

# **Role of Inflammation in peri-illness stress: potential targets/pathways in delirium**

# Disclosures

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- 5R01AG033679 (Dugan), NIH 1R01EB012284 - 01 (Gropler; Dugan Co-Inv) PET Imaging of Myocardial Oxidative Stress in T2DM,
- DP3DDL094352 (Sharma; Dugan Co-Inv) Novel Paradigms in Diabetic Complications

## Other financial relationships:

- Consulting (TBP, Inc.) Development of fullerene therapeutics for Parkinson's

**Conflicts of interest:** None

# Delirium and schizophrenia: parallels which may be informative

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Both have positive and negative signs and symptomatology:

Psychosis

Paranoia

Delusions

Disordered thinking

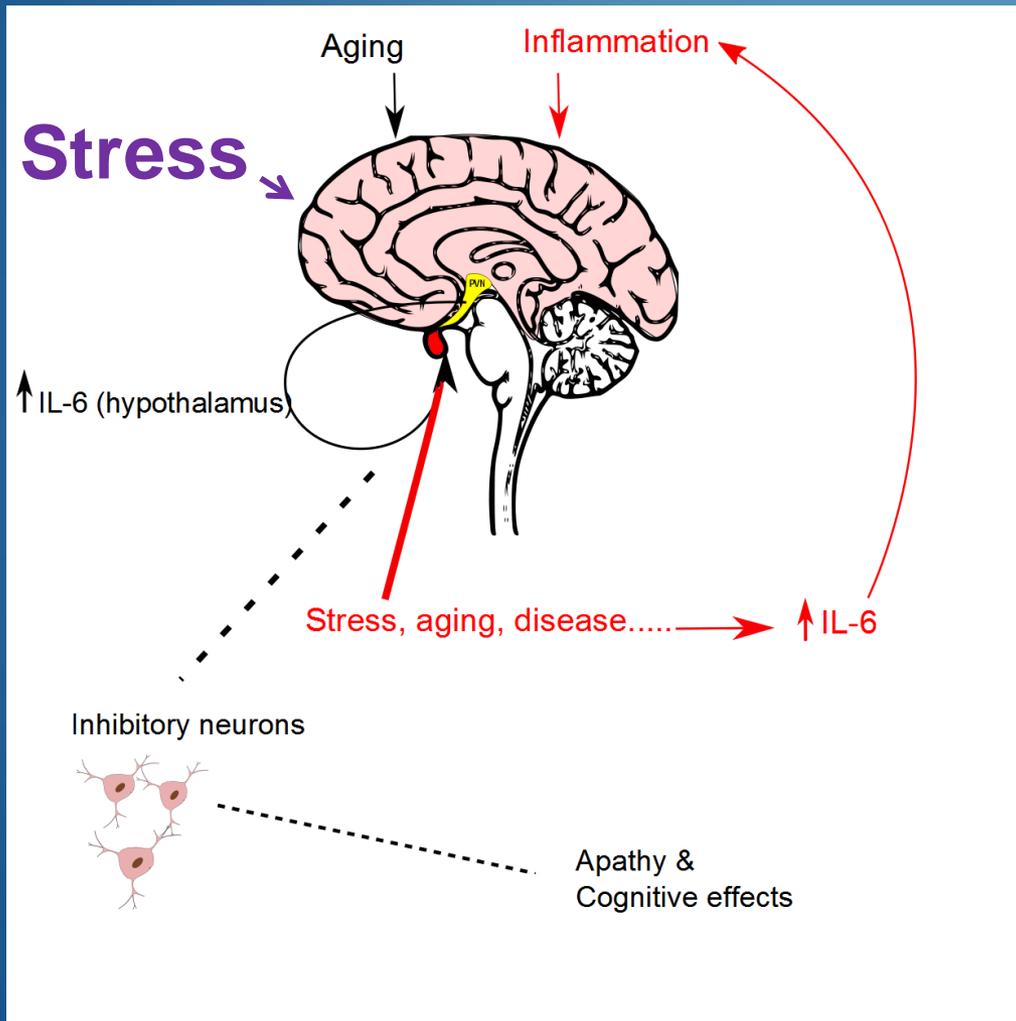
Agitation (but like delirium, schizophrenia can also produce apathy/hypoactivity in some patients)

**Schizophrenia:** developmental (inflammatory?) insult produces vulnerability to second stress

**Delirium:** environmental (and inflammatory?) insult produces vulnerability to second stress

Both may also involve dysfunction of inhibitory circuits in brain to produce multi-neurotransmitter system deficits

# Proposed interactions between inflammation, aging and risk of delirium

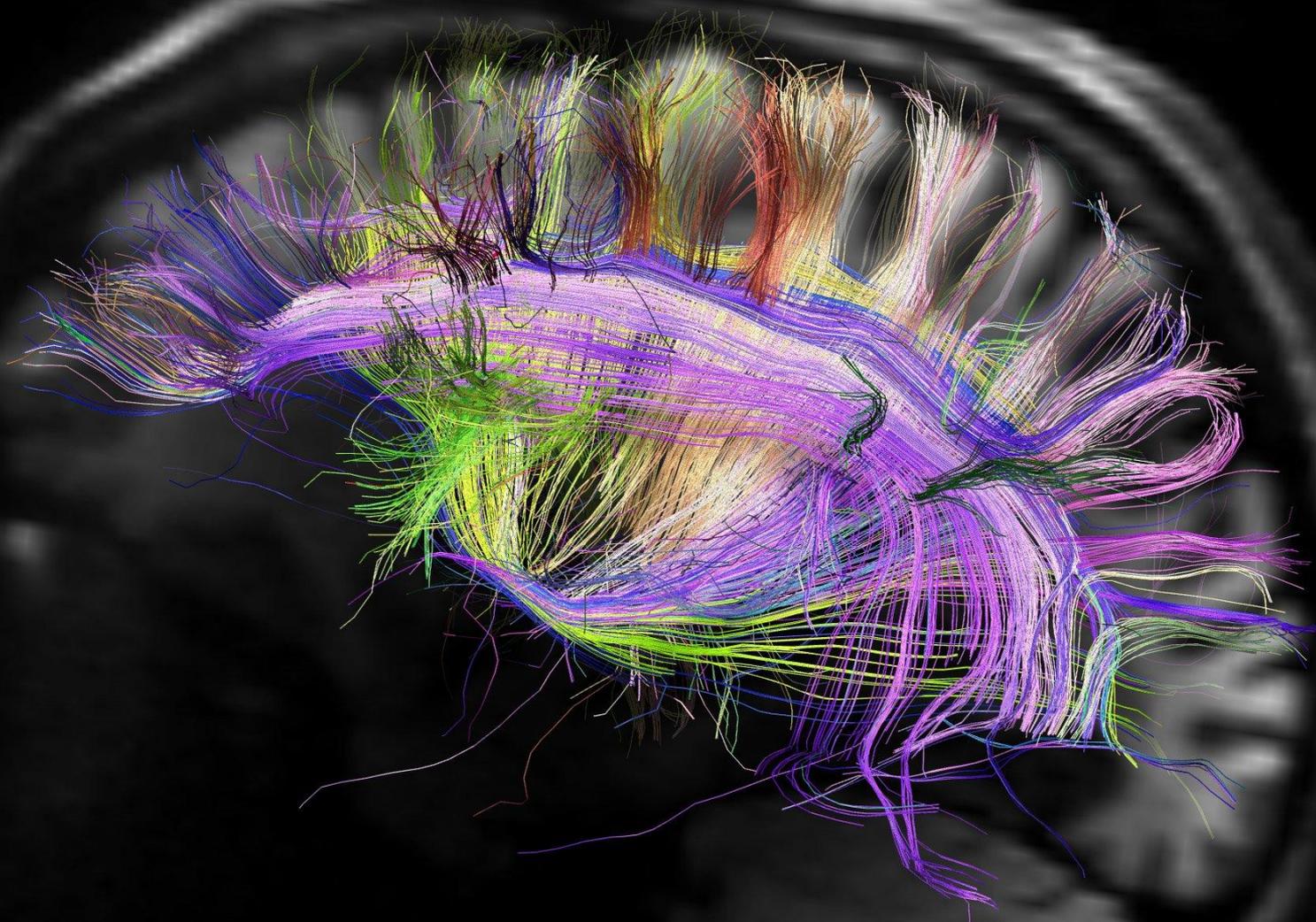


- IL-6 proposed as "Gerontologist's cytokine" by William Ershler, 1993

- Circulating IL-6 is consistently associated with diabetes, obesity, OSA, atherosclerosis, HTN, aging, Alzheimers, Parkinsons, depression, psychosis, schizophrenia

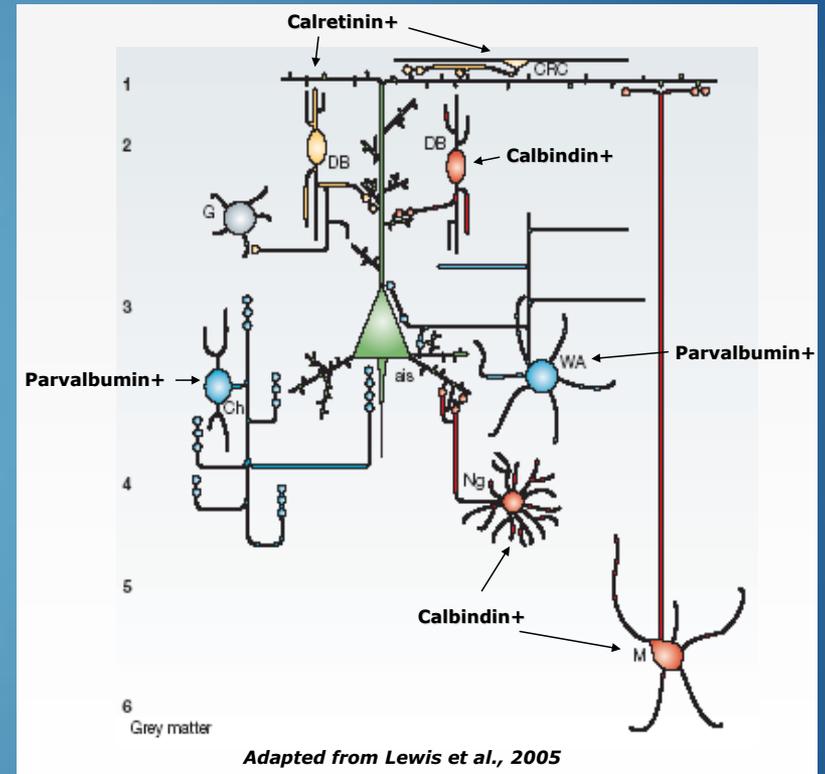
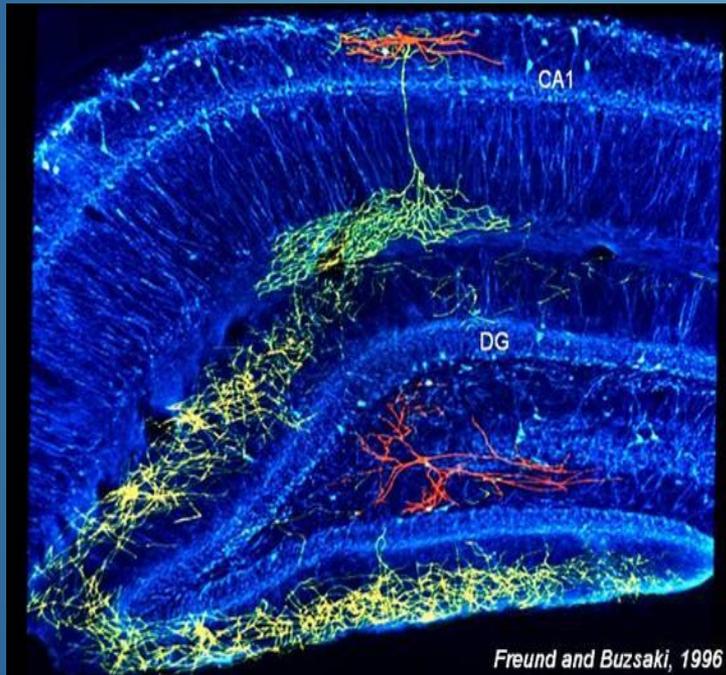
- IL-6 levels predict cognitive deficits in all these diseases, and even in healthy subjects

- IL-6 directly mediates deficits in critical inhibitory neurons which are necessary for normal information processing and encoding, learning, memory, and attention.



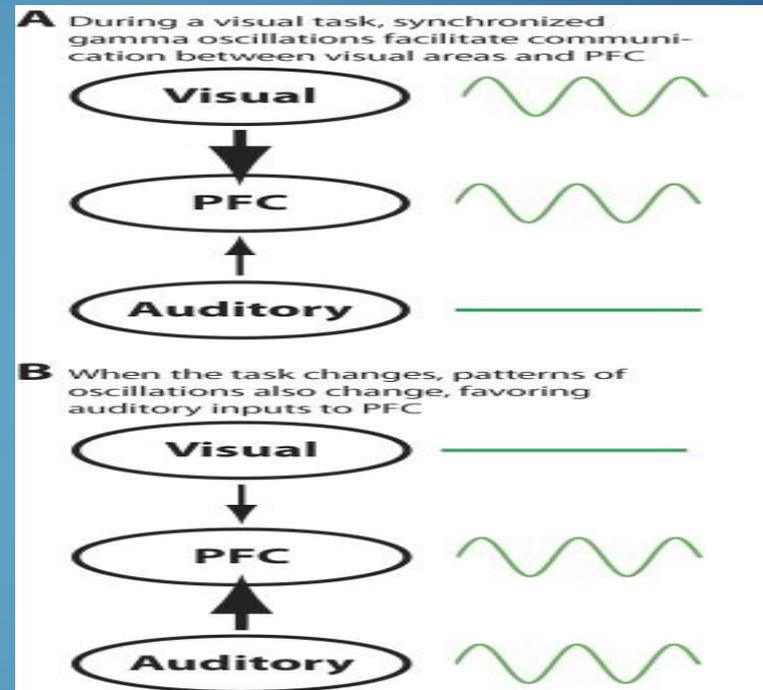
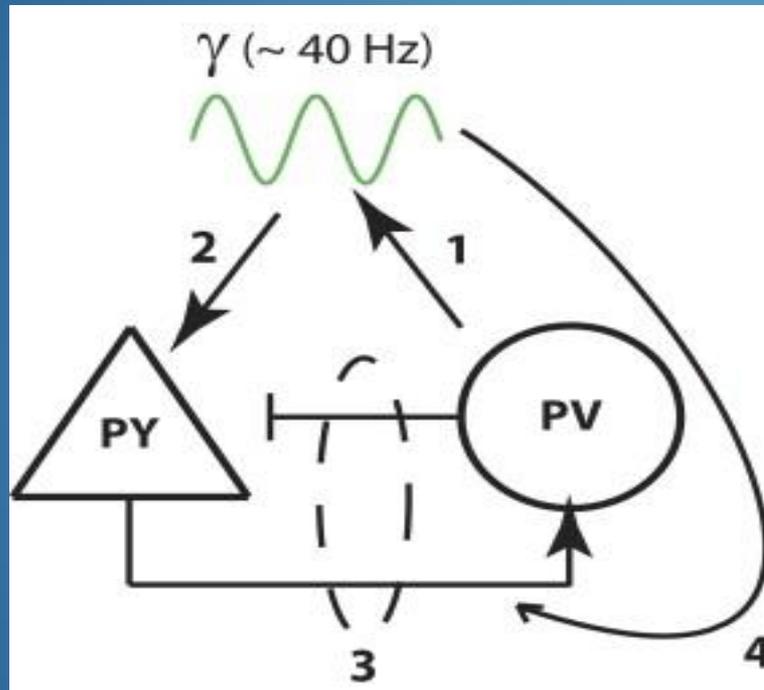
# Expected effects of inhibitory interneuron dysfunction

inhibitory axons = green  
inhibitory dendrites = red

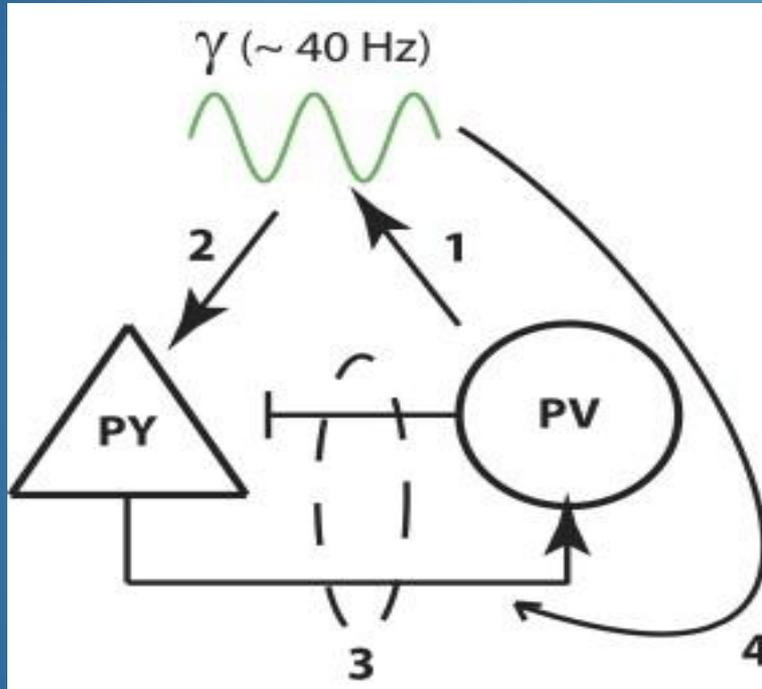


Inhibitory PV-interneurons regulate  
excitatory neurotransmission

# PV Interneurons control the Gamma oscillations needed for information processing and encoding

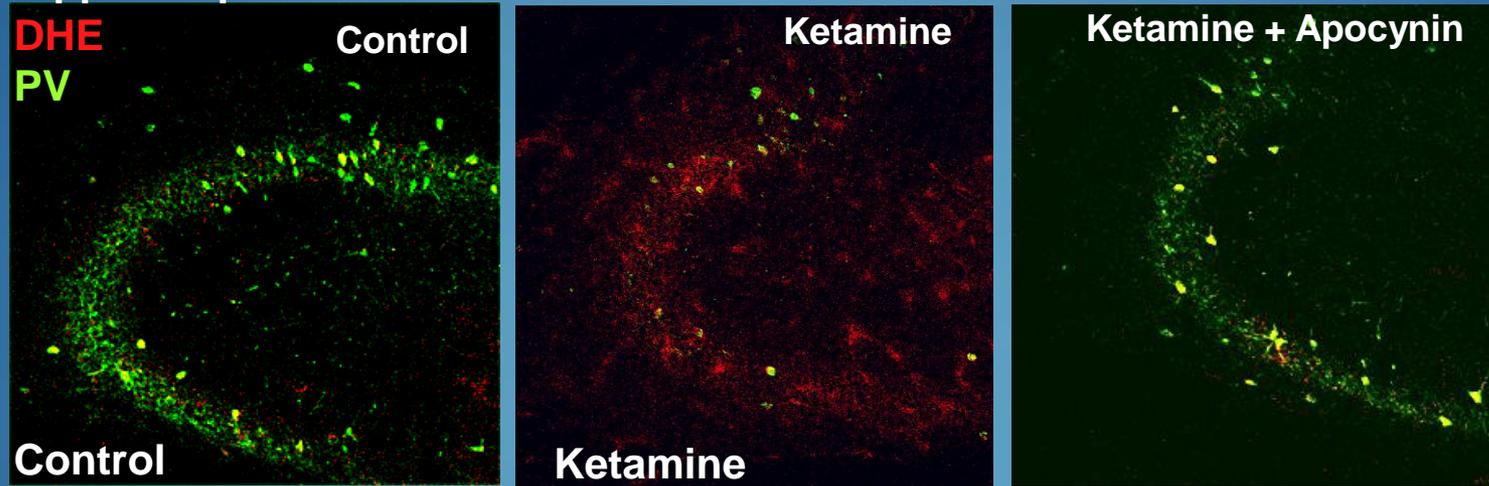


# PV Interneurons control the Gamma oscillations needed for information processing and encoding

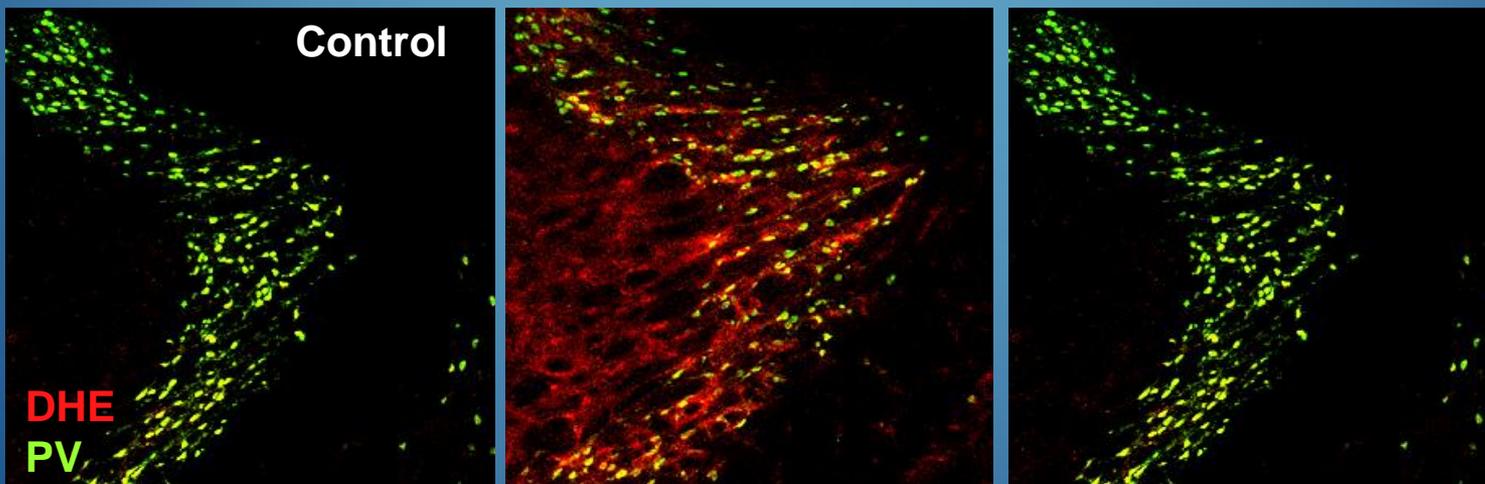


# Brain Inflammation Produced by IL-6 and Nox2: Subanesthetic Ketamine Model of Schizophrenia

## Hippocampus

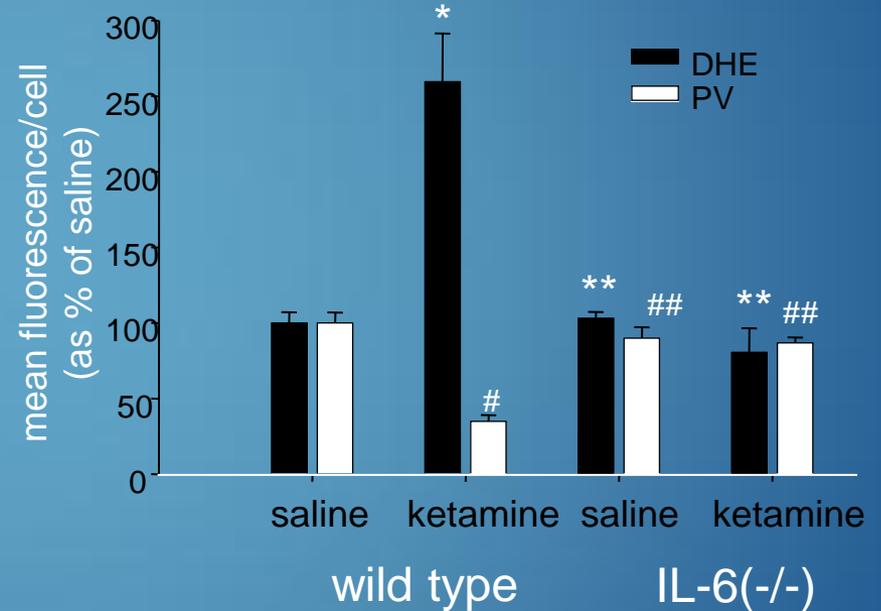
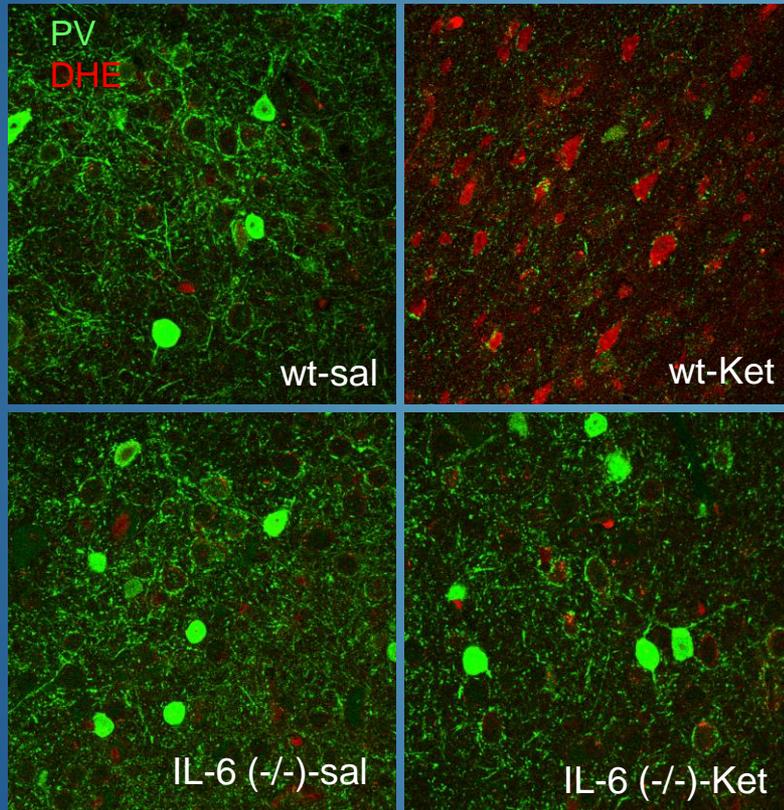


## Reticular Nucleus of the Thalamus



(Behrens, Dugan et al. Science, 2007)

# IL-6 is responsible for Nox2-dependent inflammatory superoxide production in the ketamine model *in vivo*

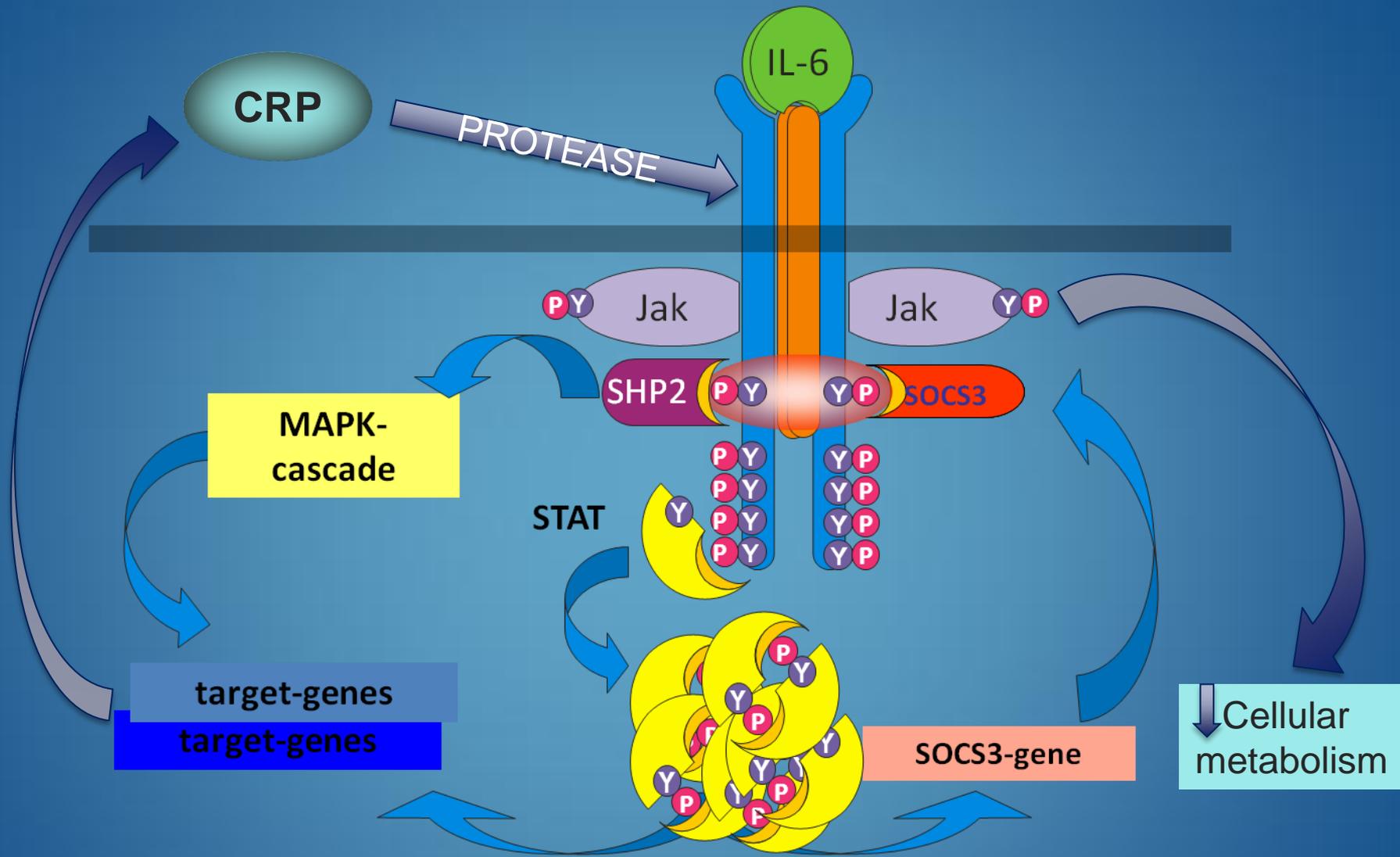


(Behrens, Dugan et al. *J. Neurosci*, 2008)

# Association of IL-6 and nervous system aging/dysfunction

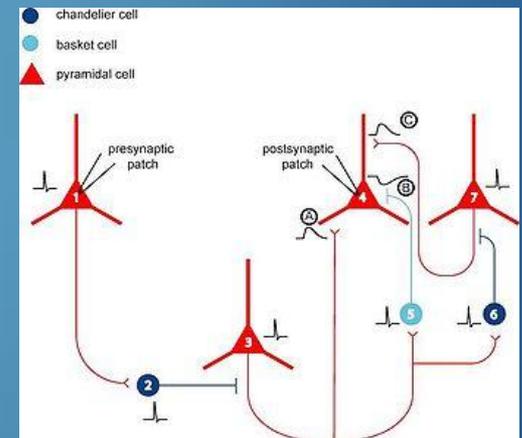
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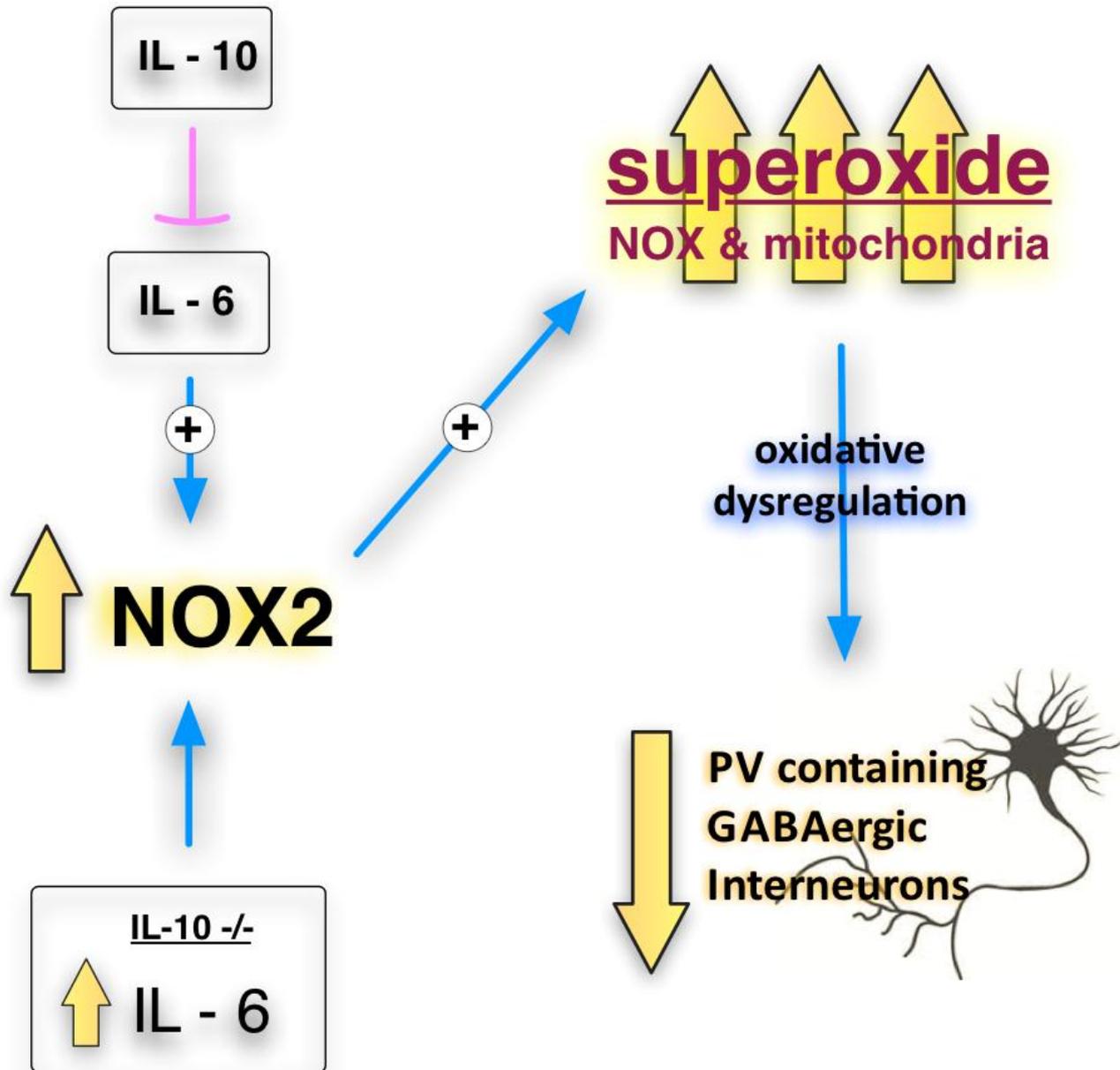
- Low concentrations needed for LTP, memory consolidation
- IL-6 mediates “sickness behavior” – cognitive impairment during infection/injury
- IL-6 is significantly associated with cognitive deficits across disease states, regardless of disease process
- IL-6 most strongly associated with cognitive impairment across diseases, even in normal healthy older patients
- Age-related changes in neural volume and microstructure associated with interleukin-6 are ameliorated by a calorie-restricted diet in old rhesus monkeys. *Willette 2010*



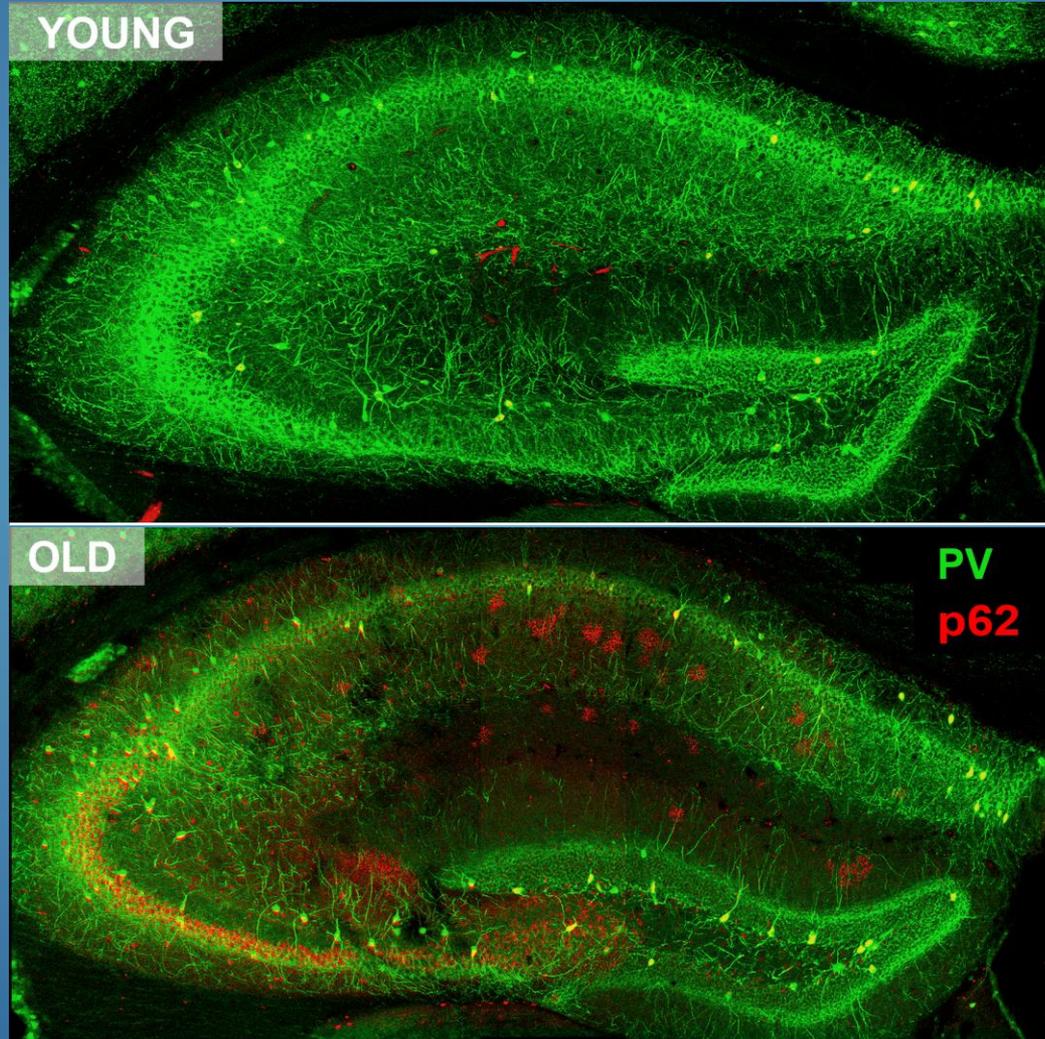
# Clinical evidence that inhibitory neurons are dysfunctional: “benzodiazepine challenge” study

- Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. **Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients.** *Anesthesiology*. 2006 Jan;104(1):21-6. *Lorazepam, but not fentanyl, morphine, and propofol was an independent risk factor for ICU transition to delirium.*
- Stonnington et al (2009) **Double-blind crossover study of the cognitive effects of lorazepam in healthy apolipoprotein E (APOE)-epsilon4 carriers.** *J Clin Psychiatry* 70:1379-1384
- Pomara et al. 2005) **Apolipoprotein E epsilon4 allele and lorazepam effects on memory in high-functioning older adults.** *Arch Gen Psychiatry* 62:209-216.





# Aging alone induces injury to inhibitory neural circuitry



# Inflammation, Aging, and Delirium

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- Increased circulating markers of inflammation predict shorter lifespan and all-cause mortality in multiple studies.
- *Low* CRP, IL-6, TNF $\alpha$  and IL-1 $\beta$  are prevalent in long-lived populations across multiple studies and populations.
- Inflammatory markers are increased in patients with chronic disease such as DM, atherosclerosis, obesity, HTN, OSA, a sedentary lifestyle, depression, and with aging itself.
- The number of individuals with increased inflammatory cytokines >80% of those over 65. IL-6 most significant in multiple studies.
- Aberrant inflammatory signaling suggested to mediate significant component of mammalian aging (Walston, Guralnik, others)

# Factors Which *Increase* IL-6

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- Sedentary Lifestyle
- Obesity
- Lack of Sleep
- Depression
- Vitamin D Deficiency
- Genetics
- Age
- Psychological stress
- Non-steroidal anti-inflammatory medications

## Factors Which *Decrease* IL-6

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- Exercise (especially weight-bearing)
- Maintaining *Appropriate* Weight
- Good Sleep Hygiene
- Psychological Coping Skills
- Diet with Limited Red Meat
- Wine (in moderation) – the French Paradox?

# Conclusions and Future Directions

1. Delirium may be an acute injury to the brain, so prevention may be key
2. Studies which carefully look at CNS inflammatory signaling and at the function of various neurotransmitter systems in delirium needed: may need new imaging tools.
3. Diurnal variation in cytokine levels and effects need to be factored into studies.
4. Development of animal models which model the anatomical, biochemical and behavioral components of delirium are needed\*\*\*\*
5. Practice change to reduce known risk factors....infection, sleep deprivation, anesthesia, benzodiazepine use and withdrawal, lack of environmental cues to assist those with sensory and/or cognitive impairment, inadequate pain control, urinary retention, and psychosocial stress.

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