

Delirium, Apo-E status, and AD CSF biomarkers

Zhongcong Xie, M.D., Ph.D.

**Geriatric Anesthesia Research Unit
Department of Anesthesia, Critical Care
and Pain Medicine**

Massachusetts General Hospital

Harvard Medical School

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Postoperative Complications in Geriatric Patients

Complication	Incidence
Pulmonary Embolism	0.5%
ARDS	0.8%
Stroke	1%
Myocardial infarction	2%
Pneumonia	4%
Death	5%
Heart Failure	6%
Delirium	15%
POCD	10 - 15%

Liu LL, et al., JAGS 48:405, 2000

Moller JT, et al. Lancet 351: 857, 1998

Monk TG, et al., Anesthesiology 108: 18, 2008

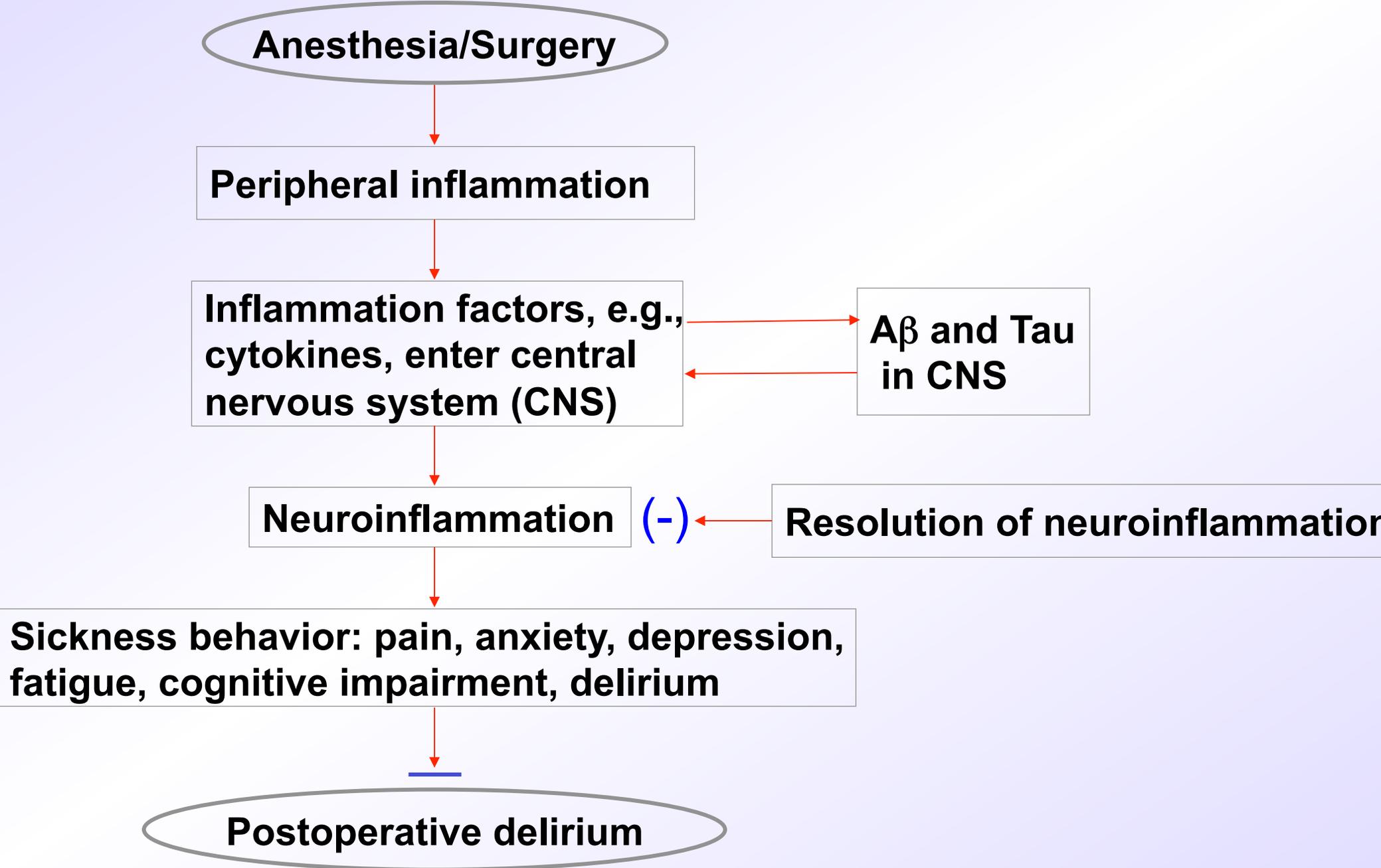
Postoperative delirium

- Postoperative delirium has been suggested to relate to neuroinflammation ([Wilson et al., 2002](#); [Ramlawi et al., 2006](#) [Rudolph et al., 2008](#)).
- Specifically, patients may develop "Sickness behavior", including fever, depression, cognitive dysfunction and delirium, after the surgery.

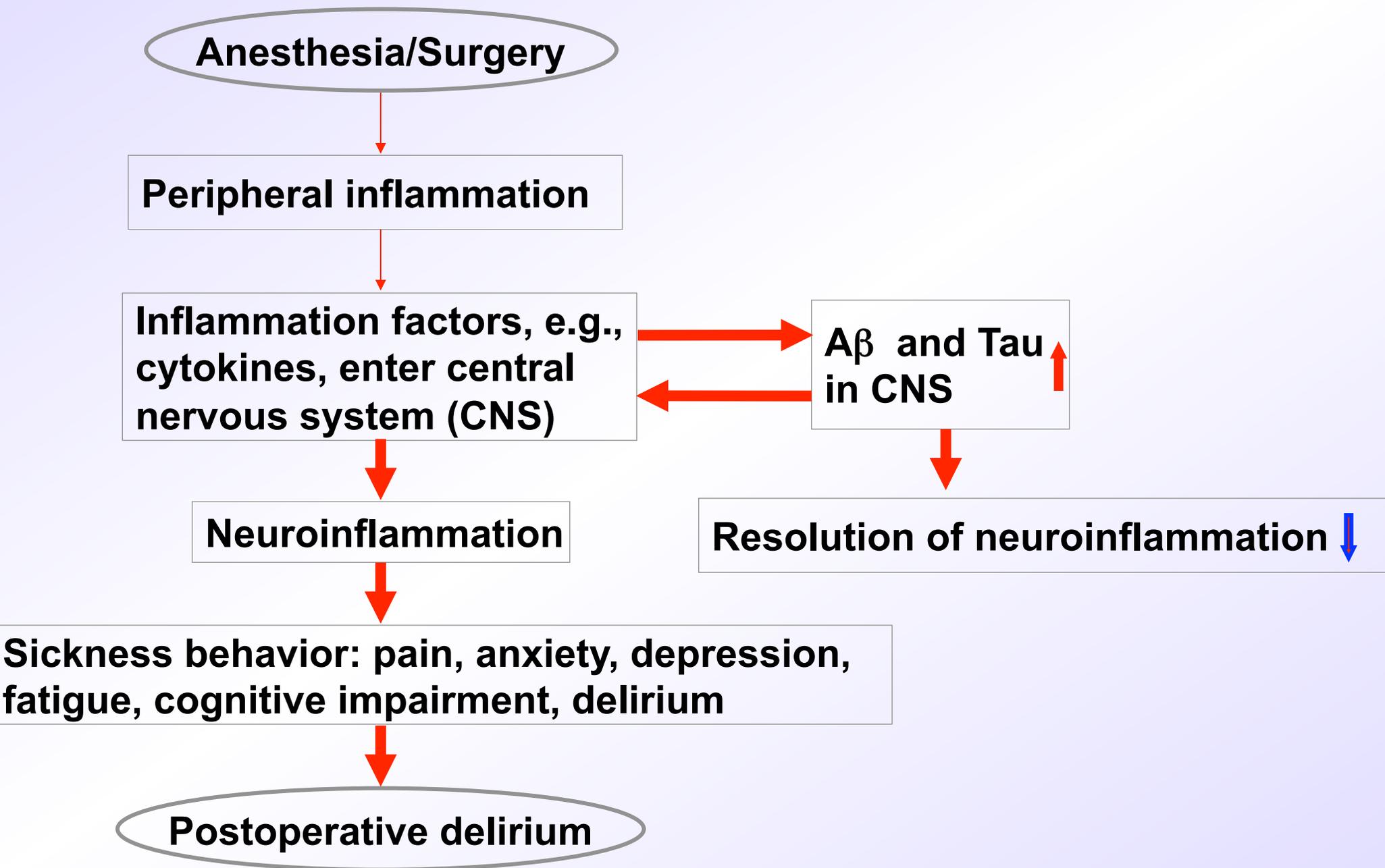
Everybody has postoperative inflammation associated with surgery.

***Why does not everybody develop
postoperative delirium ?***

A. Normal situation



B. Elevated A β and Tau levels in brain



β -Amyloid peptide ($A\beta$)

- $A\beta$ is the main component of senior plaques found in AD patient brain.
- $A\beta_{40}$ is a 40 amino acid peptide, and $A\beta_{42}$ is a 42 amino acid peptide.
- $A\beta$ is produced from its large precursor protein (amyloid precursor protein) by sequential proteolytic cleavage through two proteases, β -secretase and γ -secretase.

(*Mucke and Selkoe, 2012*)

Tau

- Tau is a microtubule-associated protein.
- Hyperphosphorylated Tau is the main component of neurofibrillary tangle, a neuropathological hallmarks of AD.
- Hyperphosphorylated Tau is involved in the neurodegeneration of AD and dementia.

(Mandelkow and Mandelkow, 2012)

Cerebrospinal fluid (CSF) A β and Tau

- CSF A β 42 in AD is decreased to approximately 50% of control levels.
- CSF total Tau in AD is increased to around 300% of control levels.
- High CSF Tau/A β 42 ratio predict mild cognitive impairment and/or dementia.
- High CSF Tau/A β 42 ratio predict cognitive decline in nondemented elders.

(*Blennow, Zettererg and Fagan, 2012*)

***CSF A β , Tau and Postoperative
Cognitive Change***

CSF A β 42/Tau ratio

TABLE 3. Correlation Between Cognitive Function and the CSF A β 42/Tau Ratio

	Unadjusted			Adjusted by Age and Sex		
	Estimate (Z Score)	Standard Error (Z Score)	P	Estimate (Z Score)	Standard Error (Z Score)	P
HVLTRet 1 wk	7.063	2.732	0.011	8.351	2.734	0.003
HVLTRet 3–6 mo	2.531	2.824	0.372	3.680	2.828	0.196
HVLTTR 1 wk	0.474	0.398	0.236	0.412	0.408	0.314
HVLTTR 3–6 mo	0.740	0.406	0.071	0.833	0.412	0.046
BVMTTR 1 wk	0.315	0.565	0.579	0.174	0.562	0.758
BVMTTR 3–6 mo	0.152	0.508	0.766	–0.022	0.515	0.966
BVMTDR 1 wk	0.067	0.236	0.778	0.001	0.240	0.995
BVMTDR 3–6 mo	–0.082	0.202	0.687	–0.099	0.208	0.635
JLO 1 wk	0.915	0.401	0.024	0.954	0.408	0.021
JLO 3–6 mo	1.139	0.436	0.011	1.242	0.446	0.007
Trails B 1 wk	–5.623	2.366	0.019	–4.724	2.396	0.051
Trails B 3–6 mo	1.442	2.221	0.518	1.158	2.285	0.614

The left panel of the table illustrates the results of the Pearson correlation analysis between CSF A β 42/tau ratio and cognitive function in humans. The right panel of the table shows the results of the linear regression analysis after adjustment with age and sex.

(Xie et al., Annals of Surgery, 2013)

CSF A β 40/Tau ratio

TABLE 4. Correlation Between Cognitive Function and the CSF A β 40/Tau Ratio

	Unadjusted			Adjusted by Age and Sex		
	Estimate (Z Score)	Standard Error (Z Score)	P	Estimate (Z Score)	Standard Error (Z Score)	P
HVLTRet 1 wk	1.900	2.797	0.498	2.367	2.791	0.398
HVLTRet 3–6 mo	–0.950	2.918	0.745	–0.742	2.893	0.798
HVLTTR 1 wk	0.259	0.400	0.519	0.267	0.404	0.509
HVLTTR 3–6 mo	0.494	0.422	0.244	0.428	0.424	0.316
BVMTTR 1 wk	–0.585	0.573	0.309	–0.399	0.566	0.482
BVMTTR 3–6 mo	0.958	0.515	0.066	1.045	0.512	0.044
BVMTDR 1 wk	–0.227	0.239	0.345	–0.230	0.241	0.343
BVMTDR 3–6 mo	0.413	0.204	0.045	0.418	0.207	0.046
JLO 1 wk	–0.067	0.409	0.869	–0.146	0.411	0.723
JLO 3–6 mo	–0.289	0.465	0.536	–0.317	0.472	0.504
Trails B 1 wk	1.855	2.409	0.443	1.882	2.391	0.433
Trails B 3–6 mo	–1.712	2.291	0.457	–1.688	2.324	0.463

The left panel of the table illustrates the results of the Pearson correlation analysis between CSF A β 40/tau ratio and cognitive function in humans. The right panel of the table shows the results of the linear regression analysis after adjustment with age and sex.

(Xie et al., Annals of Surgery, 2013)

***CSF A β , Tau and
Postoperative Delirium***

The association between postoperative delirium and the levels of CSF A β and Tau

- 76 participants aged 75 and older who had surgical repair of acute hip fracture.
- Postoperative delirium incidence: 39.5%.
- The postoperative delirium was not associated with baseline CSF A β 42, Tau and phosphorylated Tau levels.
- The potential association of CSF A β /Tau ratio with postoperative delirium was not assessed

(*Witlox et al., 2011*)

➤ **Objective:** To assess whether lower preoperative CSF A β /Tau ratio is associated with higher incidence and greater severity of postoperative delirium in patients.

➤ **Method:**

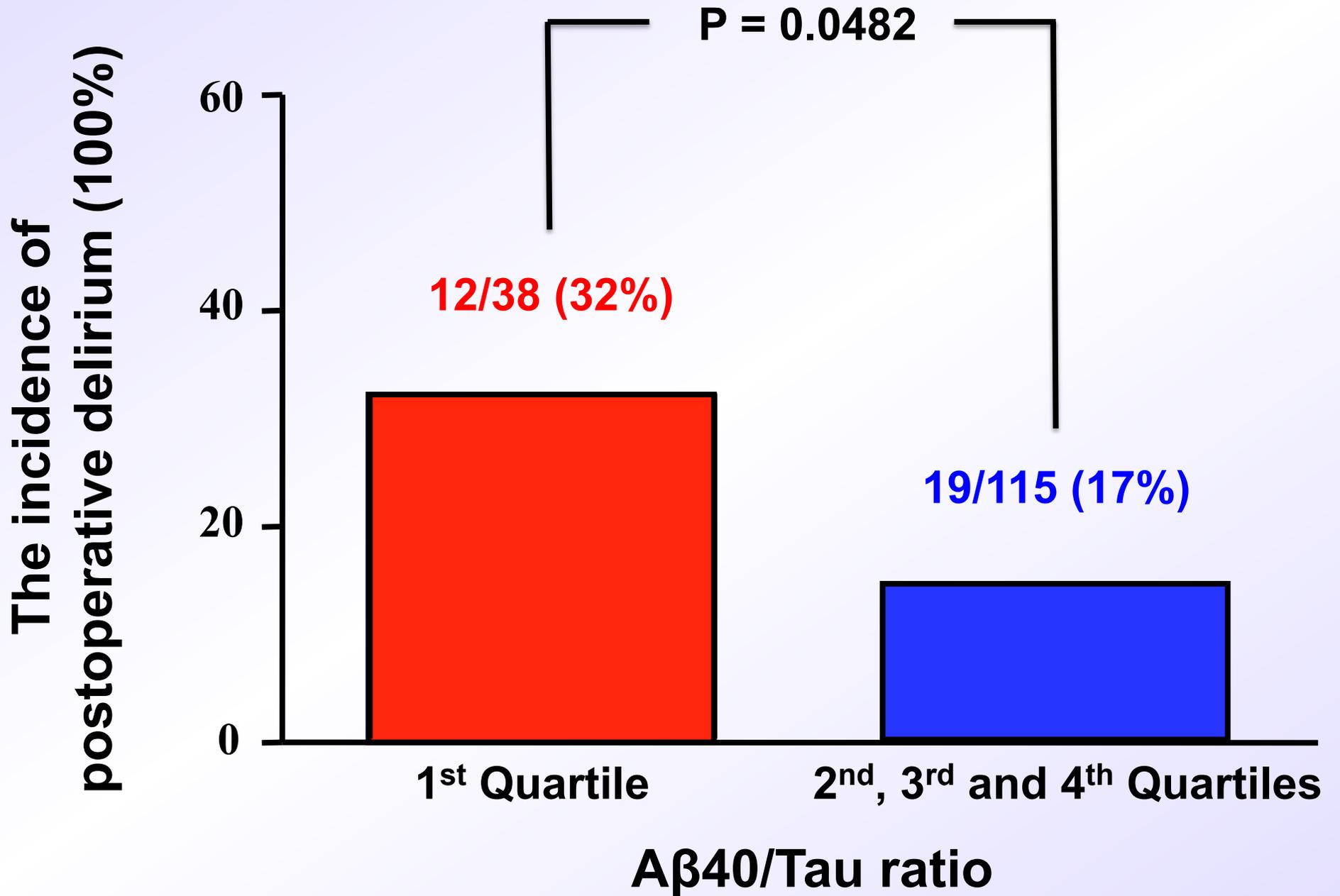
- 153 participants (71 ± 5 years, 53% males) who had total hip/knee replacement under spinal anesthesia.
- Pre-operative CSF was obtained during the initiation of spinal anesthesia.
- Postoperative delirium incidence: Confusion Assessment Method (CAM) at day 1 and 2 after surgery.
- Postoperative delirium severity: Memorial Delirium Assessment Scale (MDAS) at day 1 and 2 after surgery.
- ELISA was used to measure CSF A β 40, A β 42 and Tau levels.

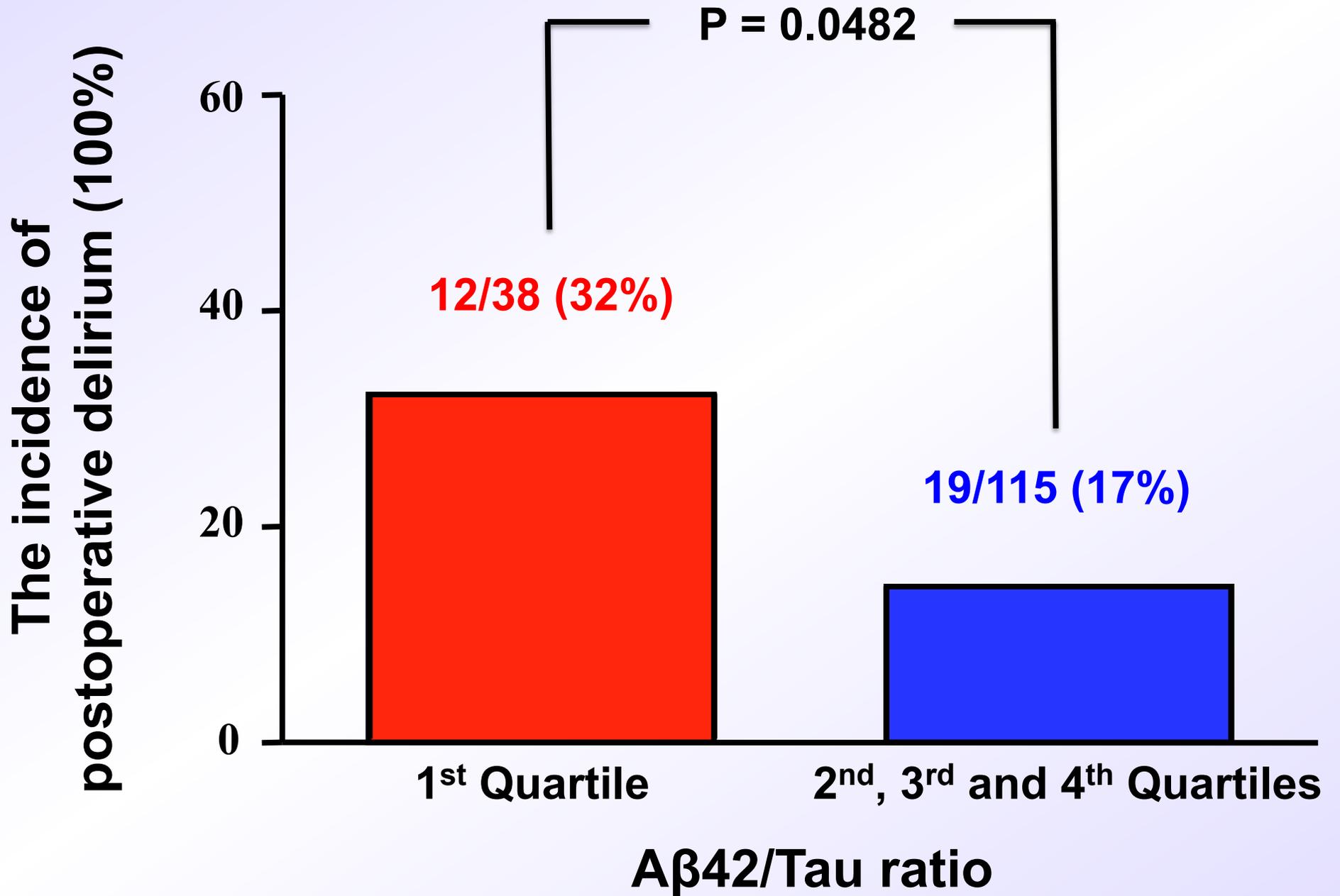
➤ **Methods:**

- 63 years old or older, proficient in English, and candidate for spinal anesthesia.
- No AD, stroke, psychosis or other neurological and psychiatric disease, and no visual or hearing impairment.

➤ Results:

- 20% (31 of 153 participants) had postoperative delirium.
- MDAS score: 3 (2 – 5) (median and 25% - 75% percentile).
- MDAS score in delirium participants: 7 (5 – 10).
- MDAS score in non-delirium participants: 3 (2 – 5).
- CSF A β 40/Tau ratio: 12.6 (9.2 – 16.1).
- CSF A β 42/Tau ratio: 1.4 (0.9 – 2.1).





Correlation between MDAS score and the CSF A β 40/Tau or A β 42/Tau ratio

Highest MDAS score

	Unadjusted		Adjusted by age and gender	
	Regression coefficient \pm SE	P	Regression coefficient \pm SE	P
A β 40/Tau ratio	-0.12 \pm 0.05	0.014	-0.12 \pm 0.05	0.018
A β 42/Tau ratio	-0.65 \pm 0.26	0.013	-0.62 \pm 0.27	0.022

APOE4 and postoperative delirium

- APOE4 is associated with longer duration of delirium in ICU patients (*Ely et al., 2007*).
- APOE4 is not associated with delirium after bypass heart operations (*Tagarakis et al., 2007*).
- APOE4 increases the risk of early (day 1 and day 2) delirium after non-cardiac surgery (*Leung et al., 2007*).
- APOE4 is associated with postoperative delirium after repair of hip fracture (*van Munster et al., 2009*).
- APOE4 is not associated with postoperative delirium after vascular surgery (*Bryson et al., 2011*).
- APOE4 is associated with shorter duration of delirium in ICU patients (*Alexander et al., 2013*).

“Apolipoprotein E plays a complex role in illness response and recovery in critically ill patients. The relationship between apolipoprotein E genotype and brain dysfunction and survival is unclear.”

(Alexander et al., 2014, American Journal of Critical Care. 2014; 23:49-57).

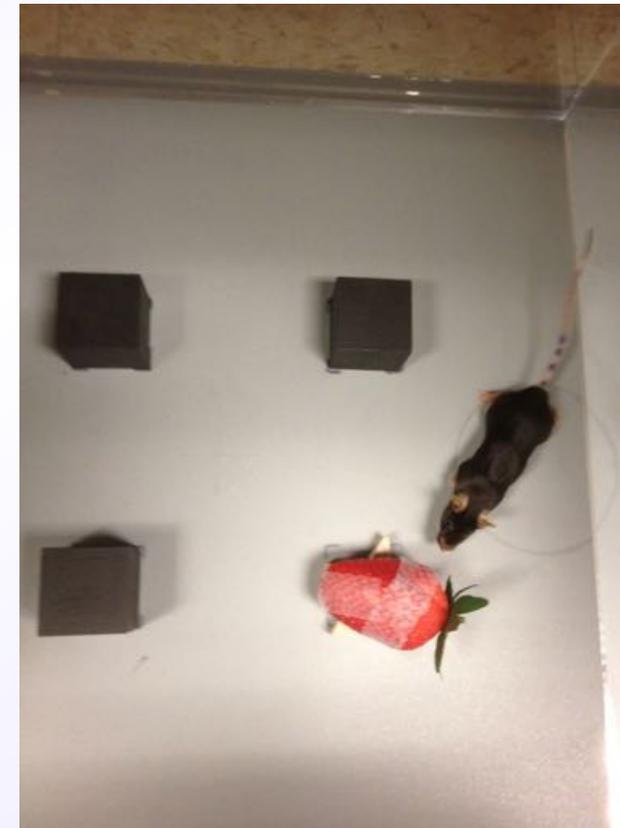
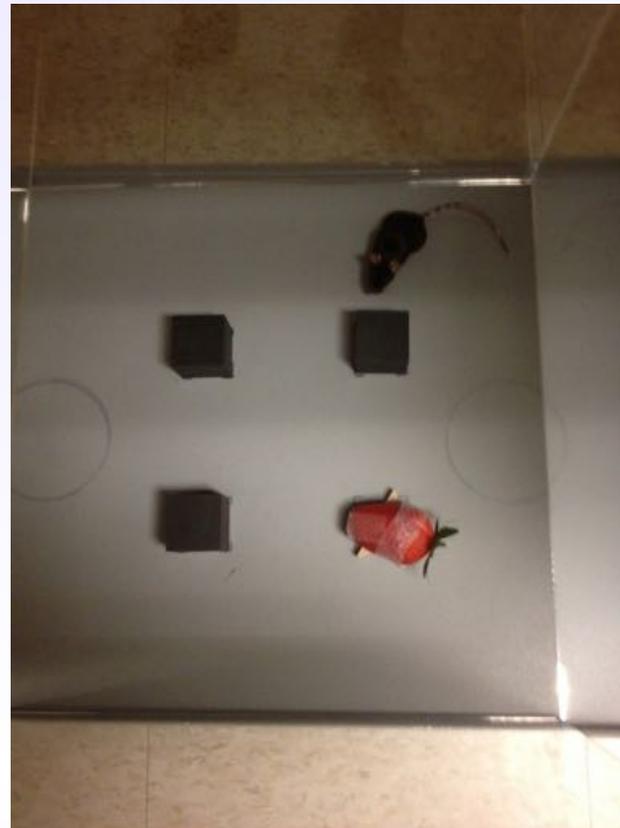
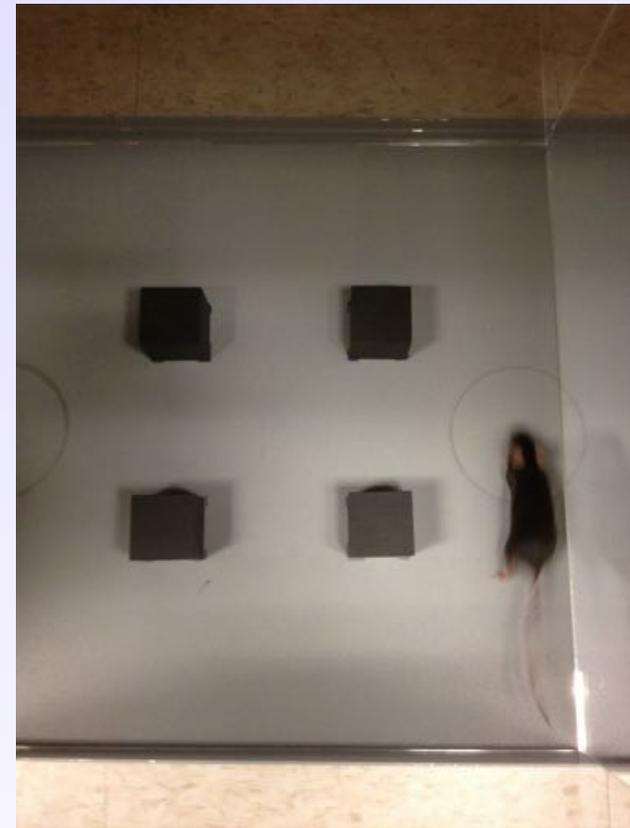
Animal studies of delirium

- There are no satisfy animal models available to study delirium at the present time.
- We have set out to observe the animal nature behavior following the treatment of scopolamine and following the abdominal surgery under isoflurane anesthesia.
- The purpose is to ultimately develop a method of "CAM in mice".

Animal studies of delirium

- Attention level (*Millecamp et al., 2004*).
- Freezing episodes.
- Timecourse investigation.

Attention level



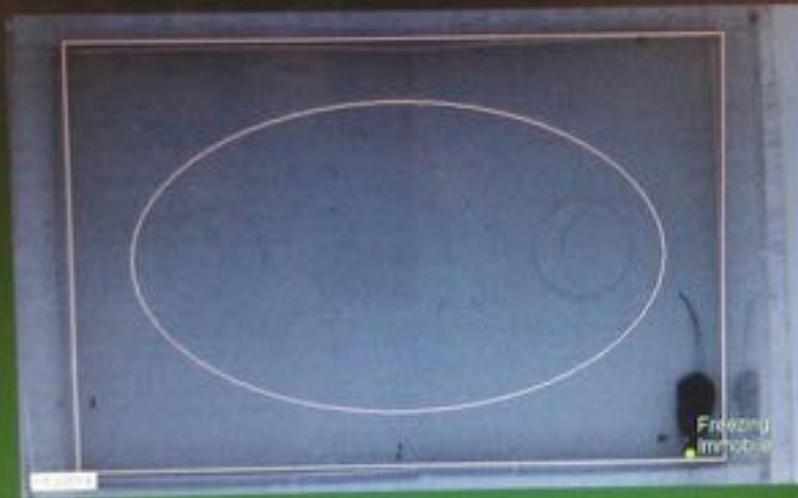
Attention level

$$= \frac{\text{Duration of the new object exploration}}{\text{Total duration of all cumulated objects exploration (i.e. 3 familiar + the new one)}} \times 100$$

(Millecamps et al., 2004)

Freezing episodes

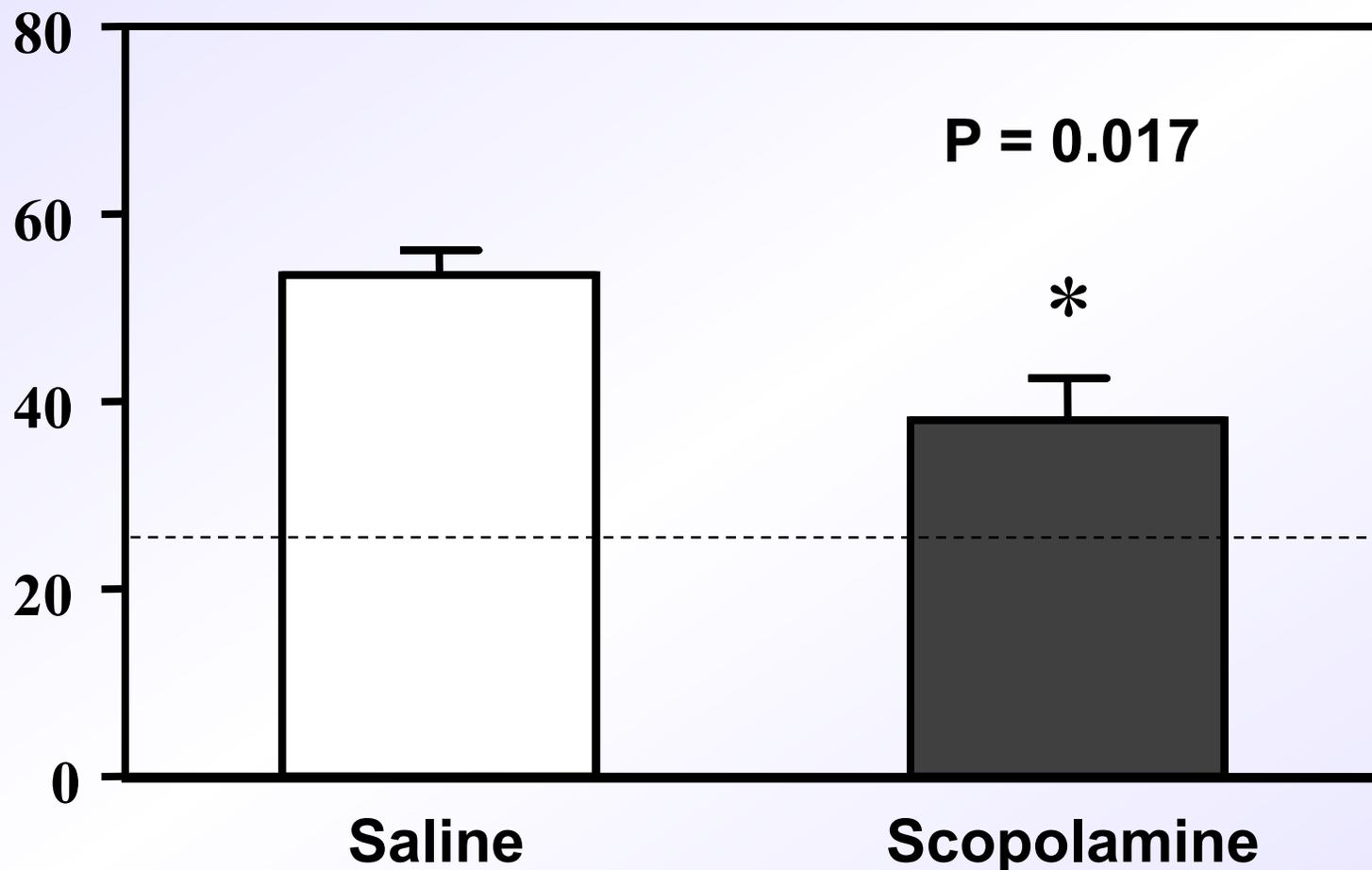
- Definition: No movement except respiration.
- Detected and analyzed by Any-Maze (Stoelting, Wood Dale, IL).



Scopolamine in mice

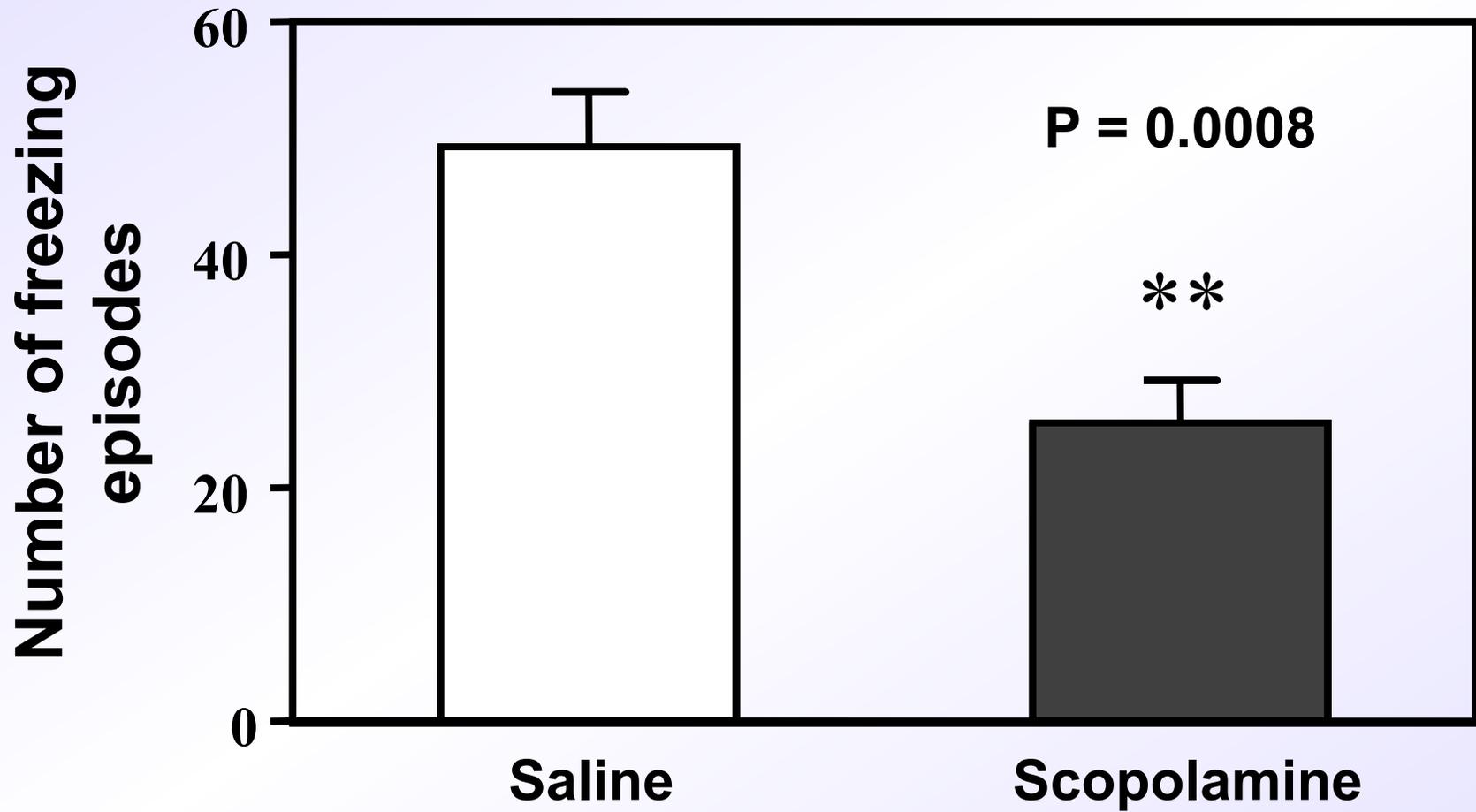
A

**Time spent exploring
new object (100%)**



**level
of chance**

B



Anesthesia and surgery in mice

Effects of Anesthesia and Surgery on mice “CAM”

	Scopolamine	Anesthesia & Surgery							
	2-8-month mice	2-8-month mice				18-month mice			
	30 min	12h	24h	48h	72h	12h	24h	48h	72h
Mean speed	↑	-	-	-	-	-	-	-	-
Attention level	↓	-	↓	-	-	↓	-	-	-
Freezing episode	↓	-	-	-	-	-	↓	-	↓

↑ and ↓ indicate significant increase ($P < 0.05$) and decrease ($P < 0.05$) compared with saline or sham group at the same time point, respectively

Summary and Conclusion

- **The patients who have lower preoperative CSF A β 40/Tau or A β 42/Tau ratio, particularly those in the lowest quartile, are more likely to develop postoperative delirium and have more severe symptoms.**
- **These results suggest that A β and/or Tau may contribute to the neuropathogenesis of delirium.**
- **These findings would promote more delirium studies, including studies in animals.**

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