Animal model of postoperative delirium

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Why do we need the animal model to study human diseases

- Clinical studies may take a long time to conduct and analyze.

- With confounding factors and other limitations.

- Therefore, there is a need to perform animal studies.

- Animal: similar physiological and anatomical level; have same organs and organ system.

Why do we need the animal model to study postoperative delirium

- Mechanistic hypothesis testing:
  - Interaction of Aβ/Tau and neuroinflammation.

- Vulnerable window assessment:
  - Age dependent?

- Are there less provocative anesthetic:
  - Isoflurane versus desflurane.

- Potential treatment and prevention:
  - Anti-Aβ, anti-Tau and anti-inflammation.
Animal models to study postoperative delirium

T-maze alternation: working memory
Dr. Colm Cunningham

- It assesses working memory in rodents.
- Mice will escape from shallow water to an exit by memory.
- “The nature of these deficits are acute and transient, with impairments in attention, recall, and short-term/working memory”.
- It needs training.
- It is a single test.

(Murray et al., Neurobiology of Aging, 2012)
Animal studies of delirium

- These tests only include single and learned behavior.

- We may need to observe multiple animal natural and learned behaviors.

(Ren et al., 2015)
“Confusion Assessment Method (CAM) in human”

Multiple tests

- Acute onset and fluctuating course.
- Inattention.
- Disorganized thinking.
- Altered level of consciousness.

“Confusion Assessment Method (CAM) in mice”

Multiple tests

- Acute onset and fluctuating course: 
  - Timecourse studies.
- Inattention:
  - Buried food test
- Disorganized thinking:
  - Open field test, Y maze test, buried food test.
- Altered level of consciousness:
  - Open field test, Y maze and buried food test.
Battery of behavior tests in mice to study postoperative delirium

- **Buried food test** *(Natural behavior)*
- **Open field test** *(Natural behavior)*
- **Y-maze test** *(Learned behavior)*

*(Peng et al., 2016)*

### Methods

- **C57BL/6J mice** *(4 months old)*
- **Control or Anesthesia/Surgery**
- **Behavior test at -24Hr, 6Hr, 9Hr and 24Hr**

Behavior test:  
- Buried food test  
- Open field test  
- Y-maze test  

*(Peng et al., 2016)*
Natural behavior observation

- Attention level.
- Freezing episodes.
- Open field tests.
- Timecourse investigation.

Freezing episodes

- Definition: No movement except respiration.
- Detected and analyzed by Any-Maze (Stoelting, Wood Dale, IL).
Open field test

- Definition: The time spent in the zone near the wall during the open field test.

- Detected and analyzed by Any-Maze (Stoelting, Wood Dale, IL).

<table>
<thead>
<tr>
<th>Table 1. Effects of the Anesthesia/Surgery on behavior in mice</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Buried food test</td>
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<tr>
<td>Latency to eat food</td>
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<tr>
<td>Open field test</td>
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<tr>
<td>Total distance</td>
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<td>Time spent in the center</td>
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<tr>
<td>Freezing time</td>
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<tr>
<td>Latency to the center</td>
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<td>Y maze test</td>
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<tr>
<td>Number of arm visits</td>
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<td>Entries in novel arm</td>
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<td>Duration in novel arm</td>
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(Peng et al., 2016)
Composite Z-score indicates the severity of the behavior impairment.

The larger values of the composite Z score suggest severer impairment of the behavior of the mice.

(Peng et al., 2016)

**Potential mechanisms of postoperative delirium**
- Apoptosis.
- Aβ accumulation.
- Tau phosphorylation.
- Neuroinflammation.
- Mitochondrial dysfunction.
- NMDA receptor dysfunction.

*(Vutskits and Xie, Nature Review Neuroscience, 2016)*

- Energy deficits:

![Energy deficits chart](chart.png)

*(Peng et al., 2016)*
> Energy deficits:

(Peng et al., 2016)

> Blood brain barrier dysfunction:

(Yang et al., submitted)
**Blood brain barrier dysfunction:**

- (Yang et al., submitted)

**Olfactory dysfunction:**

- (Zhang et al., in preparation)
Summary and conclusion

- The battery of behavioral tests ("CAM in mice") to assess both natural and learned behaviors as a model to study postoperative delirium in rodents.

- Energy deficits, blood brain barrier dysfunction and olfactory dysfunction could be the new mechanisms of postoperative delirium.

- The establishment of animal model of postoperative delirium would lead to new mechanistic studies and guide clinical intervention (targeted) investigation.

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