

# **Delirium, Apo-E status, and AD CSF biomarkers**

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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%
<b>Delirium</b>	<b>15%</b>
<b>POCD</b>	<b>10 - 15%</b>

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

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

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

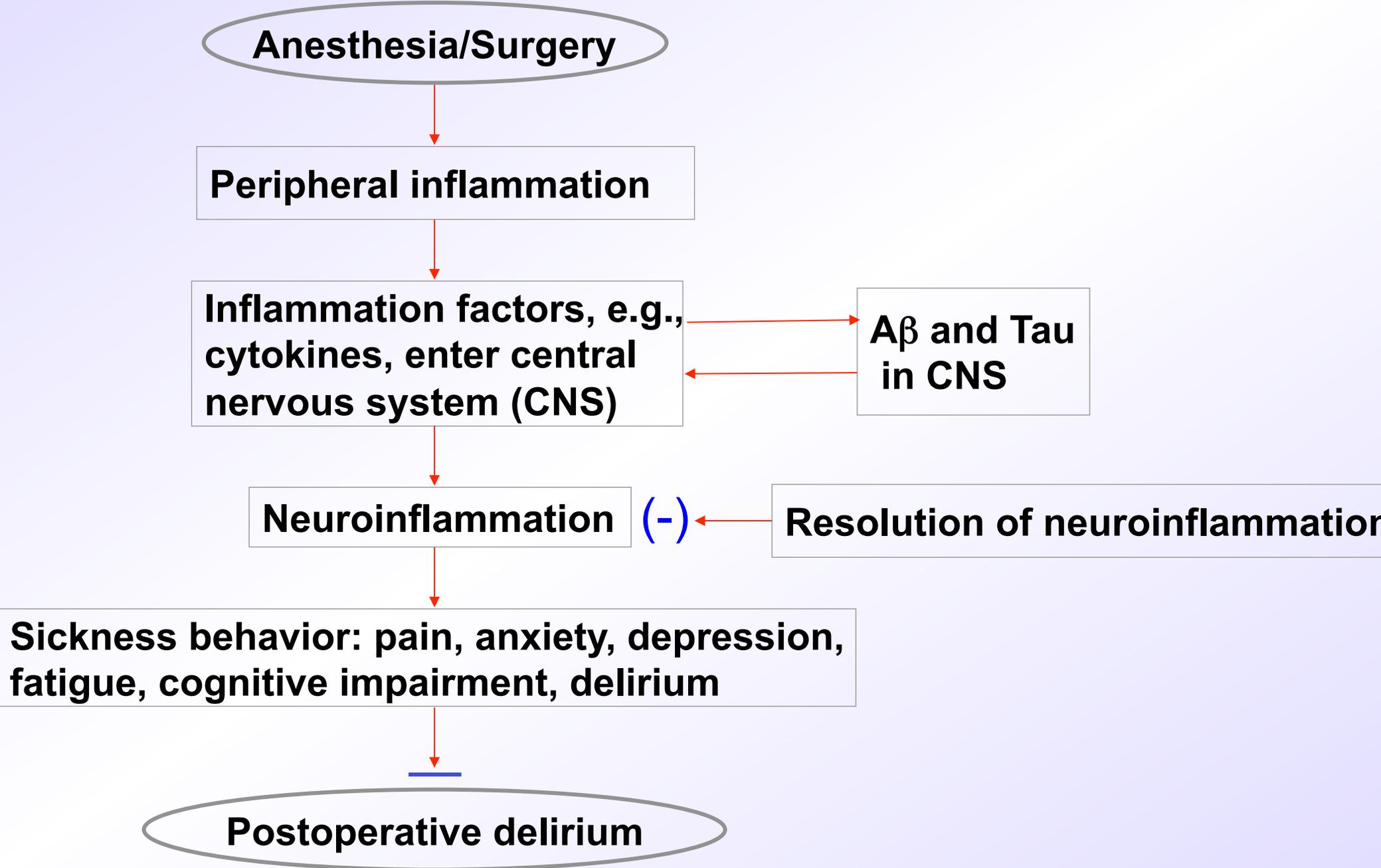
# Postoperative delirium

- 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.

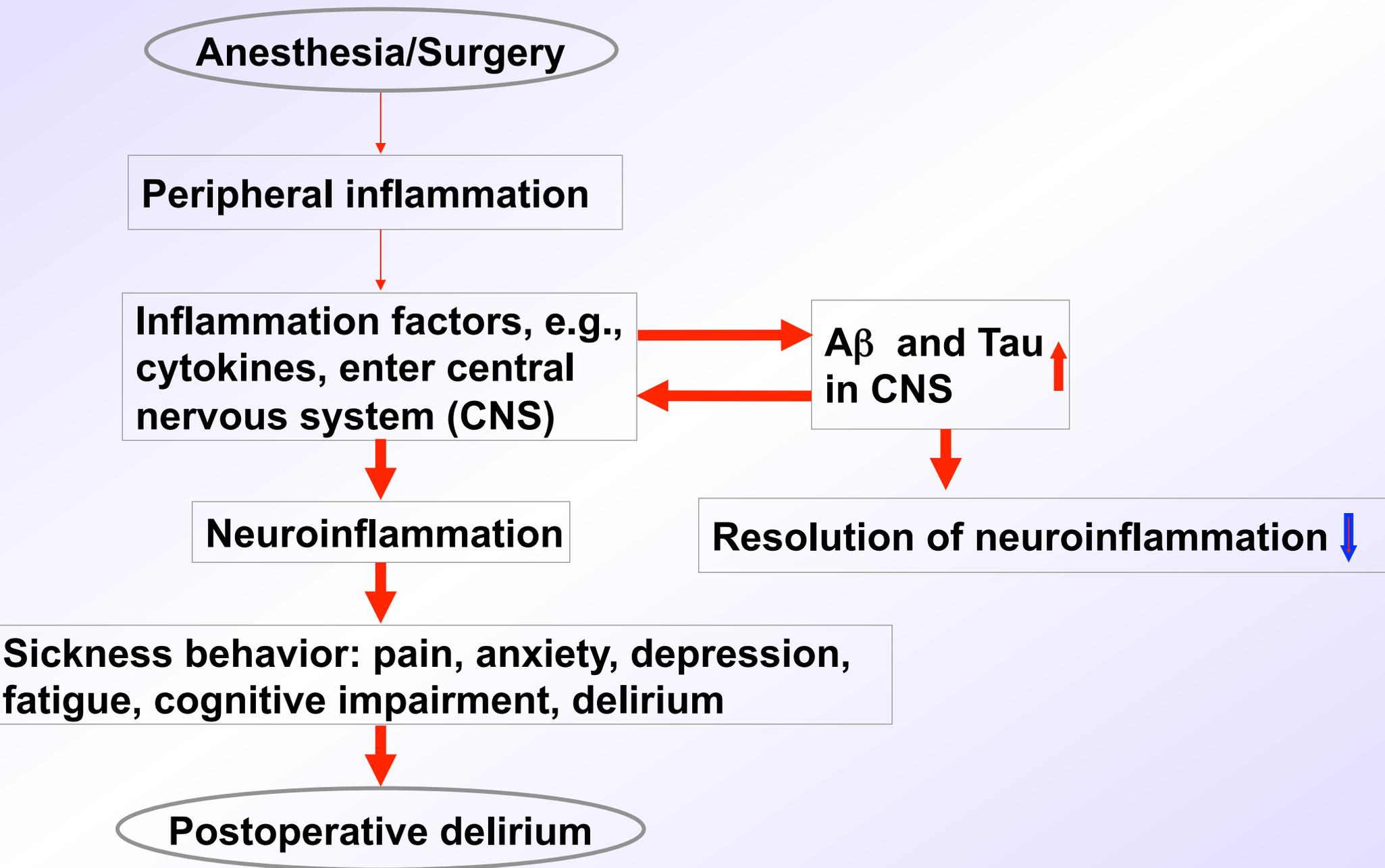
***Everybody has postoperative inflammation associated with surgery.***

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

# A. Normal situation



## B. Elevated A $\beta$ and Tau levels in brain



# $\beta$ -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,  $\beta$ -secretase and  $\gamma$ -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 $\beta$ and Tau

- CSF A $\beta$ 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 $\beta$ 42 ratio predict mild cognitive impairment and/or dementia.
- High CSF Tau/A $\beta$ 42 ratio predict cognitive decline in nondemented elders.

(*Blennow, Zettererg and Fagan, 2012*)

***CSF A $\beta$ , Tau and Postoperative  
Cognitive Change***

# CSF A $\beta$ 42/Tau ratio

**TABLE 3. Correlation Between Cognitive Function and the CSF A $\beta$ 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 $\beta$ 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 $\beta$ 40/Tau ratio

TABLE 4. Correlation Between Cognitive Function and the CSF A $\beta$ 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 $\beta$ 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 $\beta$ , Tau and  
Postoperative Delirium***

# The association between postoperative delirium and the levels of CSF A $\beta$ 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 $\beta$ 42, Tau and phosphorylated Tau levels.
- The potential association of CSF A $\beta$ /Tau ratio with postoperative delirium was not assessed

(*Witlox et al., 2011*)

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

## ➤ **Method:**

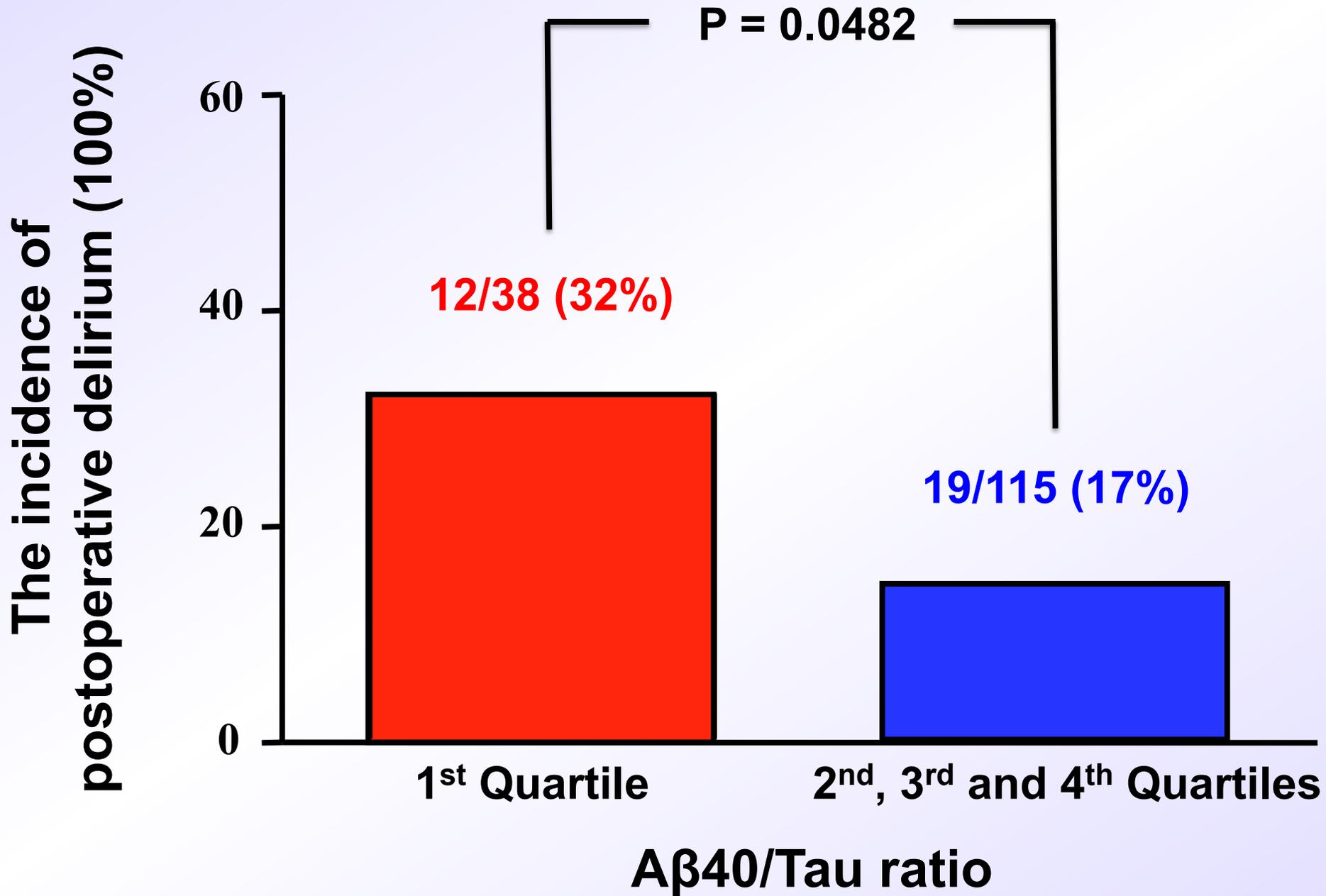
- 153 participants ( $71 \pm 5$  years, 53% males) who had total hip/knee replacement under spinal anesthesia.
- Pre-operative CSF was obtained during the initiation of spinal anesthesia.
- Postoperative delirium incidence: Confusion Assessment Method (CAM) at day 1 and 2 after surgery.
- Postoperative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

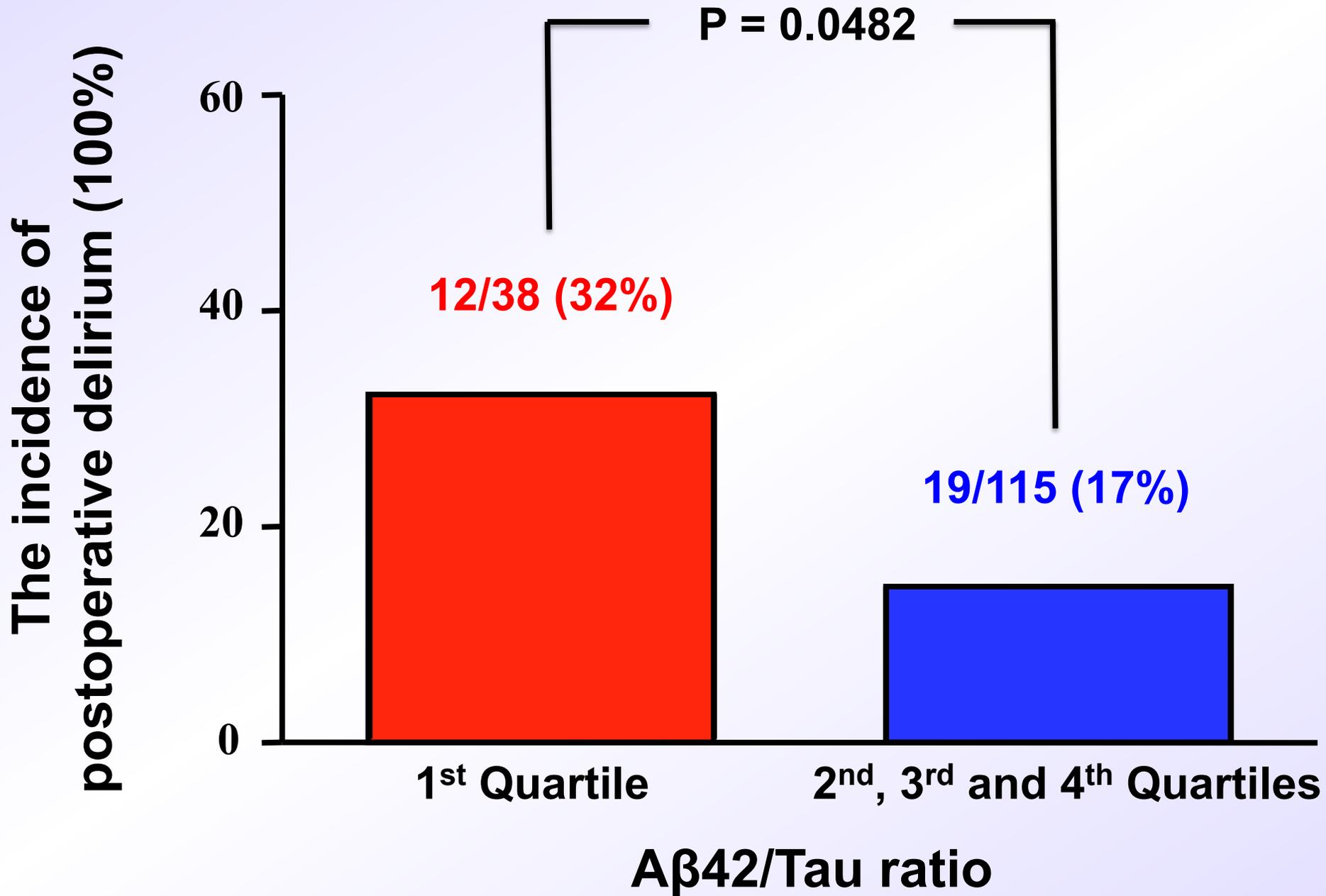
## ➤ **Methods:**

- 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 $\beta$ 40/Tau ratio: 12.6 (9.2 – 16.1).
- CSF A $\beta$ 42/Tau ratio: 1.4 (0.9 – 2.1).





# Correlation between MDAS score and the CSF A $\beta$ 40/Tau or A $\beta$ 42/Tau ratio

## Highest MDAS score

	Unadjusted		Adjusted by age and gender	
	Regression coefficient $\pm$ SE	P	Regression coefficient $\pm$ SE	P
A $\beta$ 40/Tau ratio	-0.12 $\pm$ 0.05	0.014	-0.12 $\pm$ 0.05	0.018
A $\beta$ 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).*

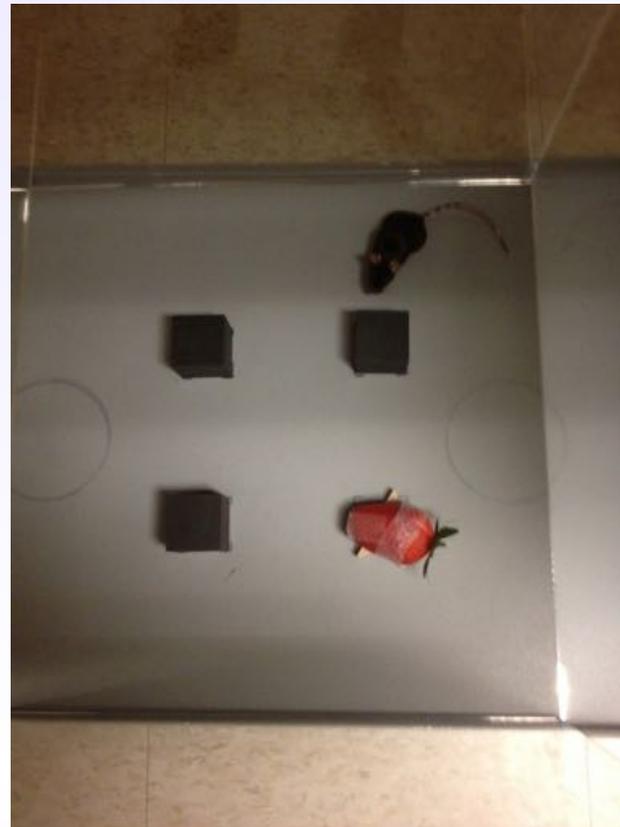
# Animal studies of delirium

- 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



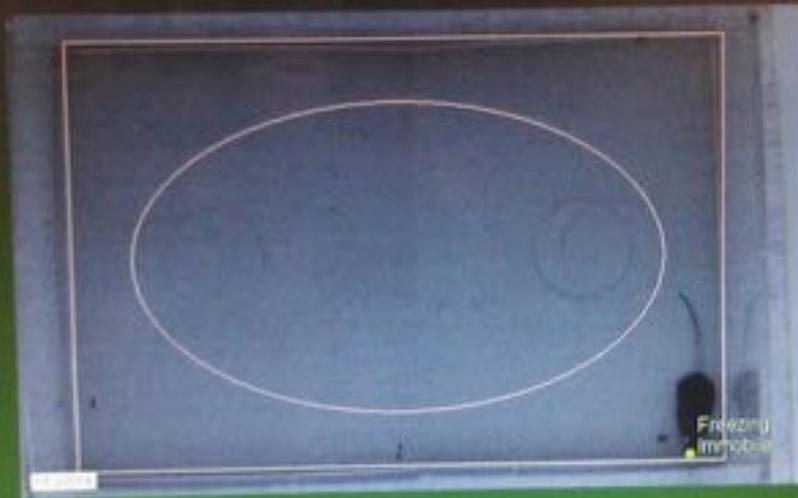
Attention level

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

(Millecamps et al., 2004)

# Freezing episodes

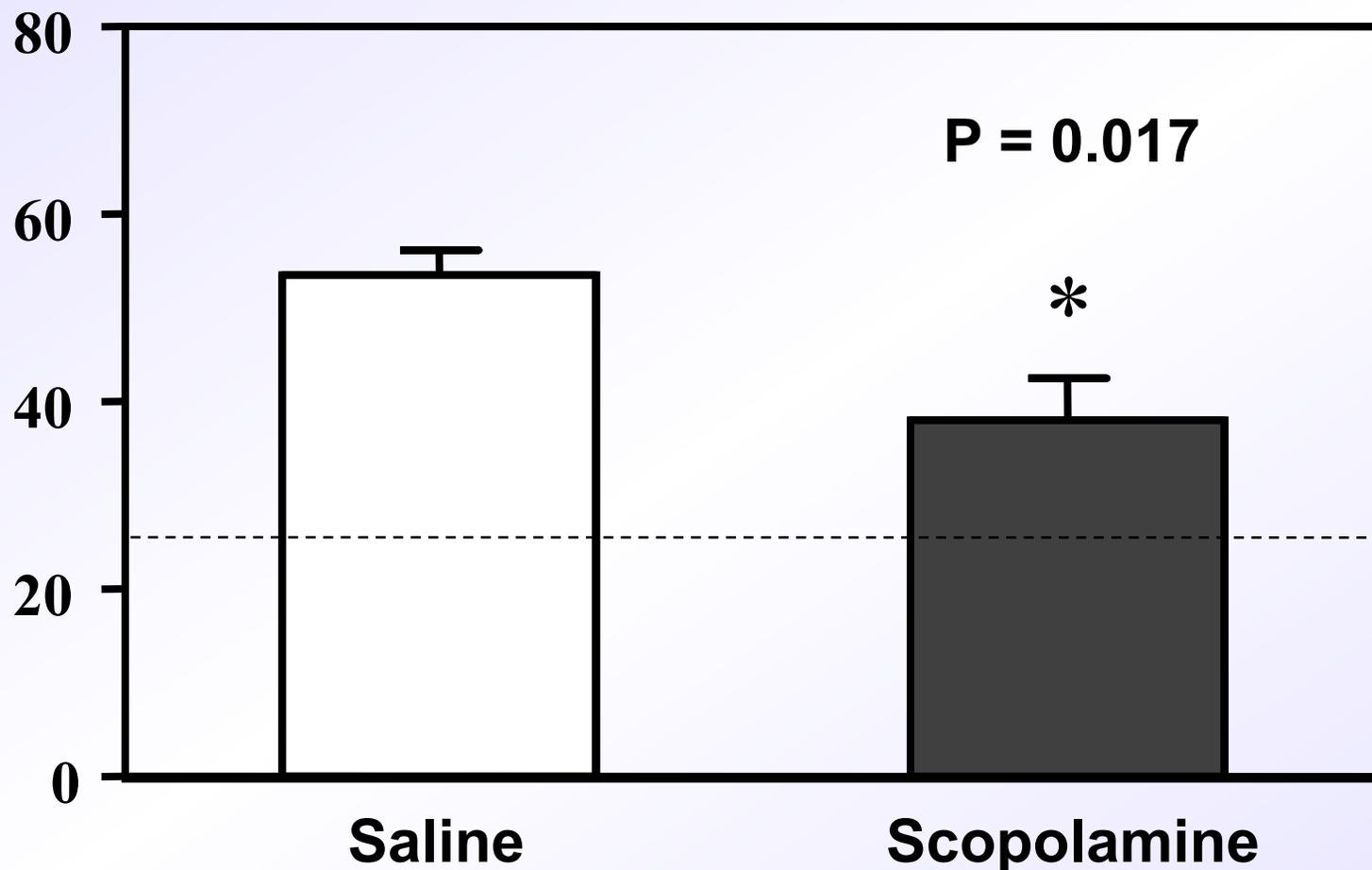
- Definition: No movement except respiration.
- Detected and analyzed by Any-Maze (Stoelting, Wood Dale, IL).



# ***Scopolamine in mice***

**A**

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

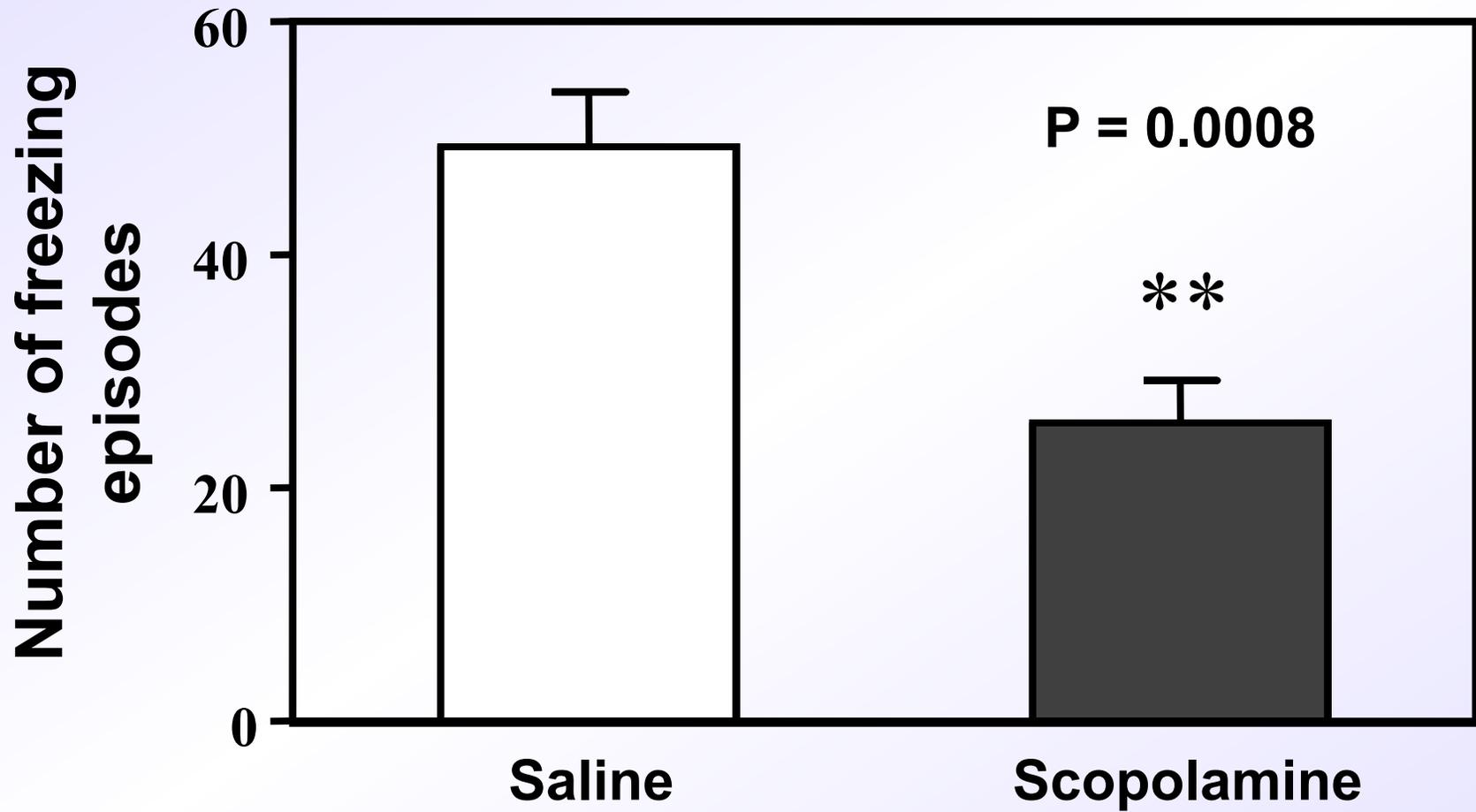


**P = 0.017**

**\***

**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 $\beta$ 40/Tau or A $\beta$ 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 $\beta$  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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