Cognitive Function and Affective Behavior in Animal Models of Ischemia

Gretchen N. Neigh, Ph.D.
Emory University
Atlanta, GA
Disclosures

- Dr. Neigh receives grant funding from NARSAD, NIMH, AHA, GSK, and Emory University.

- The data presented in this presentation were funded by NIH, a Young Investigator Award from NARSAD, a Scientist Development Grant from the American Heart Association, and start up funds provided by Emory University.
Goal

- Provide basic knowledge on how you can use cognitive testing in rodent models with the ultimate goal of providing a tool to allow you to test the efficacy of compounds and therapeutics designed to improve functional outcome after ischemia and thereby improve quality of life for ischemia survivors.
Cognitive Testing in Rodents

- Importance of experimental design
  - clarification of hypothesis
  - attention to sensorimotor deficits

- Recognition of statistical power
  - environmental control vs. sample size

- Indirect assessment of cognition
  - can only assess “performance”
Three Types of Cognitive Tasks

- **Spatial Memory**
  - Morris Water Maze (MWM)
    - Morris, 1984
  - Example: outcome after global ischemia

- **Associative Learning and Memory**
  - Active and Passive Avoidance
  - Example: outcome after MCAO

- **Working Memory**
  - Object Recognition
    - Berlyne, 1950
  - Example: outcome after microembolism infarcts
Morris Water Maze
Morris Water Maze

Memories... of the way we used to swim

Memory-impaired  No impairment
Pros and Cons of MWM

**Pros**
- can test
  * acquisition
  * retention
  * reversal
- well established
- data collection automated

**Cons**
- stressful
- sensorimotor deficits interfere
- time intensive
- space intensive
CA/CPR and Water Maze

- Assessed retention of information learned prior to cardiac arrest
  - Probe trials

- Assessed ability to learn new information
  - Reversal training
Experimental Design

Days

-10  
Begin Training in Water Maze

-2  
Rest Period Begins

0  
Surgery

7  
Water Maze Retesting Begins
Cardiac Arrest Procedure

Mean Blood Pressure (mmHg)

Neigh et al., 2004
Damage Following CA/CPR

SHAM

Cardiac Arrest/CPR

Neigh et al., JCBF, 2004
Sensorimotor Assessment

- Initiation of locomotor activity
- Coordination
- Gross visual ability
- Locomotor activity
CA/CPR Does NOT Alter Retention

Neigh et al., EJN, 2004
CA/CPR Blocks Reversal Training

Neigh et al., EJN, 2004
Visual Platform Control

Sham CA/CPR

Distance (meters)

Sham CA/CPR

Rate (m/sec)

Neigh et al., EJN, 2004
Data Acquired from MWM

- CA/CPR does not alter memory retrieval.
- CA/CPR inhibits spatial memory formation.
- Performance deficits correlate with a reduction in dendritic spines in the CA1 region of the hippocampus.
Three Types of Cognitive Tasks

- **Spatial Memory**
  - Morris Water Maze (MWM)
    - Morris, 1984
  - Example: Outcome after global ischemia

- **Associative Learning and Memory**
  - Active and Passive Avoidance
  - Example: Effects of social manipulations on outcome after MCAO

- **Working Memory**
  - Object Recognition
    - Berlyne, 1950
  - Example: Outcome after microembolism infarcts
Avoidance

Passive - Short latency to cross into “shock chamber” suggests a deficit

Active – Long latency to leave “shock chamber” suggests deficit
## Pros and Cons of Avoidance

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- can test</td>
<td></td>
</tr>
<tr>
<td>* retention</td>
<td></td>
</tr>
<tr>
<td>* acquisition and retention</td>
<td></td>
</tr>
<tr>
<td>- can test</td>
<td></td>
</tr>
<tr>
<td>* active and passive</td>
<td></td>
</tr>
<tr>
<td>- relatively little training</td>
<td></td>
</tr>
<tr>
<td>- well established</td>
<td></td>
</tr>
<tr>
<td>- data collection automated</td>
<td></td>
</tr>
<tr>
<td>- stressful</td>
<td></td>
</tr>
<tr>
<td>- sensorimotor deficits interfere</td>
<td></td>
</tr>
<tr>
<td>- purchase of chamber(s)</td>
<td></td>
</tr>
</tbody>
</table>
MCAO and Avoidance

- Determine effects of stress on retention of passive avoidance after stroke.

- Determine the effects of social interaction on acquisition and retention of active avoidance after stroke.
## Experimental Design

<table>
<thead>
<tr>
<th>Days 1-7</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Days 9-14</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 min exposure to social stress</td>
<td>Train in PA</td>
<td>MCAO/SHAM</td>
<td>Reperfusion and recovery undisturbed in home cage</td>
<td>PA retest &amp; histology</td>
</tr>
</tbody>
</table>

*Slide courtesy of A.C. DeVries*
Transient MCAO

At 60 min duration, infarct encompasses 10-15% of hemisphere

Results in very minor sensorimotor deficits

Slide courtesy of A.C. DeVries
Stress Impairs Retention of Passive Avoidance Post-Stroke

Slide courtesy of A.C. DeVries
Sugo et al., Stroke, 2002
Data Acquired from Avoidance

- Stress impairs post-MCAO retention of avoidance learning.

- The neurobiological underpinnings have been examined and are reported:
  - Hattori et al., Stroke 2000
  - Sugo et al., Stroke 2002
Three Types of Cognitive Tasks

- **Spatial Memory**
  - Morris Water Maze (MWM)
    - Morris, 1984
  - Example: outcome after global ischemia

- **Associative Learning and Memory**
  - Active and Passive Avoidance
  - Example: outcome after MCAO

- **Working Memory**
  - Object Recognition – Novel Object Preference (NOP)
    - Berlyne, 1950
  - Example: outcome after microembolism infarcts
Novel Object Preference

Training

Habituate to Chamber (15 min/day X 3 days)
Objects for 15 min

Probe Trial

Identical (but not same) object
One new but similar object
Objects for 2-5 min
# Pros and Cons of NOP

<table>
<thead>
<tr>
<th><strong>Pros</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- can test on repeated trials</td>
<td>- very susceptible to environmental confounds</td>
</tr>
<tr>
<td>- can pre and post-test</td>
<td>- inter-lab variability</td>
</tr>
<tr>
<td>- no delay trial can assess</td>
<td>- limited information provided</td>
</tr>
<tr>
<td>sensorimotor</td>
<td>- more room for operator error</td>
</tr>
<tr>
<td>- can calculate outcome with</td>
<td>- types of objects</td>
</tr>
<tr>
<td>sensorimotor deficit in mind</td>
<td>- influence of investigator</td>
</tr>
<tr>
<td>- well established</td>
<td>- apparatus errors</td>
</tr>
<tr>
<td>- inexpensive</td>
<td></td>
</tr>
</tbody>
</table>
Hints to Avoid Confounds

- Think about environment from rodent perspective
  - Nocturnal
  - Large olfactory bulbs
  - Natural predators (or signs of predation; blood)

- Be conscious of the surrounding environment
  - Weekday versus weekend differences in surroundings
  - Construction on or near your building
  - Break room in relationship to testing room

- Be aware of personnel differences
  - Personal product differences (cigarettes, lotions, perfumes)
  - “sensing fear”
  - Pets at home
  - Cell phones
Hints to Avoid Confounds

- Control the immediate environment
  - Housing effects (social as well as mechanical)
  - Light, humidity, temperature
  - Cage changes

- Consistency
  - Test control and experimental animals in same session
  - Always run tests in same order for all groups or counterbalance
  - Know the expected baselines for your strain in your lab

- Be aware of other body systems
  - Estrous can change performance in cognitive and affective tests
  - Corticosterone can change performance
  - Immune activity can change performance
Acknowledgements

Emory University
Emily Hardy
Mallory Shurte
Christina Nemeth
Joseph Manns, Ph.D.
Kerry Ressler, M.D., Ph.D.

Ohio State University
Courtney DeVries, Ph.D.
Randy J. Nelson, Ph.D.
Valerie Bergdall, DVM
Erica Glasper, Ph.D.
Ning Zhang, M.D.

Other Collaborators
Julia Kofler, M.D.
Richard Traystman, Ph.D.
Resources for Further Reading


Crawley, J.N. *What’s Wrong With My Mouse?* Wiley and Sons, 2007

Whishaw, I.Q. and Kolb, B. *The Behavior of the Laboratory Rat.* Oxford University Press, 2005