Animal model of postoperative delirium

Zhongcong Xie, M.D., Ph.D.
Henry K. Beecher Professor of Anesthesia
Geriatric Anesthesia Research Unit
Department of Anesthesia, Critical Care
and Pain Medicine
Massachusetts General Hospital
Harvard Medical School
November 7, 2016 (Boston)

Disclosures

Supported by grants from NIH, Alzheimer's Association, Cure Alzheimer's Fund and Henry Beecher Endowed Professorship.

The studies reported in the presentation have no connections with any pharmaceutical companies.

Dr. Xie is a consultant of Hengrui Pharmaceutical Co. Ltd and an invited speaker of Baxter Pharmaceutical Co. Ltd.

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.**

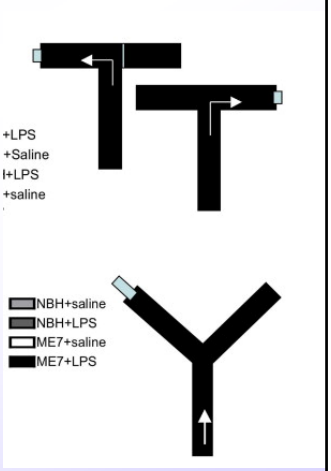
Why do we need the animal model to study postoperative delirium

- **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.**

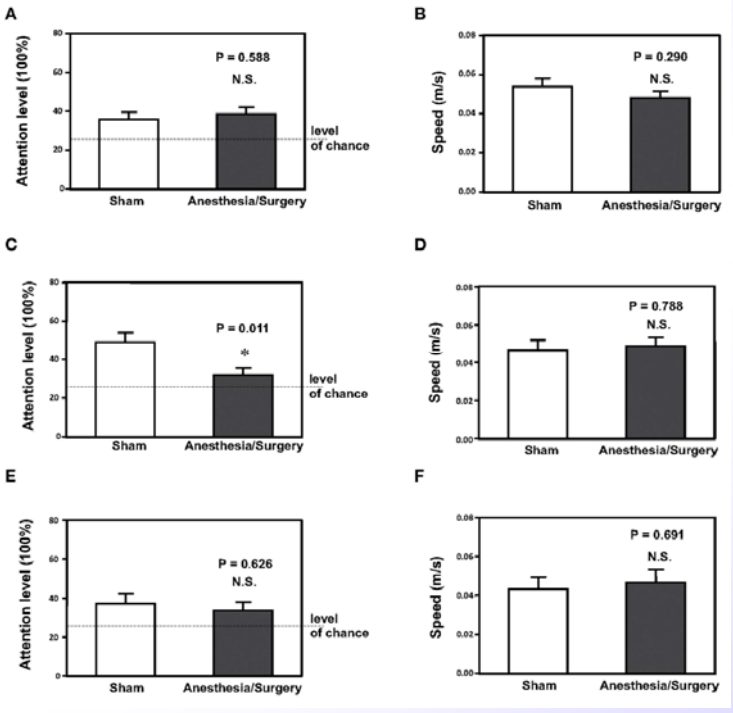
Animal models to study postoperative delirium

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)



(Ren et al., 2015)

Animal studies of delirium

- These tests only include **single** and **learned** behavior.
- We may need to observe **multiple** animal **natural** and **learned** behaviors.

"Confusion Assessment Method (CAM) in human"

Multiple tests

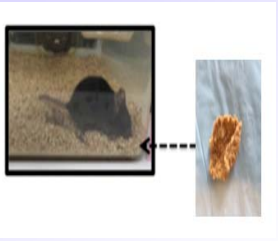
- Acute onset and fluctuating course.
- Inattention.
- Disorganized thinking.
- Altered level of consciousness.

"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

- 24Hr (Baseline) 0Hr 6Hr 9Hr 24Hr

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 1. Effects of the Anesthesia/Surgery on behavior in mice

	6Hr	9Hr	24Hr
Buried food test			
Latency to eat food	-	↑	-
Open field test			
Total distance	-	-	-
Time spent in the center	↓	-	-
Freezing time	↓	-	-
Latency to the center	-	-	-
Y maze test			
Number of arm visits	-	-	-
Entries in novel arm	↓	↓	-
Duration in novel arm	↓	-	-

(Peng et al., 2016)

Table 2. Summary of composite Z scores in Control and Anesthesia/Surgery mice

Mice	6Hr	9Hr	24Hr
Control1	0.328	-0.301	-0.154
Control2	1.287	2.842	2.176
Control3	0.586	0.045	0.444
Control4	-0.966	-0.757	-0.883
Control5	-1.758	0.219	0.318
Control6	0.346	-0.519	-0.009
Control7	-0.791	0.133	-0.918
Control8	1.396	-0.739	-1.350
Control9	0.764	-1.295	0.045
Control10	-1.031	0.421	0.587
Control11	-1.019	-0.401	1.500
Control12	1.015	-0.313	0.146
Control13	-0.553	1.056	-0.770
Control14	0.395	-0.388	-1.134
Control Mean	**0.000**	**0.000**	**0.000**
Control SEM	**0.267**	**0.267**	**0.267**
Anesthesia/Surgery1	0.715	0.389	-0.900
Anesthesia/Surgery2	1.588	1.779	0.507
Anesthesia/Surgery3	0.672	1.852	2.021
Anesthesia/Surgery4	1.451	0.905	-3.114
Anesthesia/Surgery5	0.748	1.188	-1.403
Anesthesia/Surgery6	1.535	0.330	-0.128
Anesthesia/Surgery7	2.696	0.747	0.843
Anesthesia/Surgery8	-0.401	1.209	0.479
Anesthesia/Surgery9	1.353	2.560	1.637
Anesthesia/Surgery10	2.451	3.006	0.898
Anesthesia/Surgery11	-0.815	0.356	0.143
Anesthesia/Surgery12	0.119	0.576	-1.507
Anesthesia/Surgery13	1.425	2.913	-0.078
Anesthesia/Surgery14	0.014	3.741	-0.151
Anesthesia/Surgery Mean	**0.968**	**1.539**	**-0.054**
Anesthesia/Surgery SEM	**0.271**	**0.301**	**0.360**
P Value	0.017*	0.0007***	0.906

*P< 0.05; ***P<0.001

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.

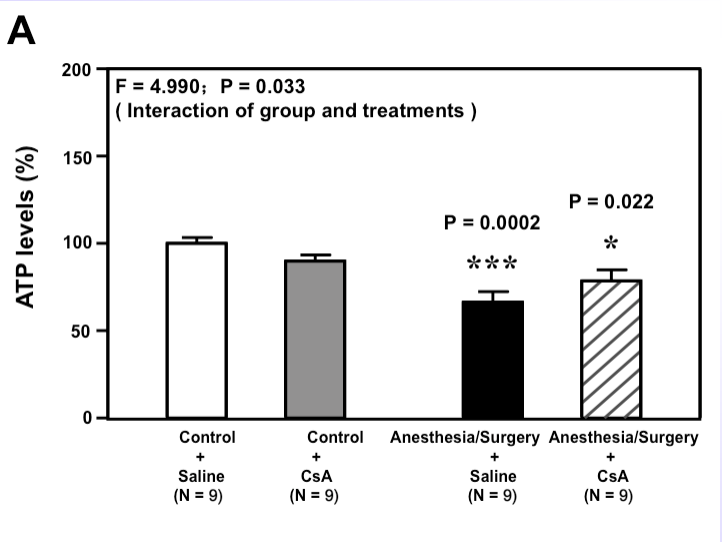
(Peng et al., 2016)

Potential mechanisms of postoperative delirium

- **Apoptosis.**
- **Aβ accumulation.**
- **Tau phosphorylation.**
- **Neuroinflammation.**
- **Mitochondrial dysfunction.**
- **NMDA receptor dysfunction.**

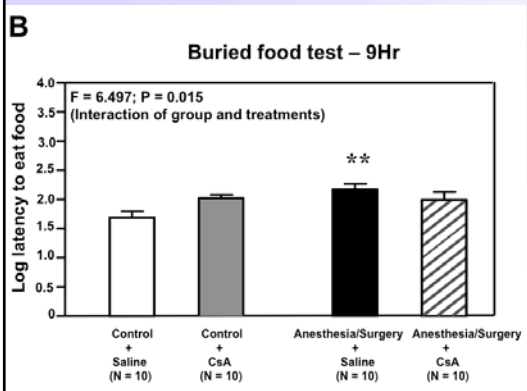
(Vutskits and Xie, Nature Review Neuroscience, 2016)

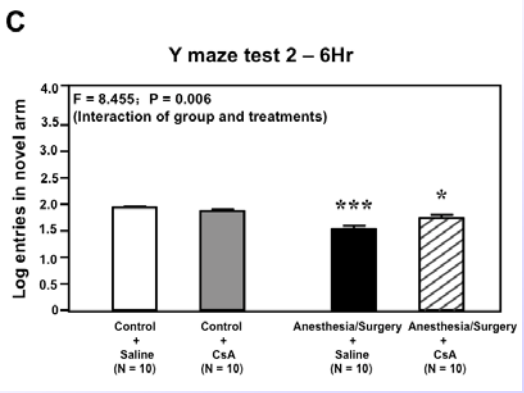
- **Energy deficits:**



(Peng et al., 2016)

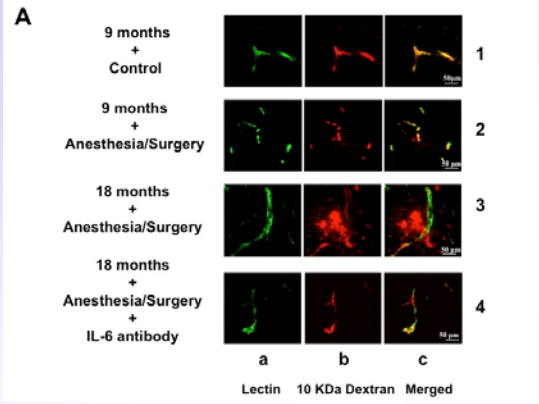
➢ Energy deficits:

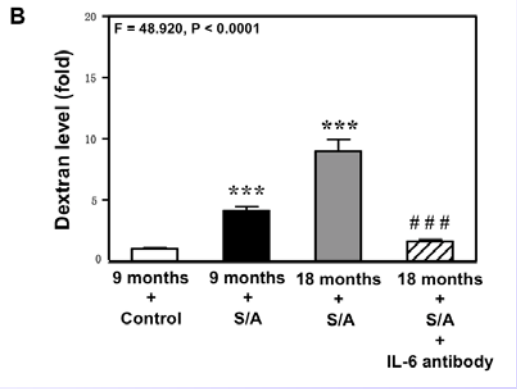




(Peng et al., 2016)

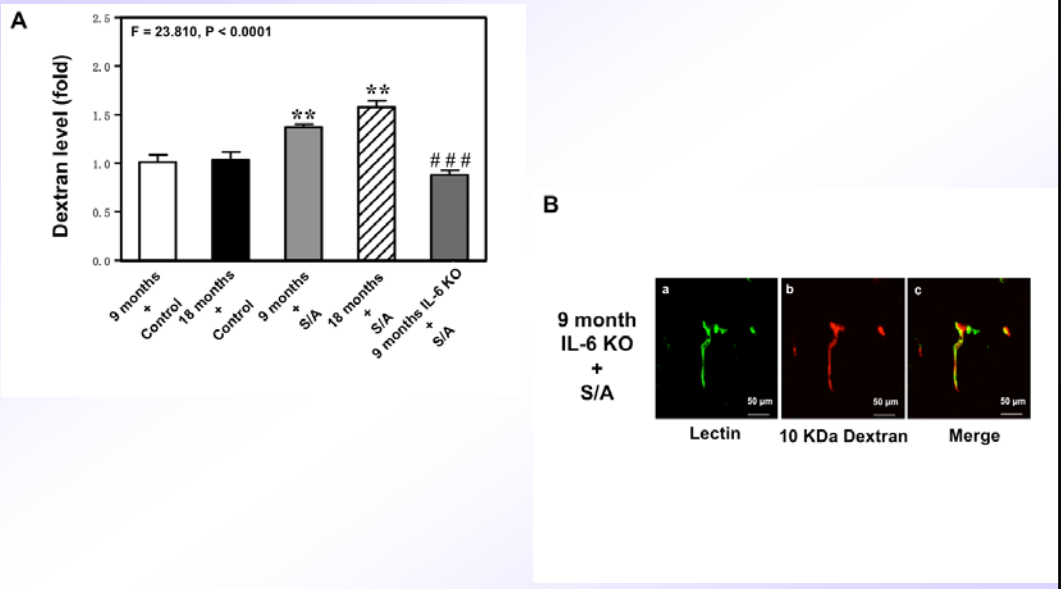
➢ Blood brain barrier dysfunction:





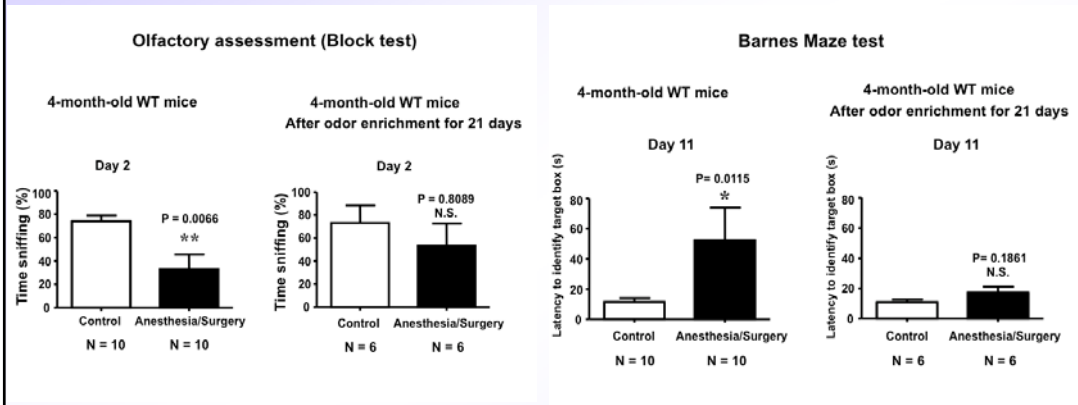
(Yang et al., submitted)

➢ 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.

Acknowledgements

Xie lab:

Yuanlin Dong
Yiying (Laura) Zhang
Mian Peng
Feng Liang
Shimin Yang
Yang Yu
Huihui Miao
Han Lu
Ce Zhang
Kali Stevens
Diana Shapoval
Liqi Su

Collaborators:

Harvard-
Gregory Crosby
Deborah Culley
Qimin Quan
Rudolph Tanzi

Capital Medical University, Beijing-
Tianzuo Li
Anshi Wu
Ming Tian
Chuxiong Pan

Tongji University, Shanghai-
Jialin Zheng
Yuan Shen

Central South University
Yangwen Ou

Supports:

NIH R01 GM088801

NIH R01 AG041274

NIH R21 AG038994

NIH R01 HD086977

Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital

Henry K. Beecher Endowed Professorship from Harvard University