<th>Best Eye Response</th>
<th>Best Verbal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - No eye opening</td>
<td>1 - No verbal response</td>
</tr>
<tr>
<td>2 - Eye opening to pain</td>
<td>2 - Incomprehensible sounds</td>
</tr>
<tr>
<td>3 - Eye opening to verbal command</td>
<td>3 - Inappropriate words</td>
</tr>
<tr>
<td>4 - Eyes open spontaneously</td>
<td>4 - Confused</td>
</tr>
</tbody>
</table>

**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

**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
Incidence of PVS in Severe Head Injury
Braakman et al. (1988)

<table>
<thead>
<tr>
<th>Time Since Injury (Months)</th>
<th>% in PVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

US Prevalence: 16,250,000 (1994)

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

Reticular Activating System Rediscovered?

- Moruzzi & Magoun (1949)
  - Lesions, Stimulation in Cats
    - Anterior Lesions – Hypersomnia
    - Posterior Lesions - Insomnia
  - "Desynchronized" EEG
    - Sign of Cortical Activation
- RAS Extends into Thalamus
A “Proto-Self”?

- 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?

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

“Locked-In” Syndrome

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

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
Recovery from the Persistent Vegetative State

Levin et al. (1991)

<table>
<thead>
<tr>
<th>Duration of PVS</th>
<th>% Recovering</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 Months</td>
<td>45</td>
</tr>
<tr>
<td>&lt; 1 Year</td>
<td>35</td>
</tr>
<tr>
<td>&lt; 3 Years</td>
<td>19</td>
</tr>
</tbody>
</table>

Terri Schiavo (1963-2005)

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

Minimally Conscious State

Giacino et al. (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
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

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)

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)
Evidence of Semantic Processing

Perrin et al. (2006)

% P3 in ERP

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

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
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

fMRI Response to Imagery Tasks
Monti et al. (2010)

Motor Spatial Motor Spatial

5/54 Patients:
4 PVS (17%)
1 MCS (3%)
Useful for Communication?

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

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%)
Differential Response to Command
Cruse et al. (2011, 2012); Owen (2013)

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

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
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

General Anesthesia as “Controlled Coma”

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

Pain Relief in Pre-19th-Century Surgery

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

Sedation
Muscle Relaxation

Anxiety
Lack of Response

Balanced Anesthesia

Anesthesia
Awareness

Analgesia
Pain

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
Inducing Anesthesia

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

Maintaining Anesthesia

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

Reversing Anesthesia

- Reverse Muscle Relaxation
  - Anticholinesterase Agent
    - Neostigmine
- Restore Normal Breathing
- Intravenous Narcotic Analgesic
  - Morphine
    - Post-Operative Pain
General Anesthesia as “Controlled Coma”

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

Two Continua of Consciousness

After Laureys (2005)

Awareness

Conscious Wakefulness

Drowsiness

REM Sleep

Light Sleep

Deep Sleep

General Anesthesia

Coma

Wakefulness

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
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

Dual-Process Theory of General Anesthesia

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

Pharmacological Mechanisms

- Halogenated Ethers
  - Alters Lipid Membrane
  - Alters Action of Sodium Pump
    - "Depolarization"
- Narcotics
  - Interfere with Postsynaptic Uptake
    - "Lock and Key"
Clinical Assessment of Consciousness

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

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

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
PRST Score
Autonomic Nervous System Index of Consciousness

- Blood Pressure
- Heart Rate
- Sweating
- Secretion of Tears

Central Nervous System Indices of Consciousness

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

Event-Related (Evoked) Potential

- Stimulus
  - Auditory
  - Visual
  - Somatosensory
- Components
  - Early (Brainstem)
  - Middle (Subcortical)
  - Late (Cortical)
- Auditory “AEP Index”
  - Abolish late components
  - Delay Midlatency Components
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 $f < 8-12$ Hz

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

Explicit and Implicit Memory
Following General Anesthesia
Kihlstrom, Schacter, Cork, et al. (1990)

Immediate Test

<table>
<thead>
<tr>
<th>Memory Test</th>
<th>% of Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cued Recall</td>
<td>0.1</td>
</tr>
<tr>
<td>Recog</td>
<td>0.3</td>
</tr>
<tr>
<td>Free Ass'n</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Critical vs. Neutral

Implicit Memory Following General Anesthesia
Merkle & Daneman (1996)

Mean Effect Size (r)

<table>
<thead>
<tr>
<th>Retention Interval</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 hrs</td>
<td>0.25</td>
</tr>
<tr>
<td>12-36 hrs</td>
<td>0.20</td>
</tr>
<tr>
<td>&gt; 36 hrs</td>
<td>0.15</td>
</tr>
</tbody>
</table>
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?

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

Isolated Forearm Technique
Tunstall (1977)

- Balanced Anesthesia
  - Induction
  - Muscle Relaxant
  - Maintenance
- Forearm Ischemia
  - Prevents Muscle Relaxant from Circulating to One Arm
Awareness During Caesarian Section
King et al. (1993)

![Graph showing the percentage of awareness during caesarian section assessment.](image)

### 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

### 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
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