Presenilins:
a group of novel calcium channel modulators.

Simon Kaja, Ph.D.

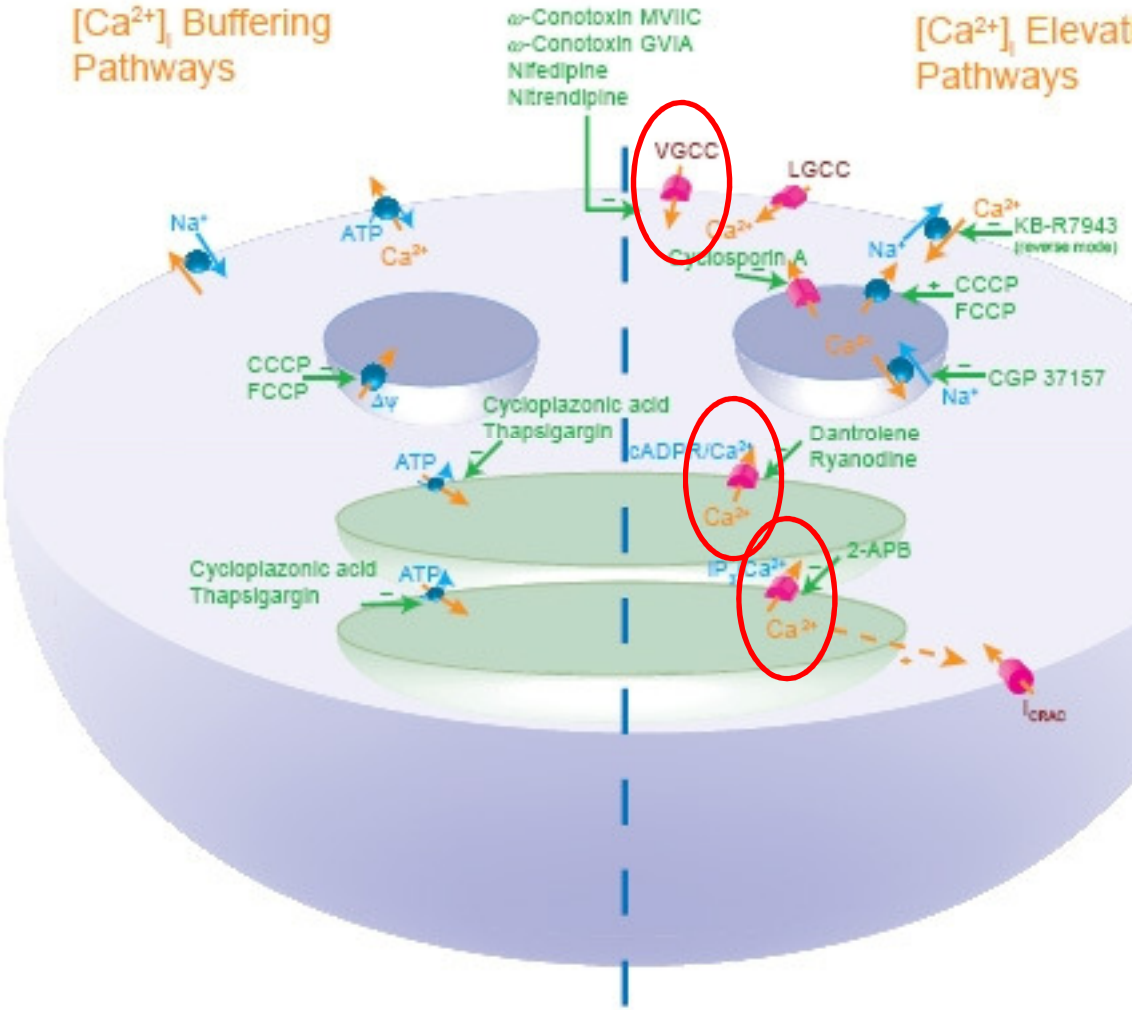
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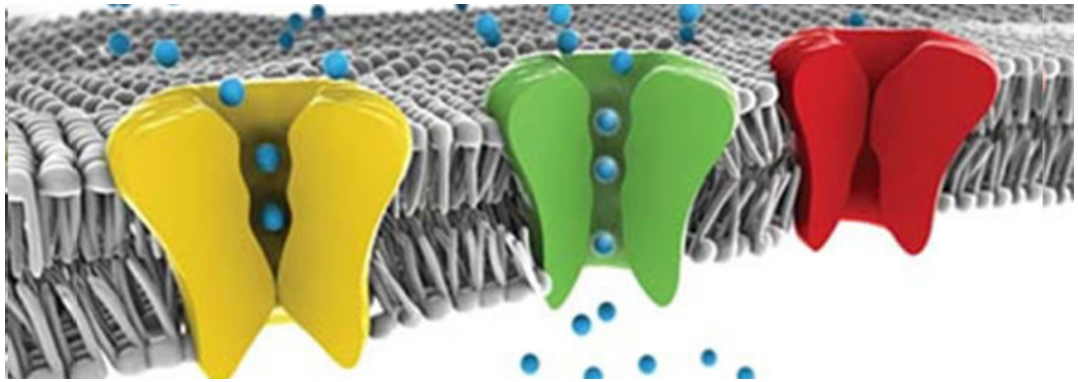
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Ca^{2+} signaling

- 1/3 of the genome are regulated by Ca^{2+}
- Calcium-mediated processes: -
  - Gene transcription
  - Cell growth and differentiation
  - Apoptosis
  - Synaptic plasticity
  - Secretion
  - Neurotransmitter release
  - Cell motility & contraction
  - Enzyme activity
- $[Ca^{2+}]$ elevating pathways
  - Voltage-gated Ca^{2+} channels
  - Intracellular Ca^{2+} channels
- $[Ca^{2+}]$ buffering pathways



Calcium signaling in disease



Mutations in calcium channels:

- Migraine
- Ataxia
- Epilepsy
- Polycystic kidney disease
- Hypothermia
- Night-blindness
- Cardiac arrhythmia
- Turner's syndrome
- …

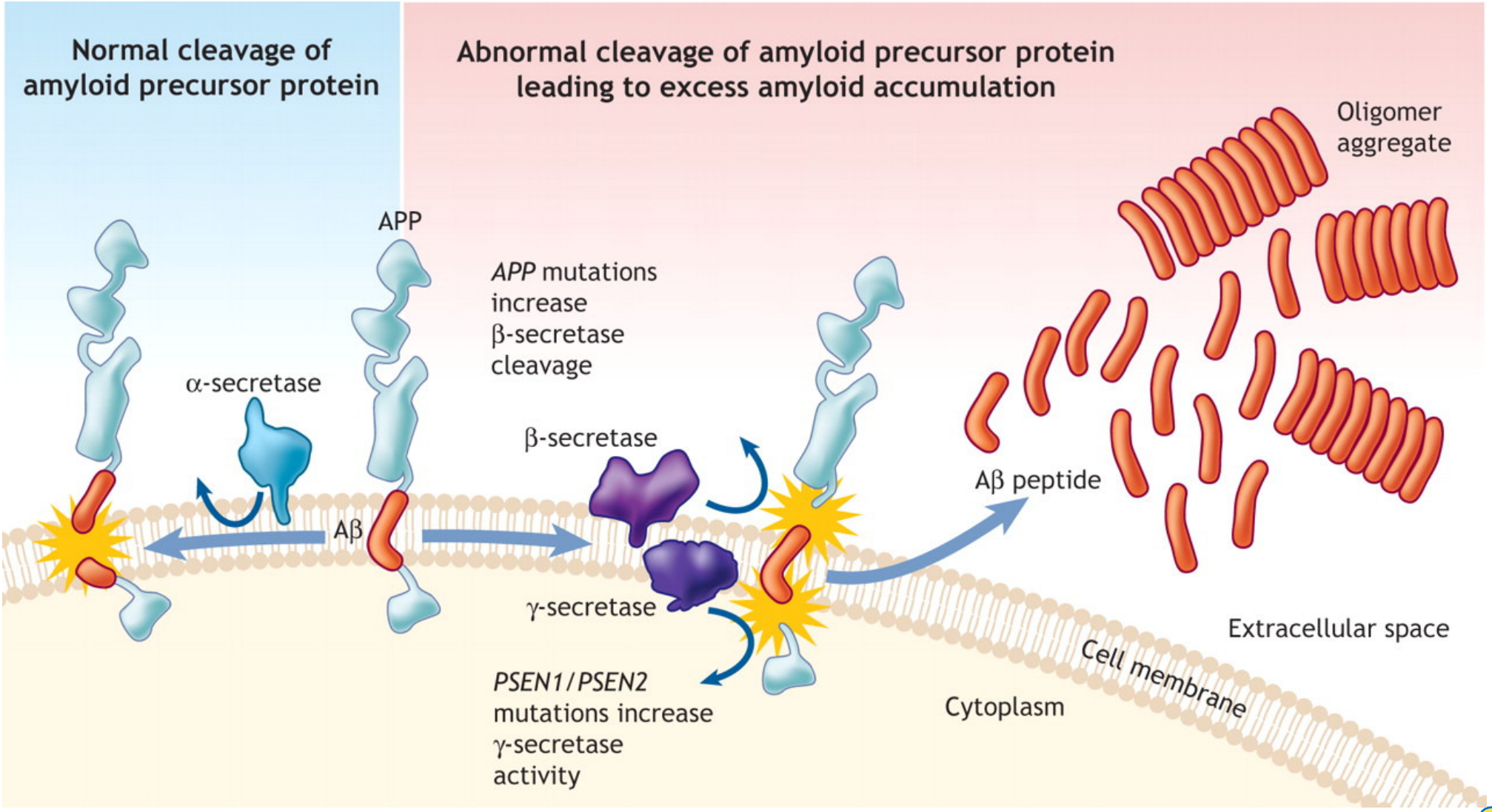
Mutations in accessory proteins:

- Cerebellar ataxia
- Alzheimer's disease
- Autism
- Movement disorders
- Hypercalcemia
- …

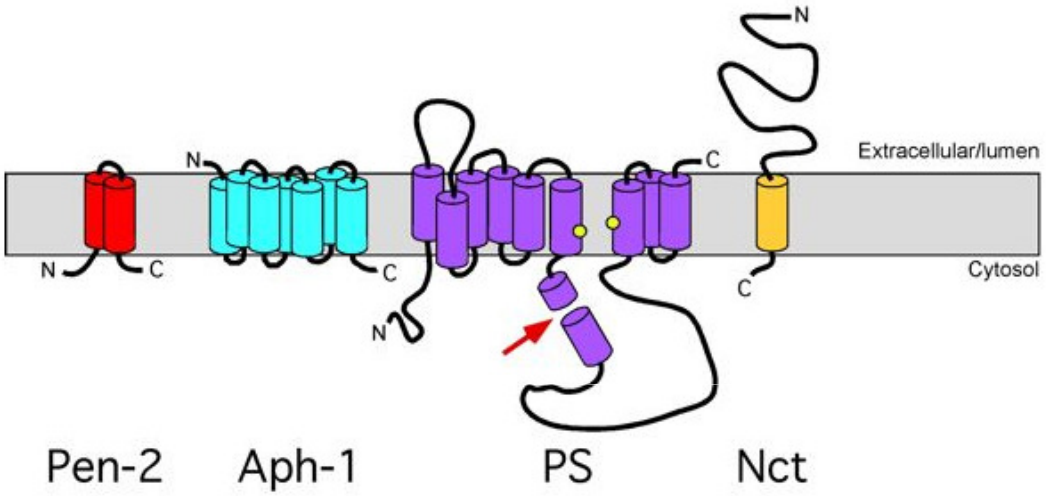
Age-related changes in Ca^{2+} signaling:

- Healthy aging
- Alzheimer's disease
- Glaucoma
- Dementia
- Parkinson's Disease
- Dry-eye disease
- …

Pathological cleavage of APP in AD



Presenilin proteins



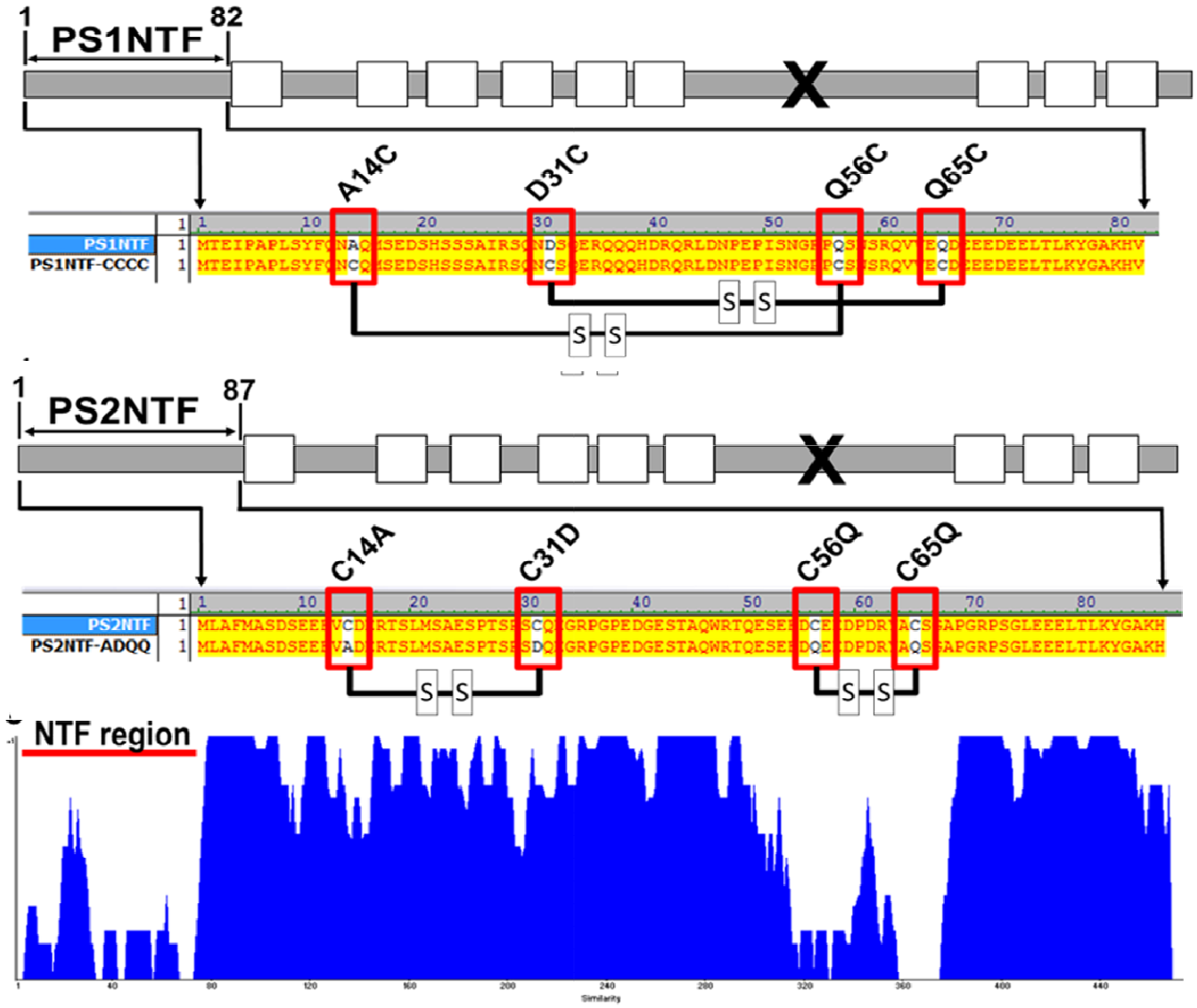
Structure and function:

- Component of the γ-secretase
  - aspartyl protease component of the γ-secretase complex
- Two proteins: PS1 and PS2
- PS mutations linked to familial AD
  - PS1 and PS2 mutations increase γ-secretase activity
- 9 TM SR/ER proteins

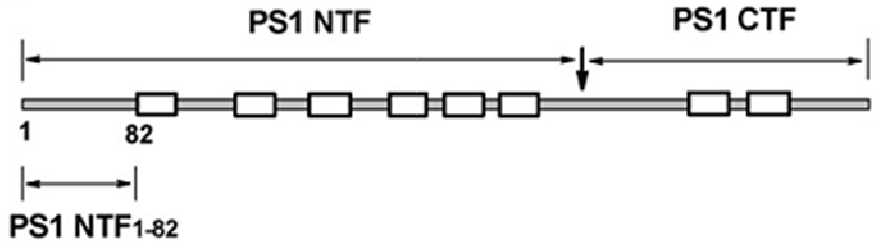
Rationale:

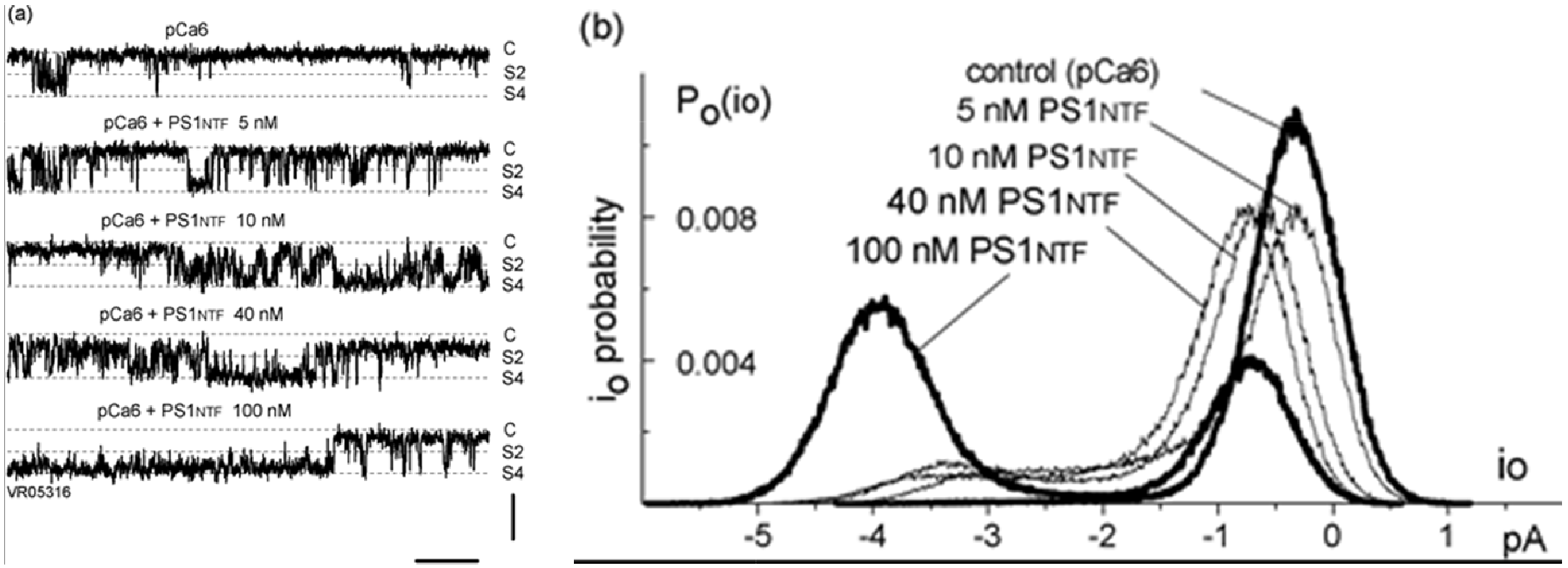
- PS mutations increase [RyR]

Presenilin homology



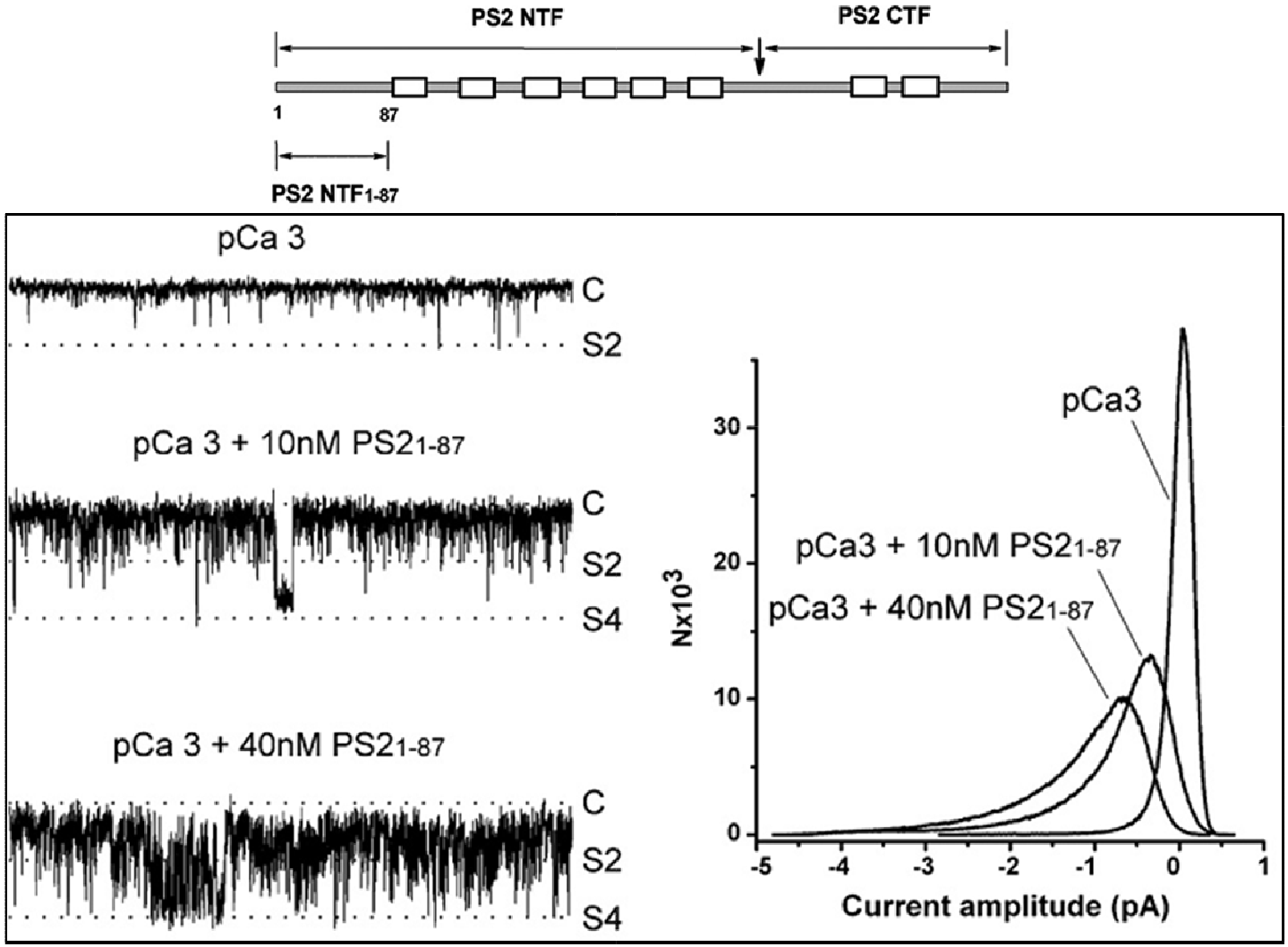
PS1 NTF increases open probability of the brain RyR





Rybalchenko et al., 2008; and Hayrapetyan et al, 2008

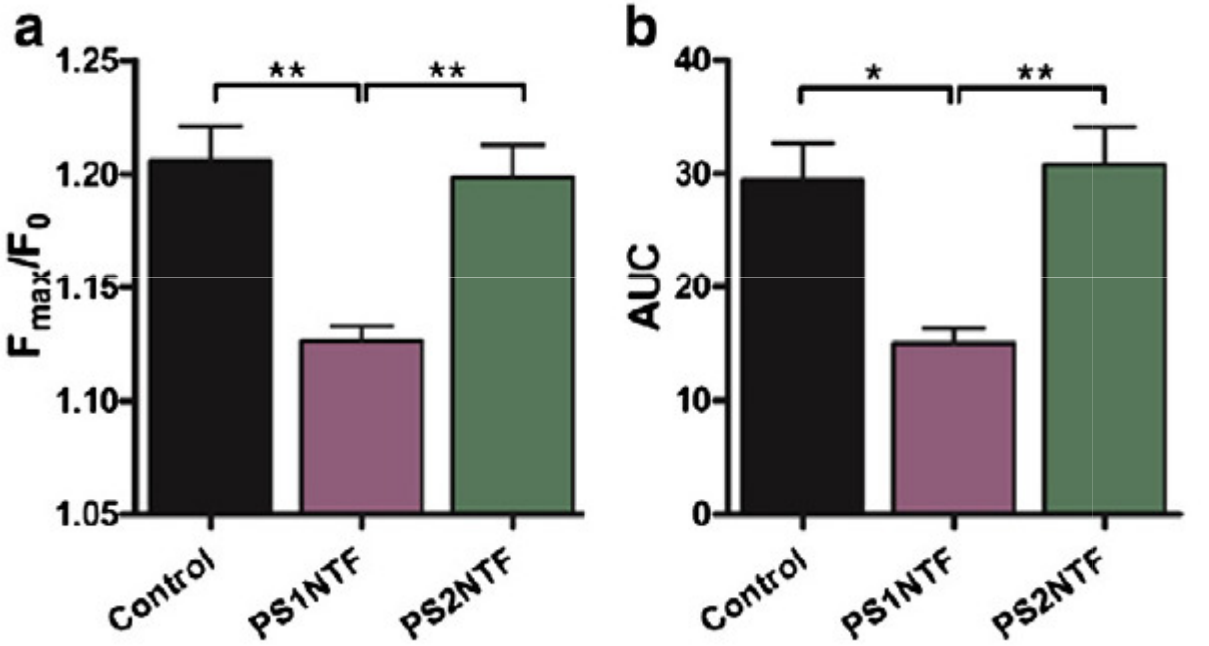
PS2 NTF increases open probability of the brain RyR

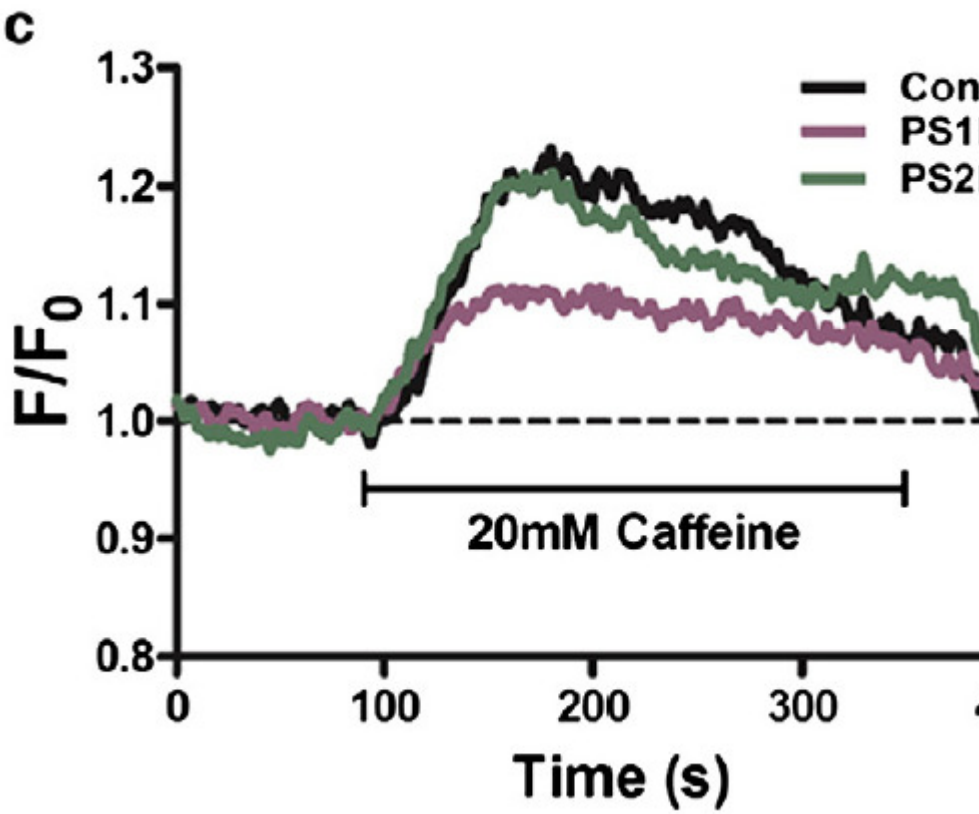


Rybalchenko et al., 2008; and Hayrapetyan et al, 2008

PS NTFs differentially modulate intracellular Ca^{2+} release

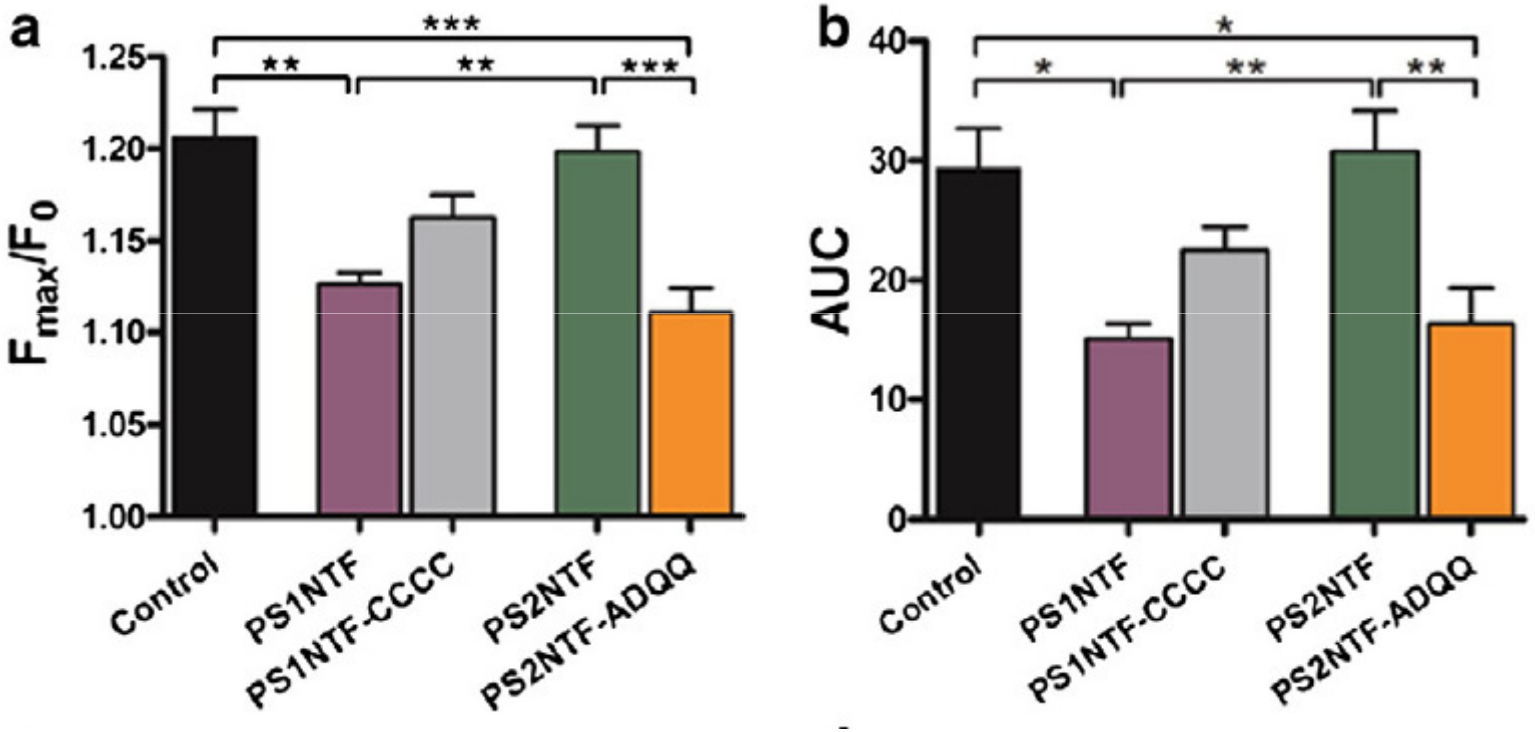
Functional Ca^{2+} imaging in SH-SY5Y neuroblastoma cells overexpressing PS1 or PS2





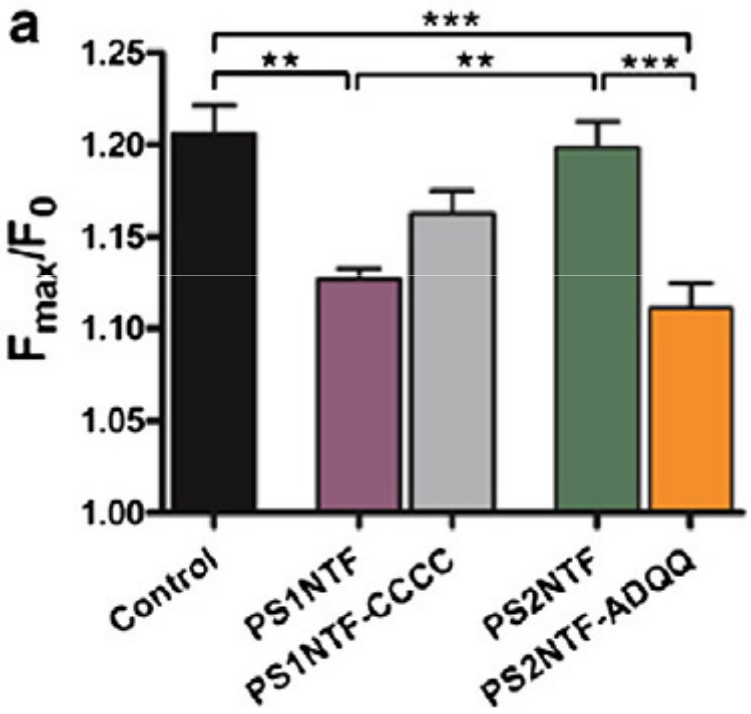
Payne et al., 2013

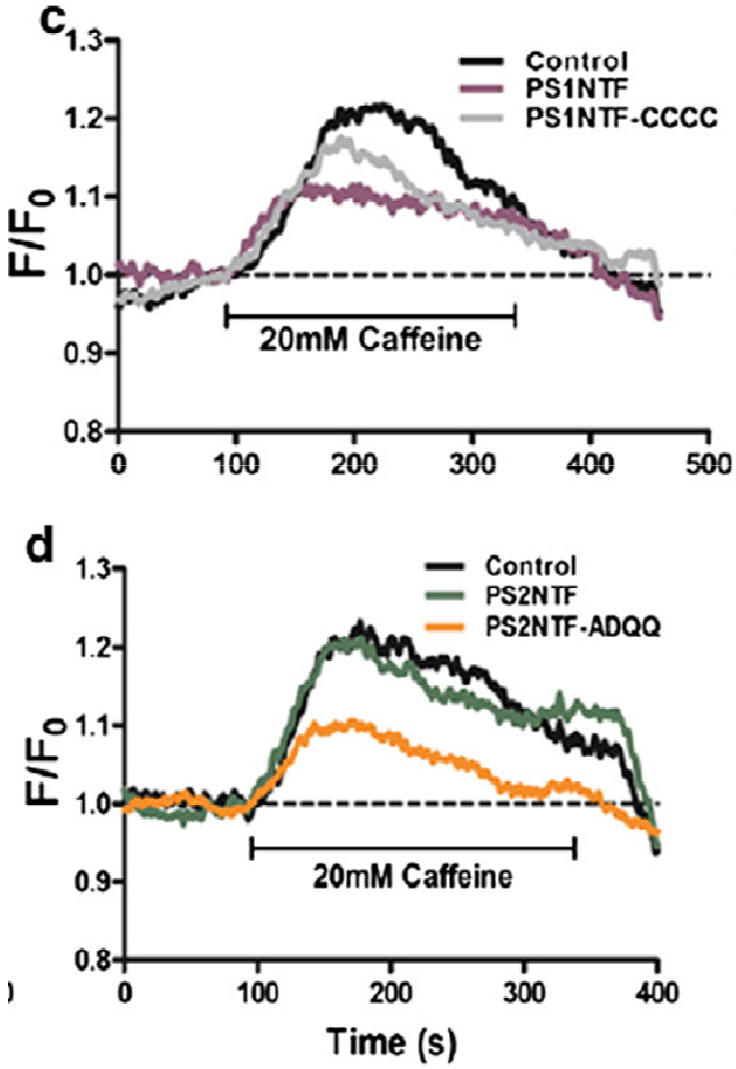
PS NTFs differentially modulate intracellular Ca^{2+} release



Payne et al., 2013

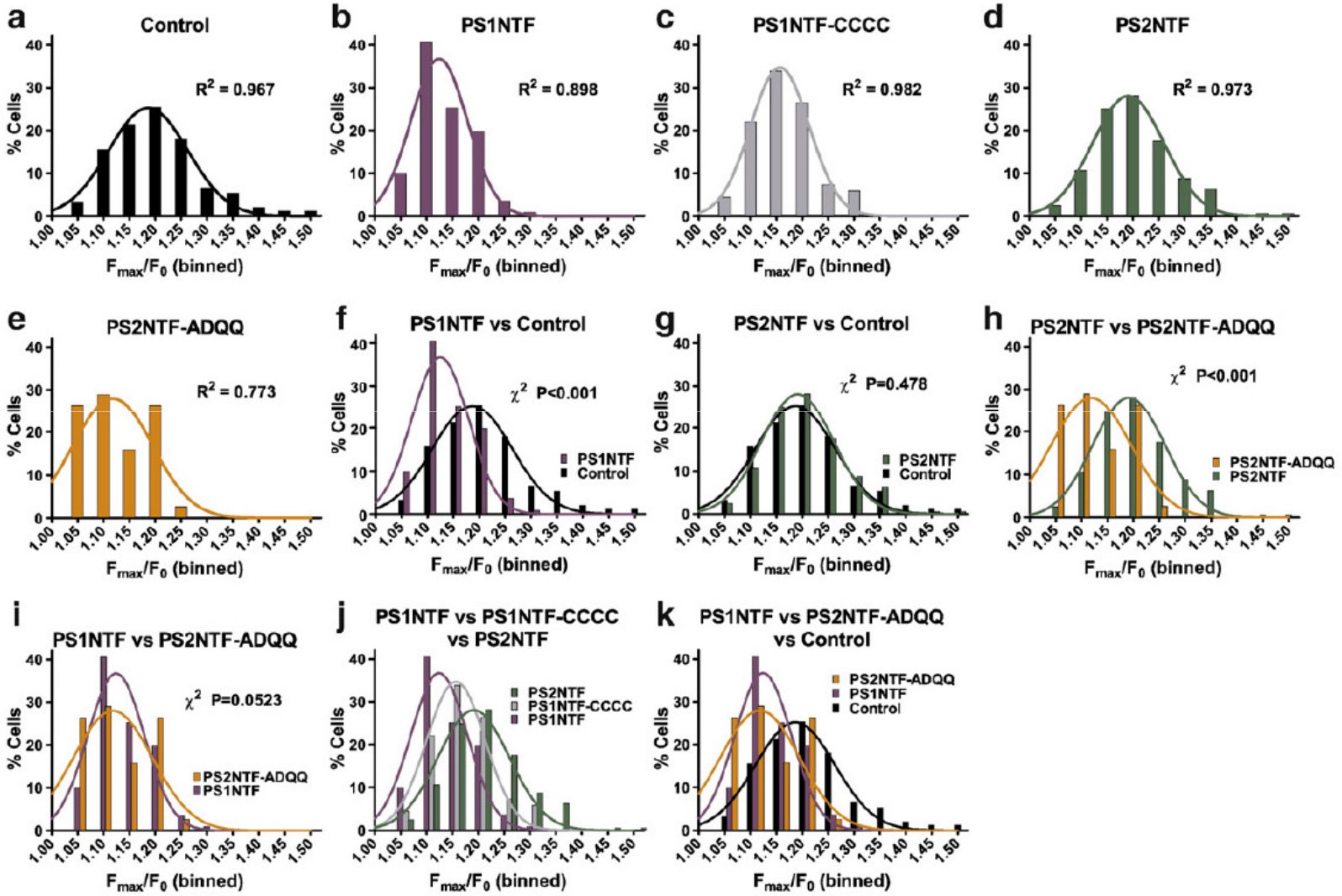
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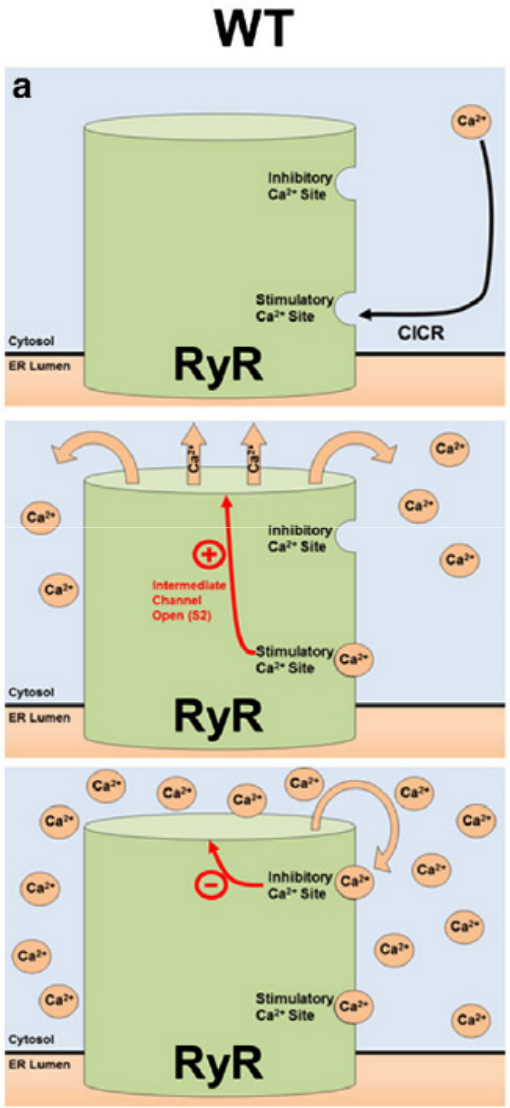
Payne et al., 2013

PS NTFs differentially modulate intracellular Ca^{2+} release



Payne et al., 2013

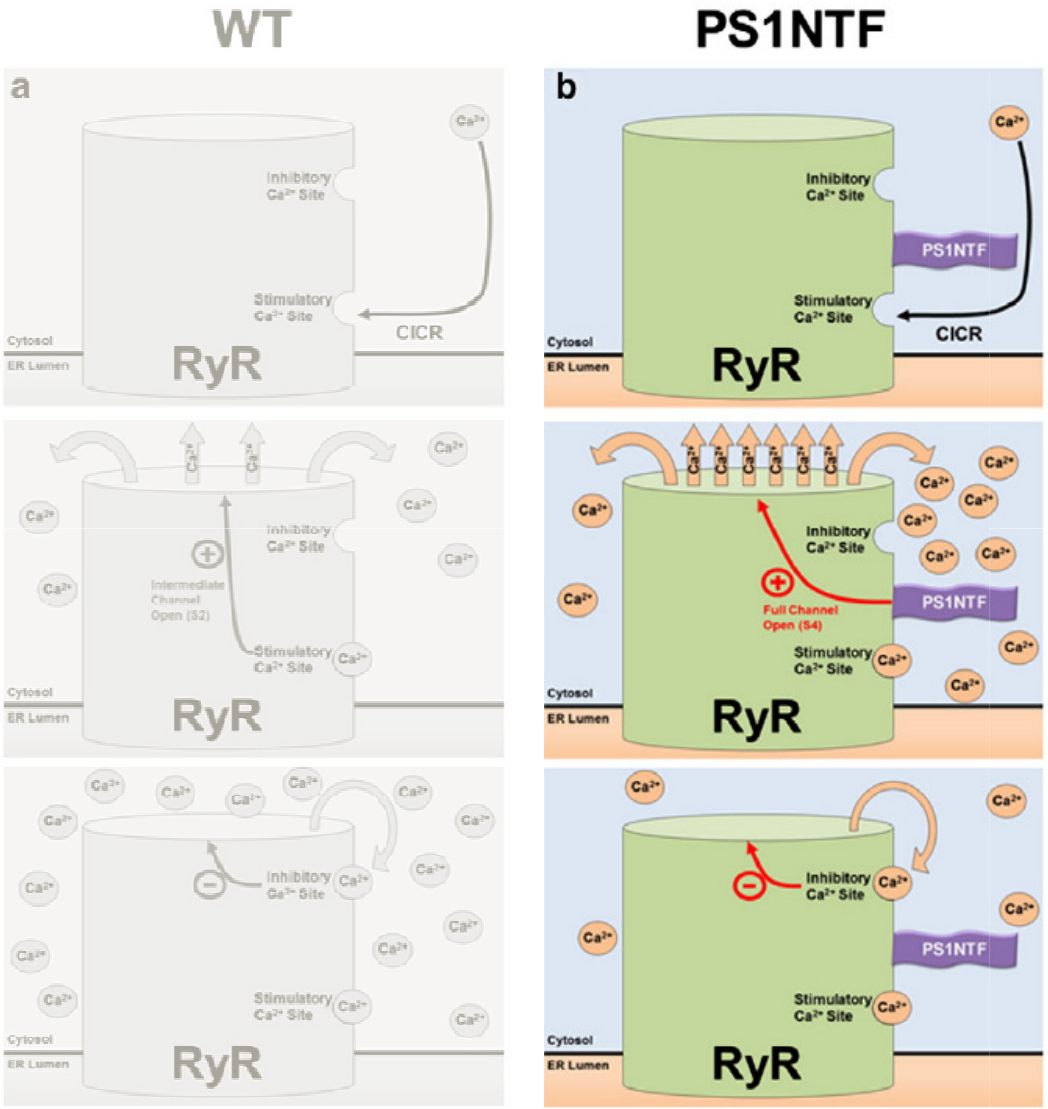
Model of PS modulation of the RyR



a) Ca^{2+} binds the high affinity stimulatory site resulting in moderate channel opening.

b) Sustained Ca^{2+} release will result in Ca^{2+} occupying the low affinity, inhibitory Ca^{2+} binding site resulting in channel closure.

Payne et al., 2013

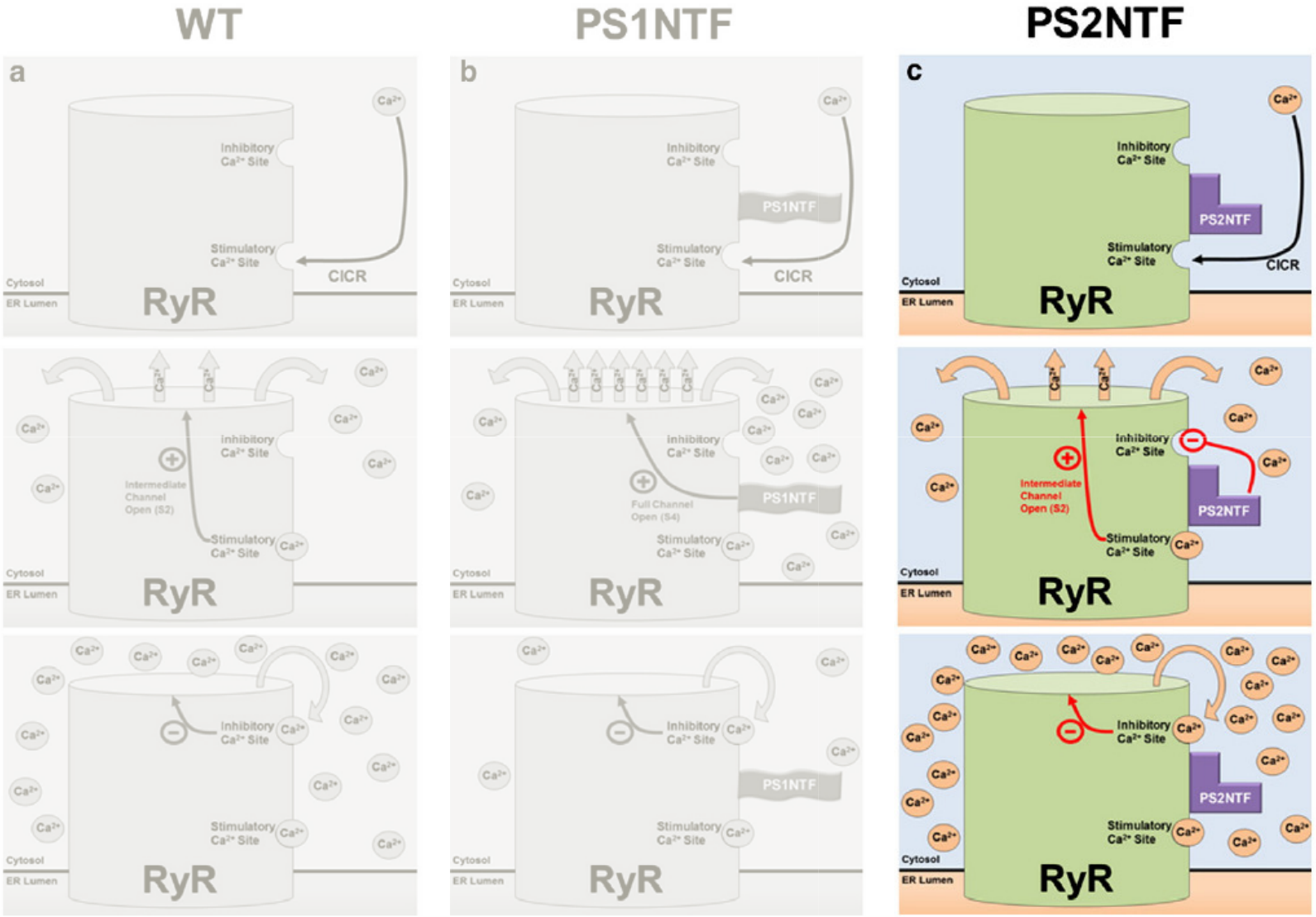


a) PS1NTF increases channel opening, causing rap Ca^{2+} release.

b) The increased rate of Ca^{2+} release results in an overall reduced Ca^{2+} release as inhibitory concentrations are reached faster.

Payne et al., 2013

Proposed mechanism



a) PS2NTF has no effect channel gating but blo Ca^{2+} inhibition of the R channel at high cytoso Ca^{2+} concentrations.

b) Significantly elevated cytosolic Ca^{2+} concentrations lead to eventual binding of Ca at the low affinity inhibitory site, closing t channel and resulting i an overall higher cytosolic Ca^{2+} concentration.

Payne et al., 2013

Presenilins in “healthy” aging

- Aged wild-type C57/B6 mice
- 6 months vs. 24 months

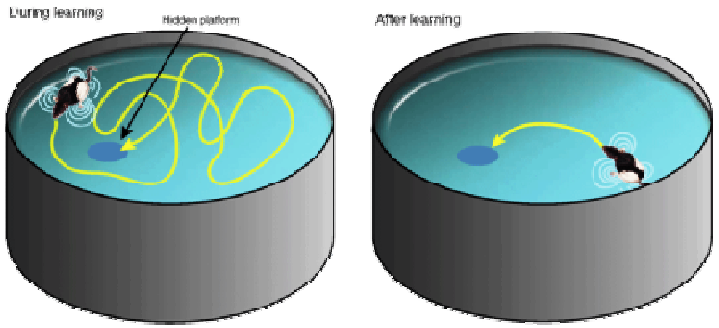


- **Advantages:**
  - Established non-genetic, inbred model
  - Closely mimics human condition
  - Many transgenic strains are based on B6 background
  - Mild phenotypes compared with genetic models

- **Experimental approach:**
  - Behavioral characterization
  - Quantification of Ca^{2+} signaling pathways
  - Correlation between Ca^{2+} signaling molecules and behavioral phenotypes

Behavioral paradigms

- **Water maze test**



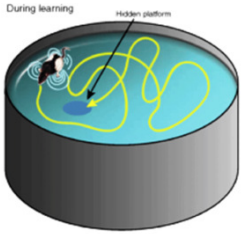
- Assess spatial learning and memory
- Areas involved: cortical
- Measures: speed, latency, pathlength
- **Learning Index**

- **Bridge walking test**



- Assesses motor function and fine tuning
- Areas involved: cerebellum
- Measures: Latency to Fall (LTF); time limit: 60 sec
- **Latency to Fall (LTF)**

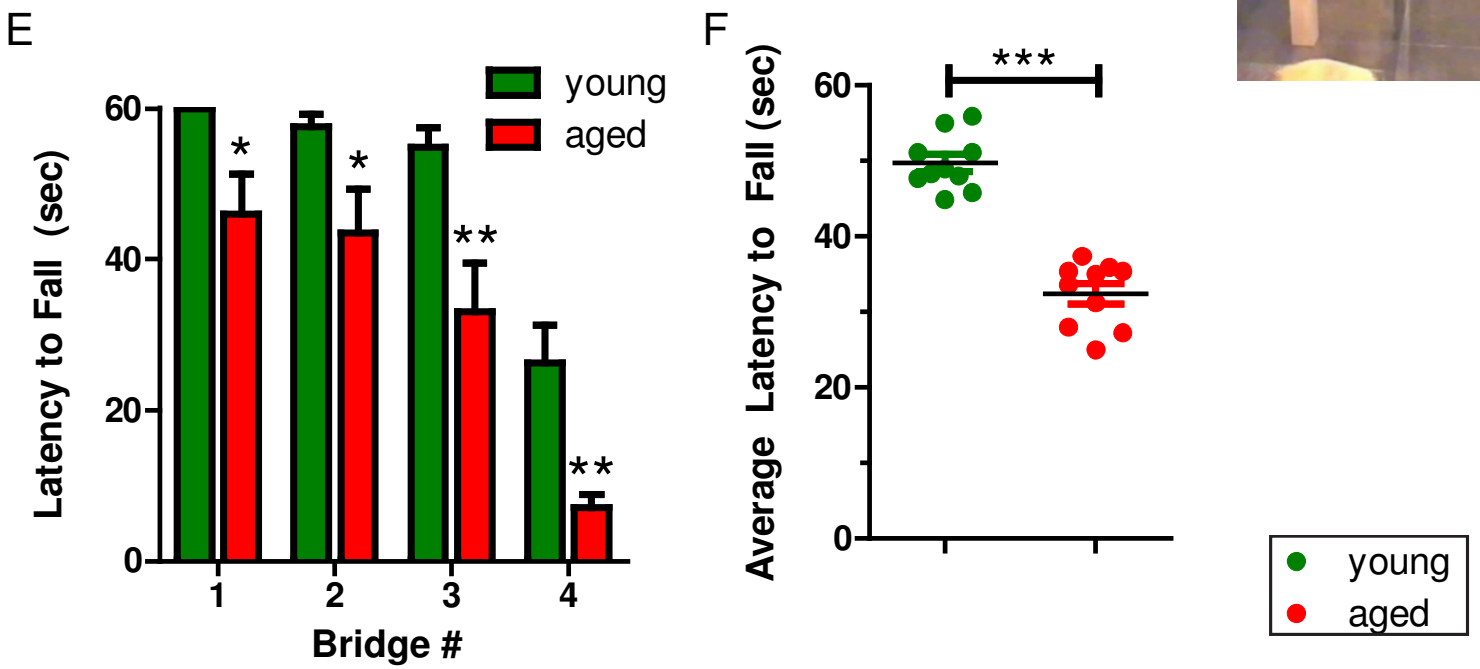
Impaired spatial learning & memory with age



Kaja et al., 2013; Kaja et al., *in press*

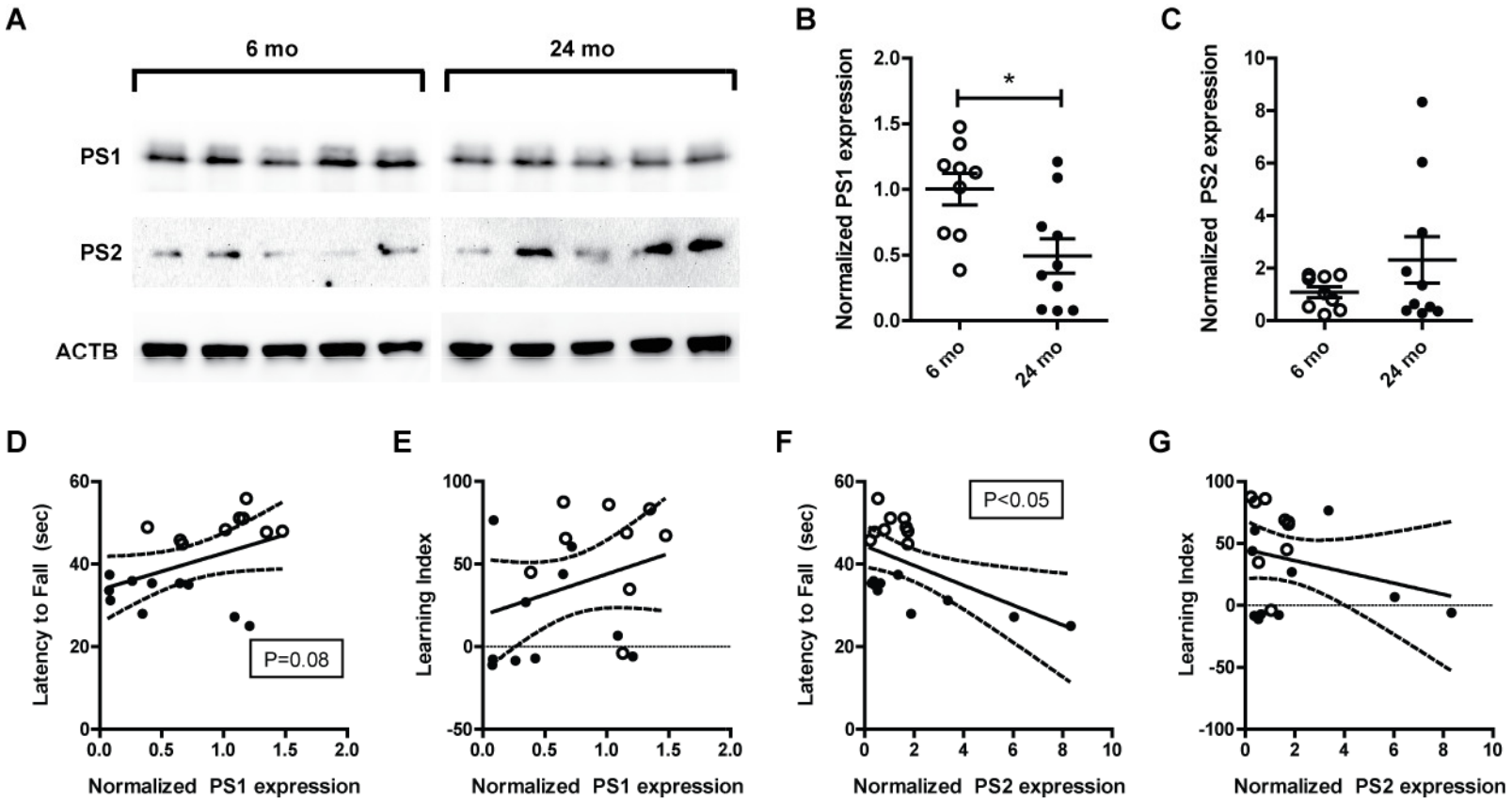
Impaired motor function with age





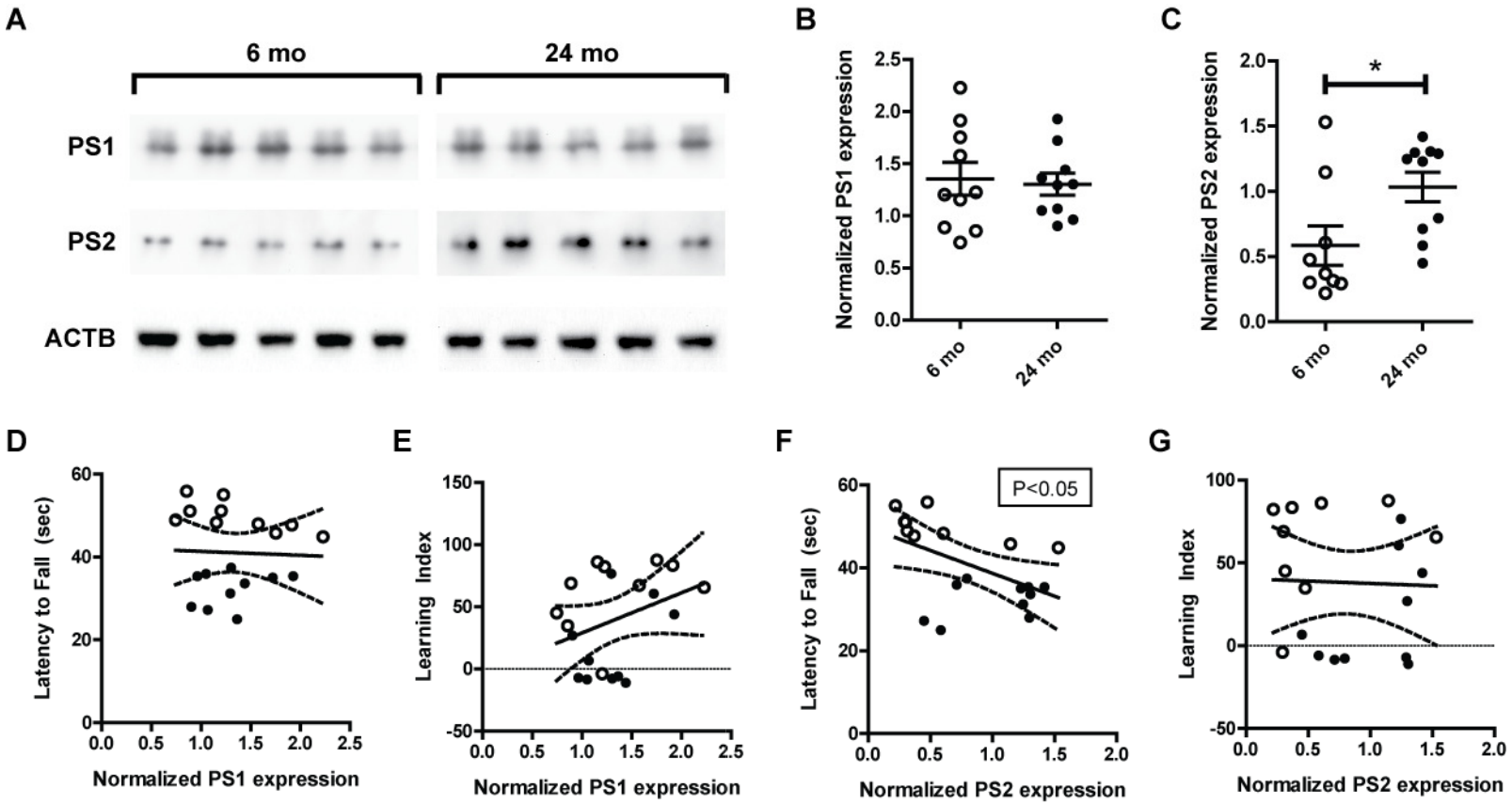
Kaja et al., 2013; Kaja et al., *in press*

Increased in PS2 in aged cerebellum



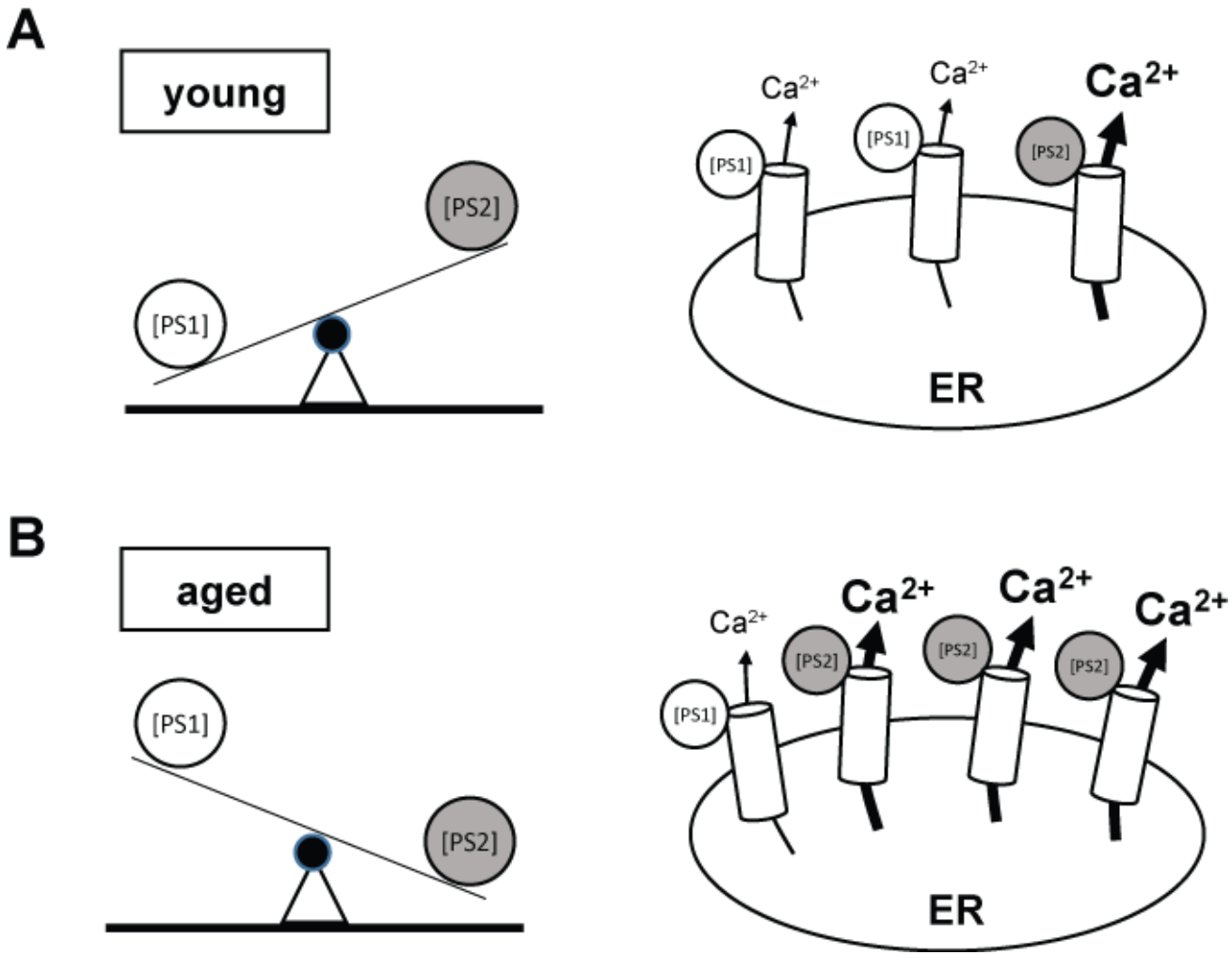
Kaja et al., *in press*

Increased PS levels in aged forebrain



Kaja et al., *in press*

Proposed mechanism



Kaja et al., *in press*

Conclusions

- Presenilins are potent modulators of intracellular RyR calcium channels
  - The N-terminal fragment of PS increases RyR-mediated calcium release through a direct mechanism

- The ratio of PS1 to PS2 is decreased in the aging brain
  - Increased PS2 levels correlate with motor function deficits and cognitive decline

➢ PS2 likely contributes to AD pathogenesis when increased cytosolic calcium concentrations are present.

➢ Our data supports a role of PS proteins as part of both the calcium hypothesis and the Aβ hypothesis of AD.

➢ PS proteins represent novel drug targets for neuroprotection and modulation of the intracellular calcium concentration.

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