INTRANASAL INSULIN AND ALZHEIMER'S DISEASE:

Diversifying The AD Therapeutic Portfolio

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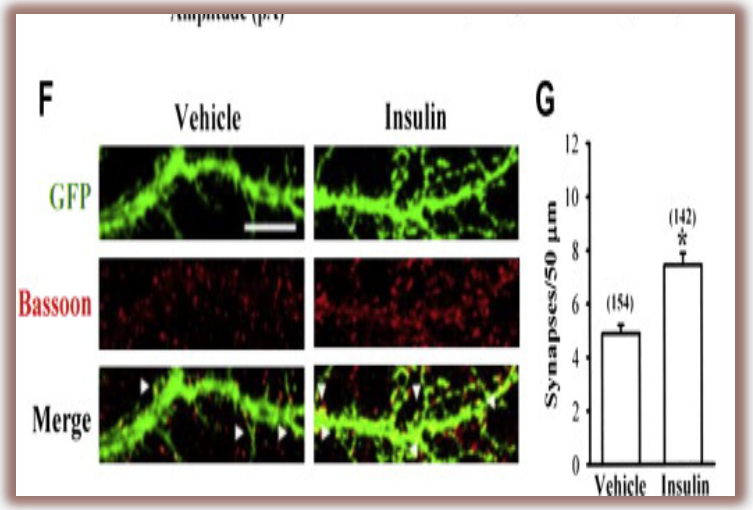
Overview

- Insulin plays multi-faceted role in normal brain function and cognition
- Dysregulation of insulin (insulin resistance) increases risk for pathological brain aging: cognitive impairment, AD & other neurodegenerative diseases
- Potential mechanisms of increased risk
- Targeting brain insulin dysregulation with intranasal insulin as a therapeutic or prevention strategy

Insulin's Multi-faceted Role in Normal Brain

- **Dense receptor distributions in hippocampus, entorhinal cortex, frontal cortex, choroid plexus** [Apelt et al. 2001]
- **Insulin readily crosses the BBB**
  - Transport reduced with chronic hyperinsulinemia, obesity
  - Transport modulated by triglycerides, systemic inflammation [Banks et al. 2014]
- **Insulin production within brain**
  - GABA-ergic neurogliaform cells provide insulin in cortical microcircuits
  - Modulate memory consolidation, slow wave sleep, tonic neuronal excitability
- **Insulin modulates GLUT4/glucose uptake in HC, promotes dendritic spine & synapse formation via PI3K/Akt/motor pathways**
- **Insulin/IGF play important role in neural stem cell regulation, injury repair** [Ziegler et al. 2014]



Lee et al. 2011

Insulin Resistance and AD

- **Insulin resistance**
  - **Inability of insulin to invoke normal signaling in target tissue**
  - **Insulin resistance and associated conditions (prediabetes, T2D, HTN, CVD) AD risk factors** [Ott et al. 1999; Luchsinger et al. 2004]
  - **Caused by poor diet, physical inactivity, obesity, sleep disruption, stress, genetic vulnerability**
  - **Associated with high peripheral insulin and reduced transport across BBB, resulting in reduced brain insulin levels/activity**
  - **Molecular signature: Serine phosphorylation of IRS-1**

- **Pathological processes linking insulin resistance and AD**
  - **Reduced cerebral glucose metabolism**
  - **Increased synapse loss, cerebral/hippocampal atrophy**
  - **Aβ dysregulation, tau hyperphosphorylation**
  - **Vascular dysfunction, inflammation, dyslipidemia**

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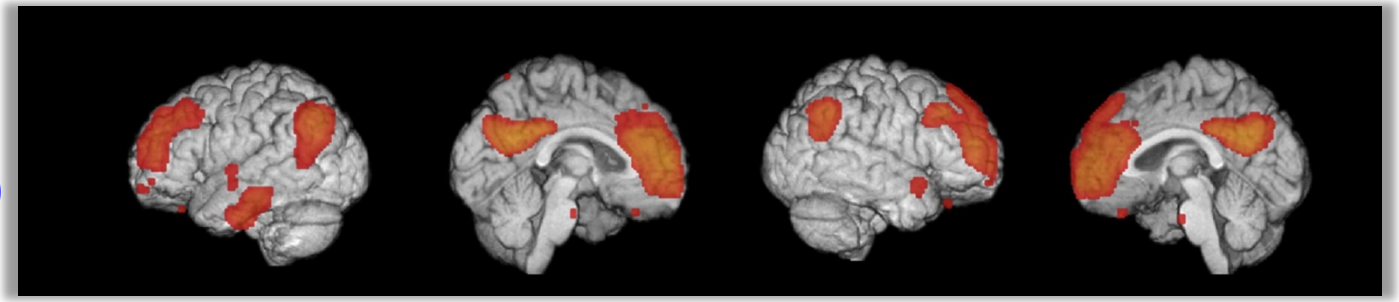
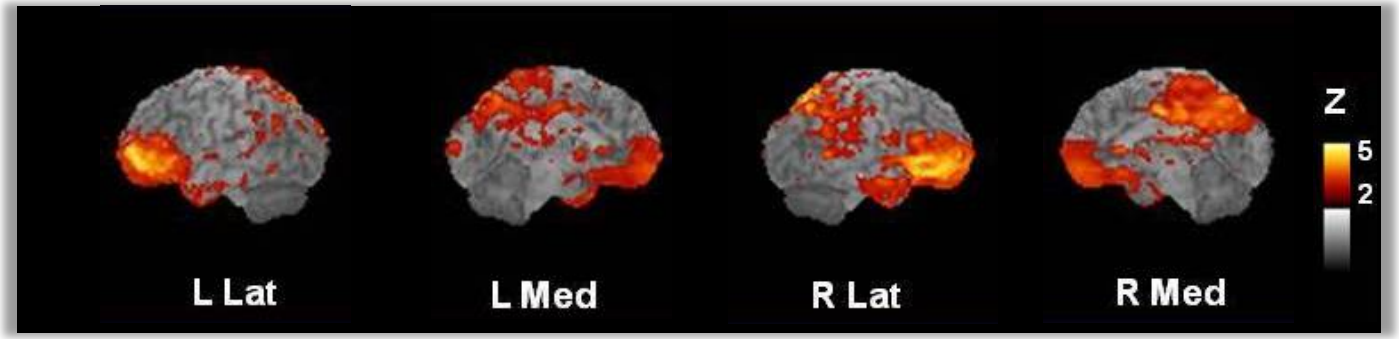
Pathological Links: Insulin Resistance is Associated with AD-Like Cerebral Hypometabolism

AD Pattern
Langbaum et al. 2009

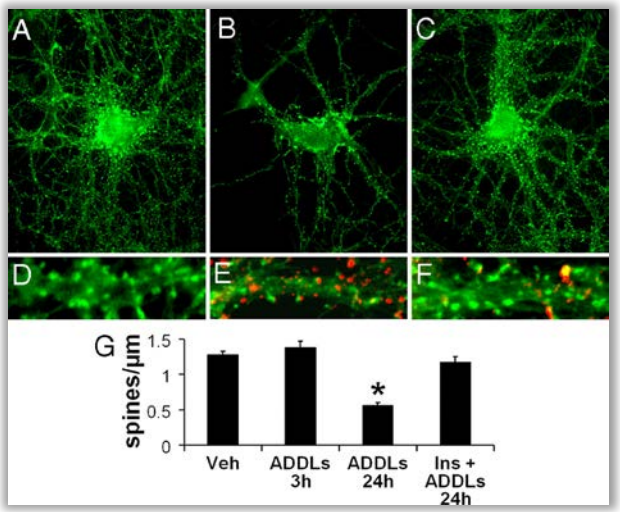


Insulin Resistant Pattern
Baker et al. 2010



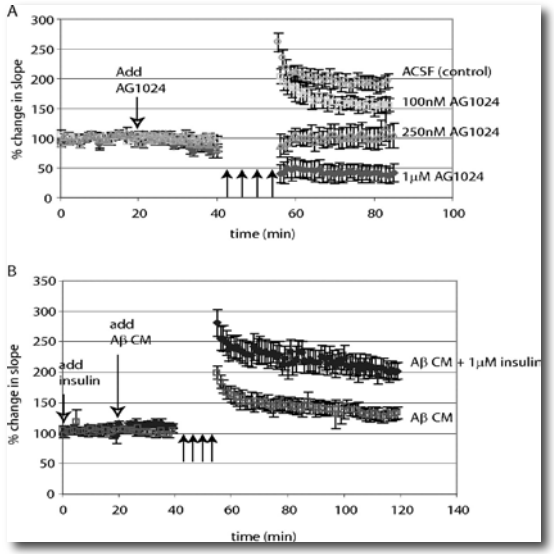
- Regions in which greater insulin resistance (HOMA-IR) correlates with hypometabolism in <u>cognitively normal</u> insulin-resistant older adults

Pathological Links: Insulin & Aβ Interactions



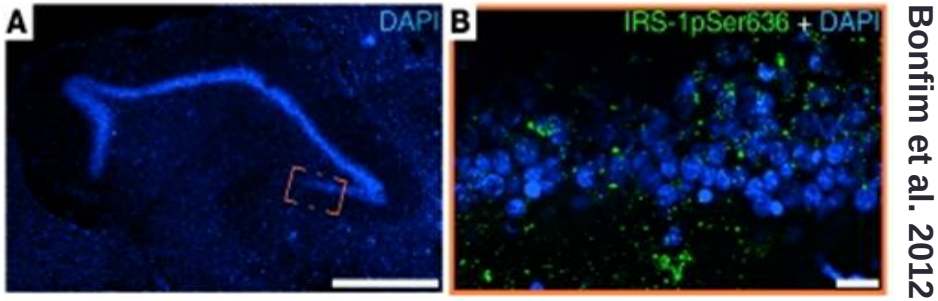
De Felice et al. 2009

- Insulin blocks Aβ-induced synapse loss



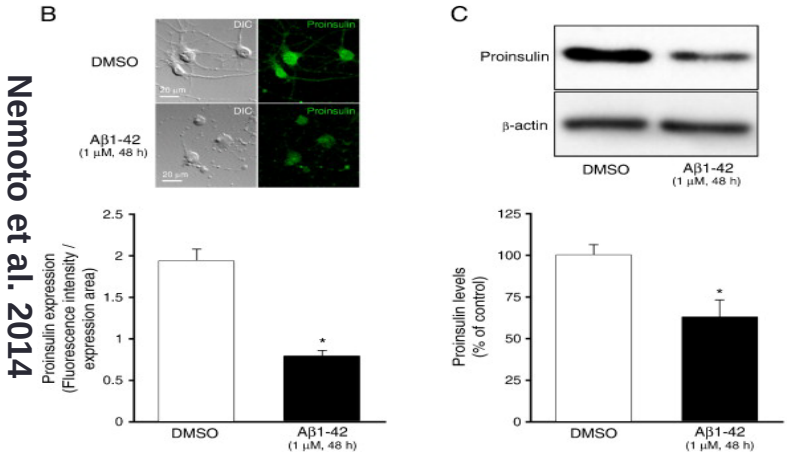
Townsend et al. 2007

- Insulin receptor inhibition disrupts LTP in HC slices
- Inhibitory effect of Aβ-rich CM on LTP rescue with insulin



Bonfim et al. 2012

- ICV Aβ causes HC insulin resistance (IRS-1pSer) in non-human primates

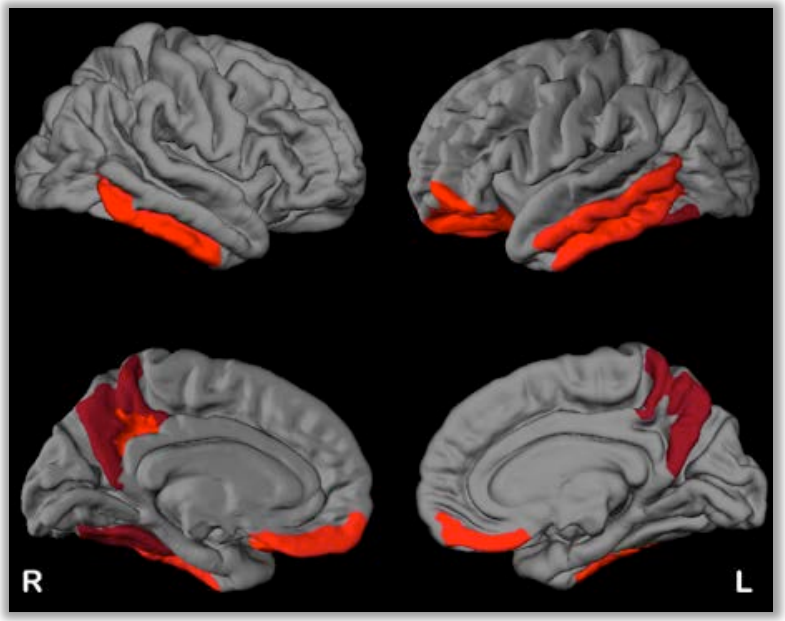


Nemoto et al. 2014

- Aβ reduces insulin secretion/proinsulin expression in hippocampal neurons

Insulin Resistance is Associated with Greater Brain Amyloid Deposition in Middle Age

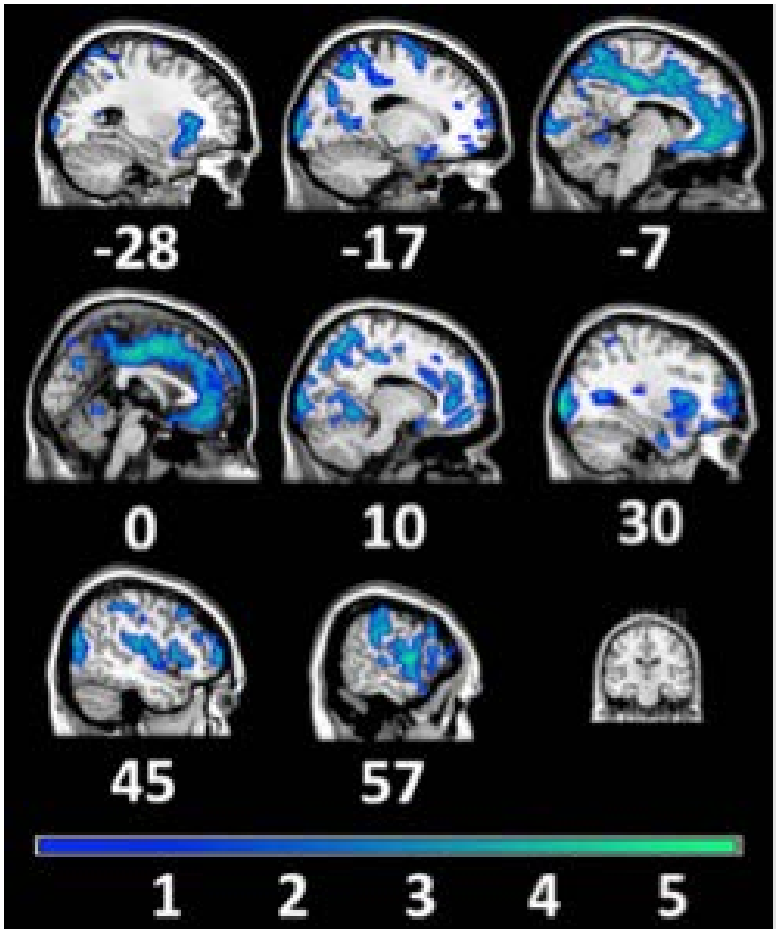
Demographics	Low HOMA-IR	High HOMA-IR
N	108	65
Age (years) mean ± SD	59.81 ± 5.54	60.75 ± 5.95
Gender (F/M)	82/26	39/26
APOE E4+/E4-	42/66	25/40
BMI (kg/m^2) mean ± SD	26.60 ± 4.6	30.93 ± 5.3
HOMA-IR	1.24 ± 0.4	3.86 ± 2.4



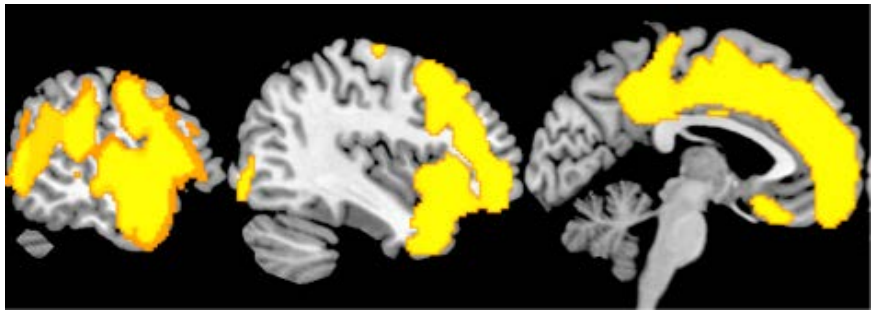
Adapted from
Willette et al. 2014

HOMA-IR Predicts Longitudinal Gray Matter Atrophy and Reduced CBF (pcASL) in Middle-Aged Adults

Gray matter reductions over 4 years (n=121) [Willette et al. 2012]

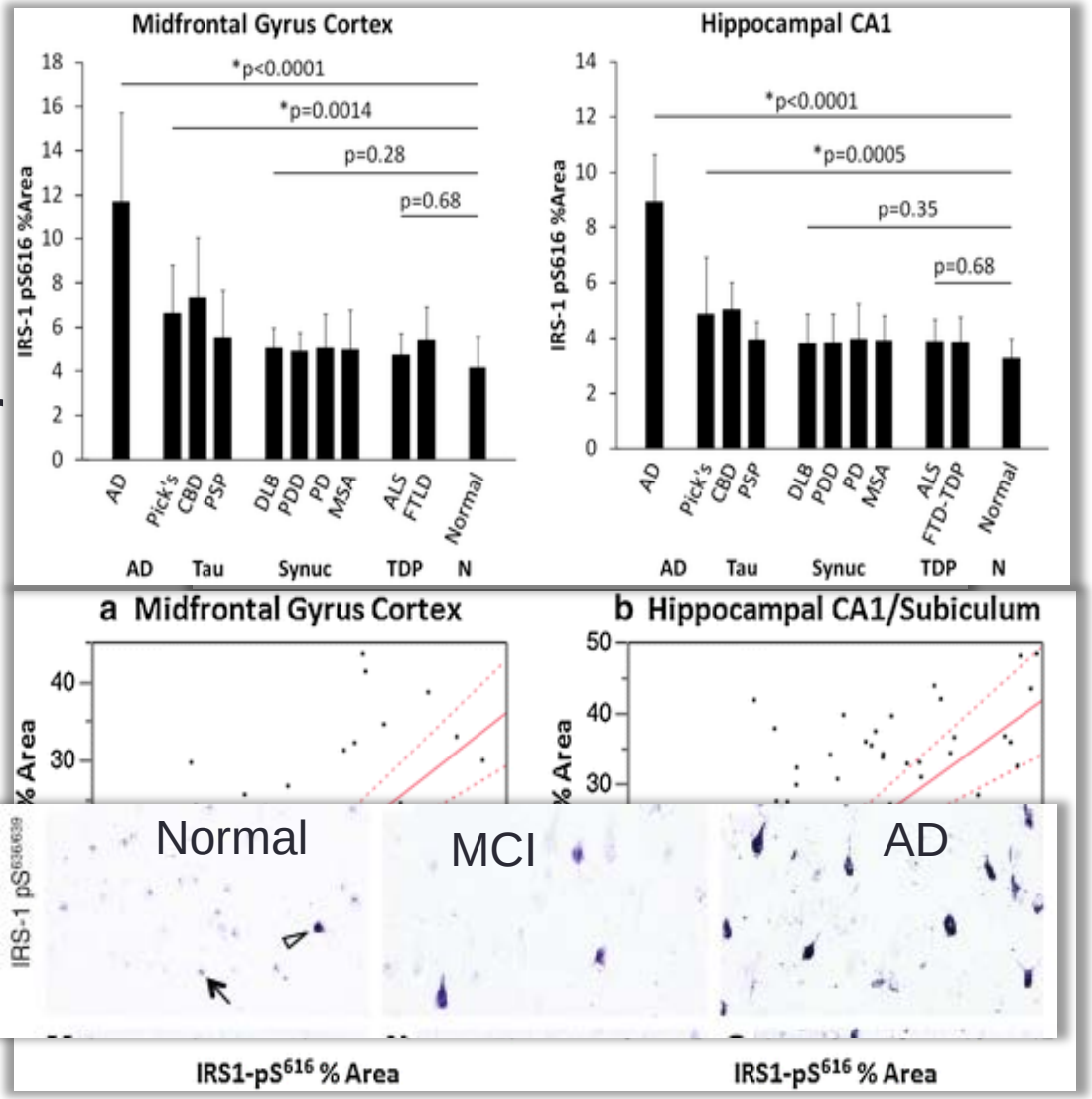


Regions of reduced CBF in middle-aged adults with insulin resistance (n=29) compared with non-insulin resistant adults (n=40)
[Birdsill et al. 2014]



CNS Insulin Level and Activity are Reduced in AD

- **Reduced CSF insulin levels in AD** [Craft et al. 98]
- **Insulin resistance marker IRS-1 pSer+ neurons increased in MCI and AD** [Talbot et al. 2013]
- **Increased (IRS-1 pSer) associated with PHF tau in MCI and AD** [Yarchoan et al. 2014]

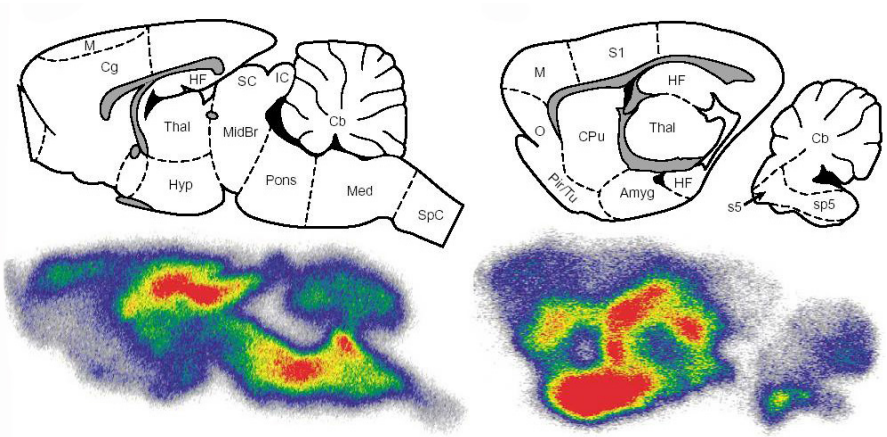


Pharmacologic Strategies to Address CNS Insulin Resistance or Deficiency in AD

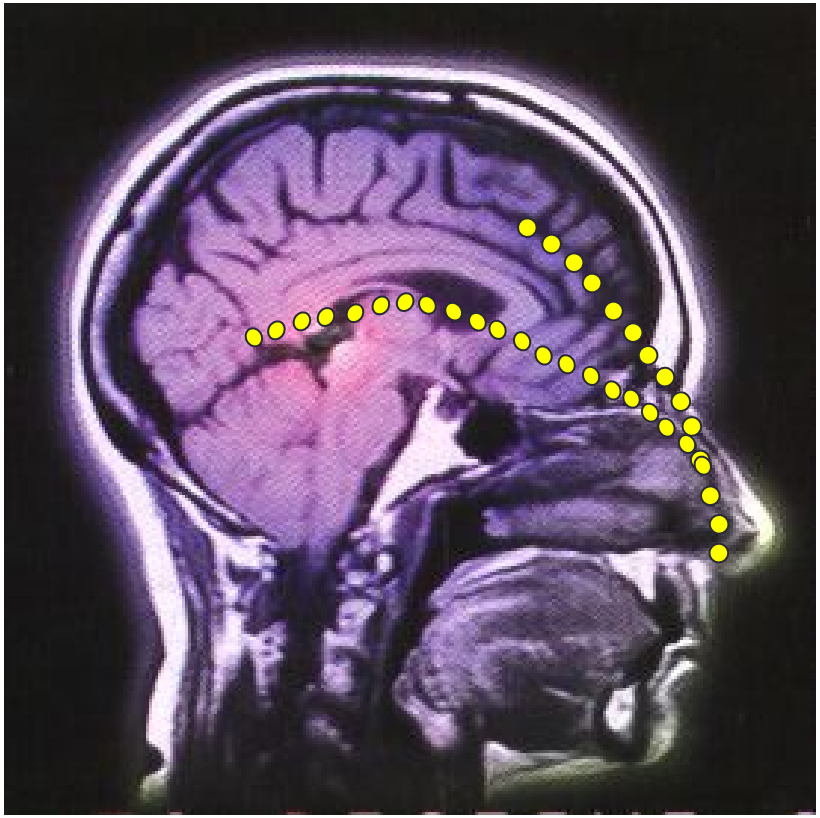
Intranasal insulin administration:

- **Increases CSF insulin & improves memory within 30 min in young, healthy adults without changing plasma glucose or** insulin [Born et al. 2002; Benedict et al. 2004]

- **Insulin-like peptide signal measurable in rat hippocampus, amygdala, frontal cortex 30 min after intranasal administration**
  [Thorne et al. 2004]



Pharmacologic Strategies: Intranasal Insulin

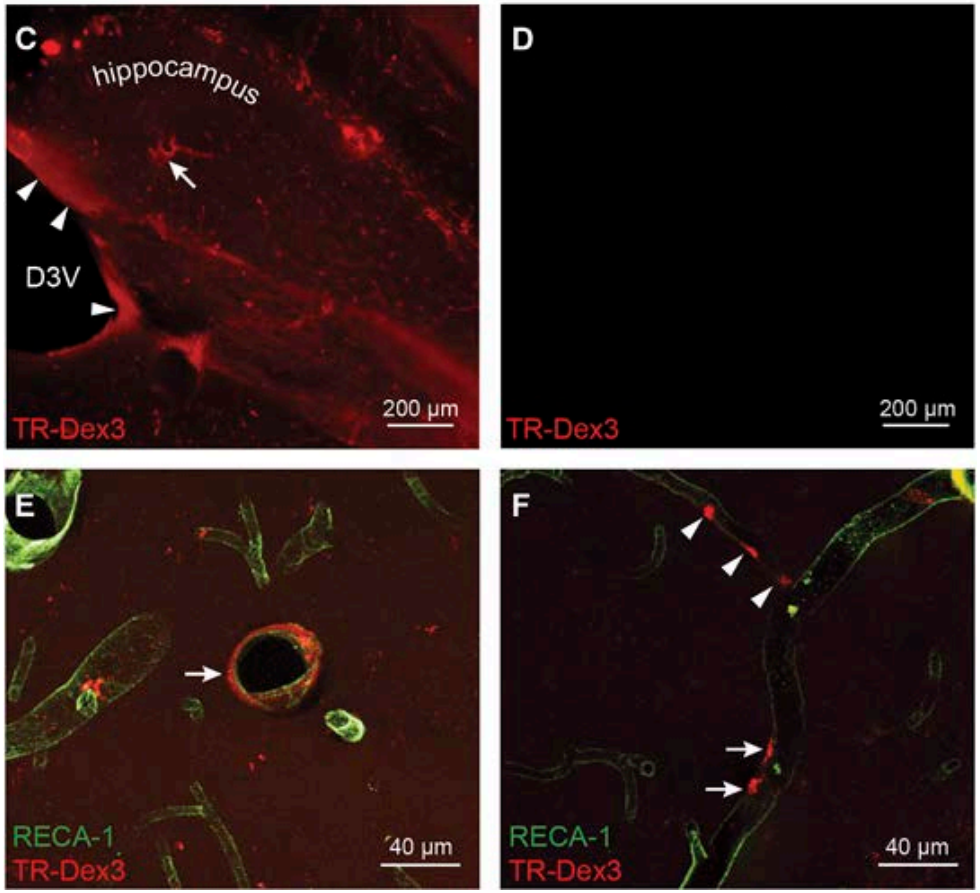


- Axonal transport through olfactory neurons, which require hours to reach brain
- Bulk flow along rostral (olfactory) or caudal (trigeminal) perivascular channels; agents reach brain in minutes [Thorne 2001]

Intranasally Administered Peptides Achieve Widespread Brain Access via Convection in Perivascular Spaces

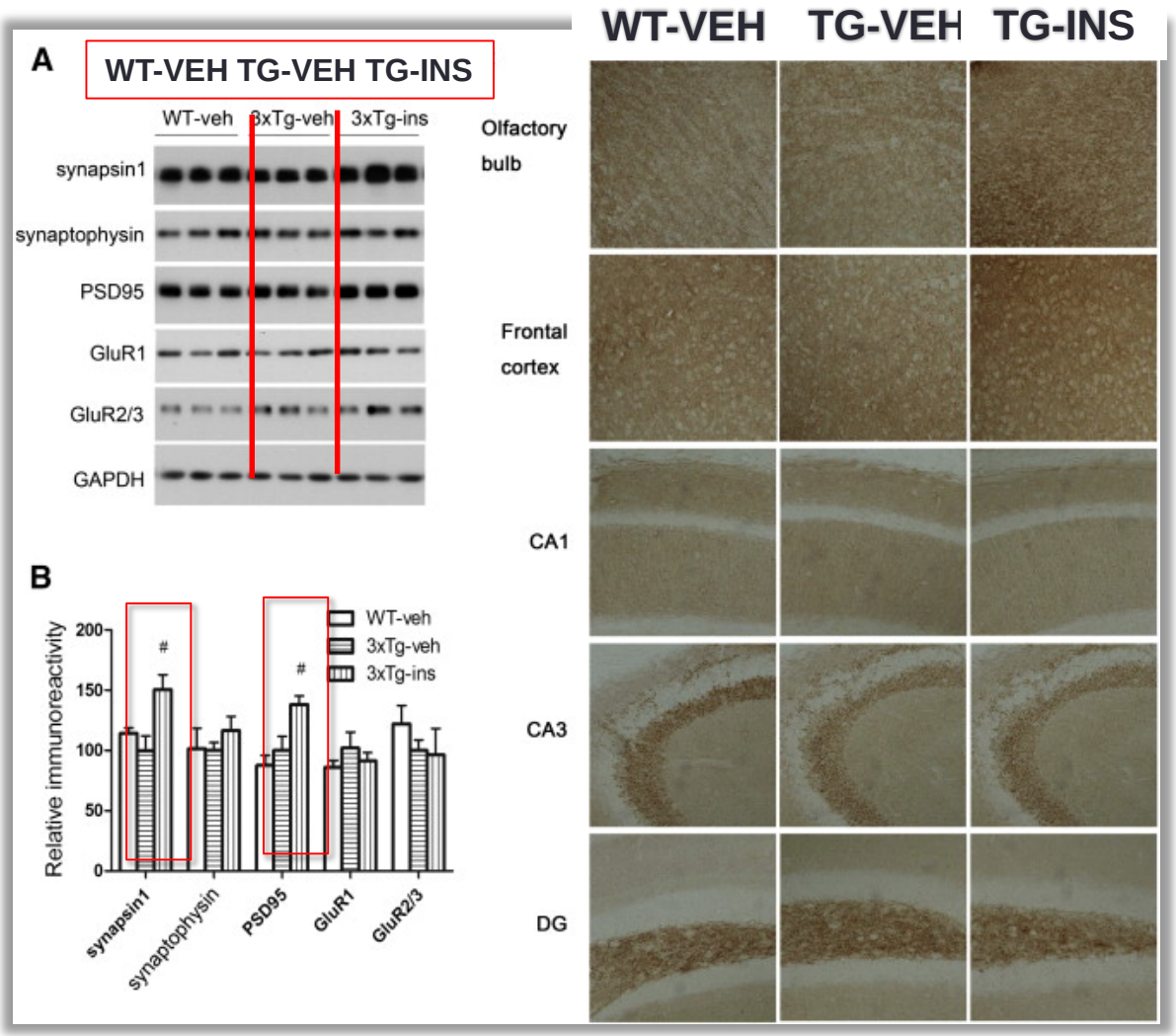
Texas Red-labeled dextran fluorescence 20 min after IN (L) or intra-arterial (R) administration

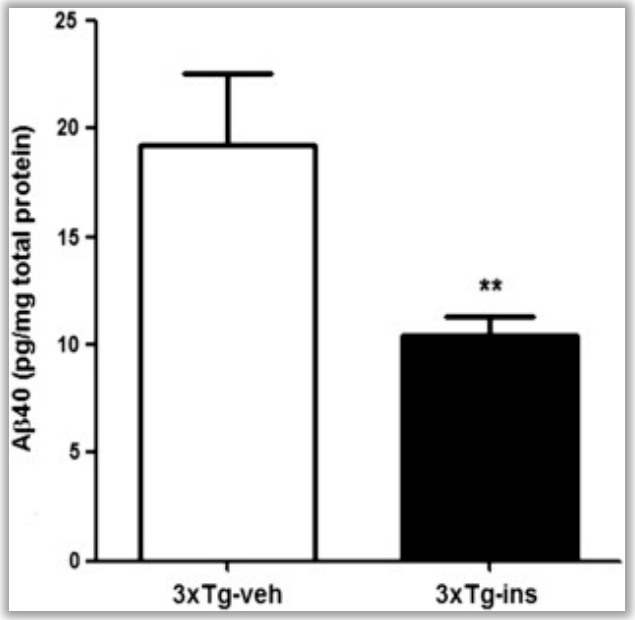
Fluorescence surrounding blood vessel in S1 (L) and in blood vessel and capillary branch in hippocampus (R)



Lochhead et al. 2015

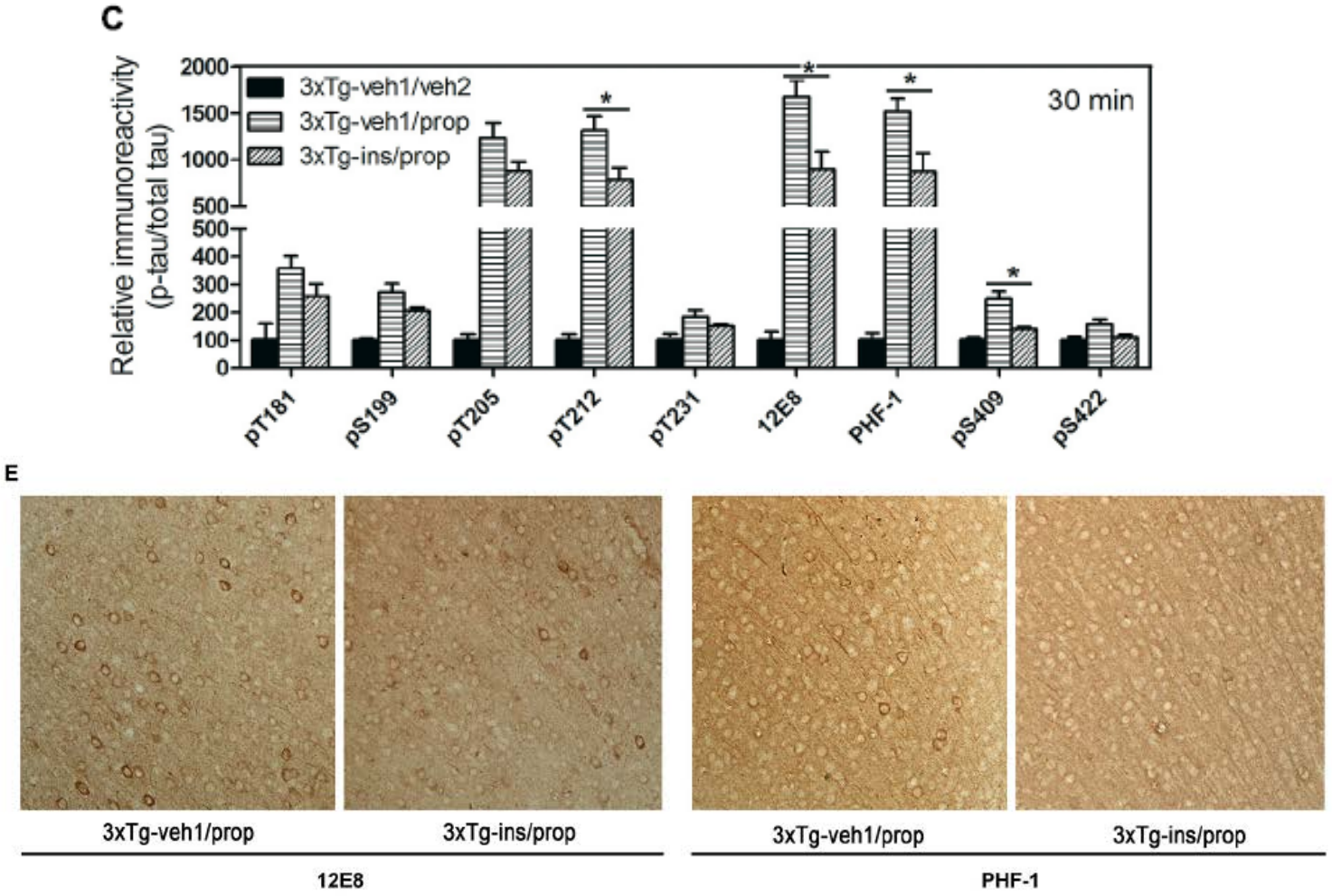
Pre-Clinical Evidence: INI Increases Synaptic Proteins & Lowers Aβ40 in 9 mo 3xTg-AD Mice





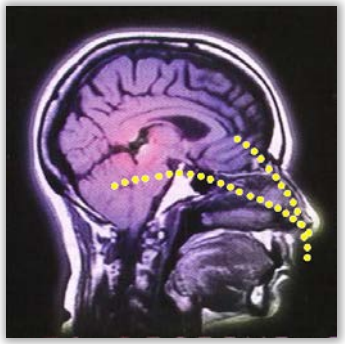
Chen et al. 2014

INI Reduces Tau Hyperphosphorylation in 9 mo 3xTg-AD Mice Treated with Propofol



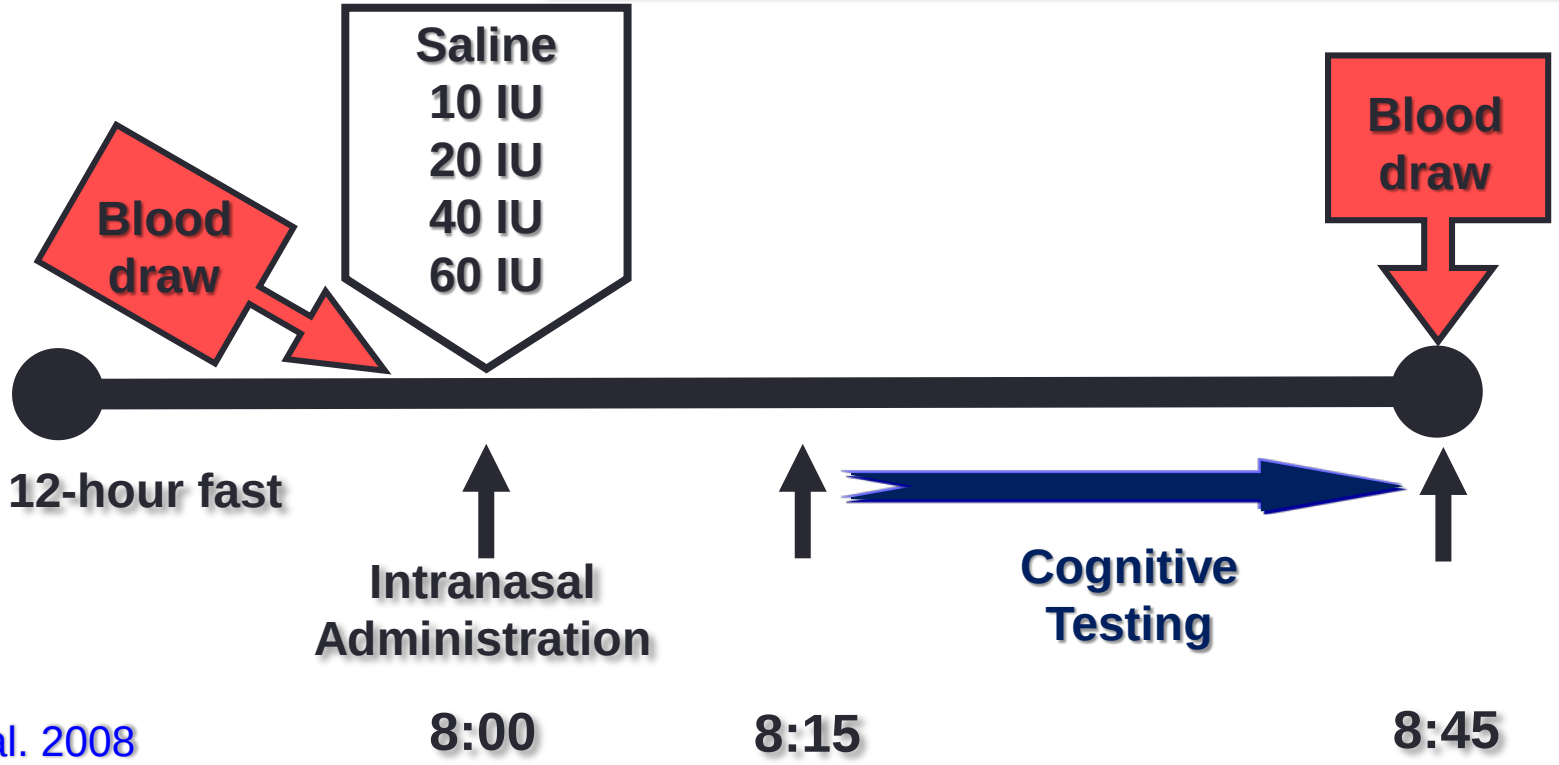
Zhang et al. 2014

Intranasal Insulin for MCI/AD



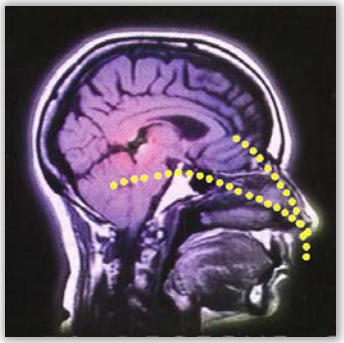
Subject Characteristics

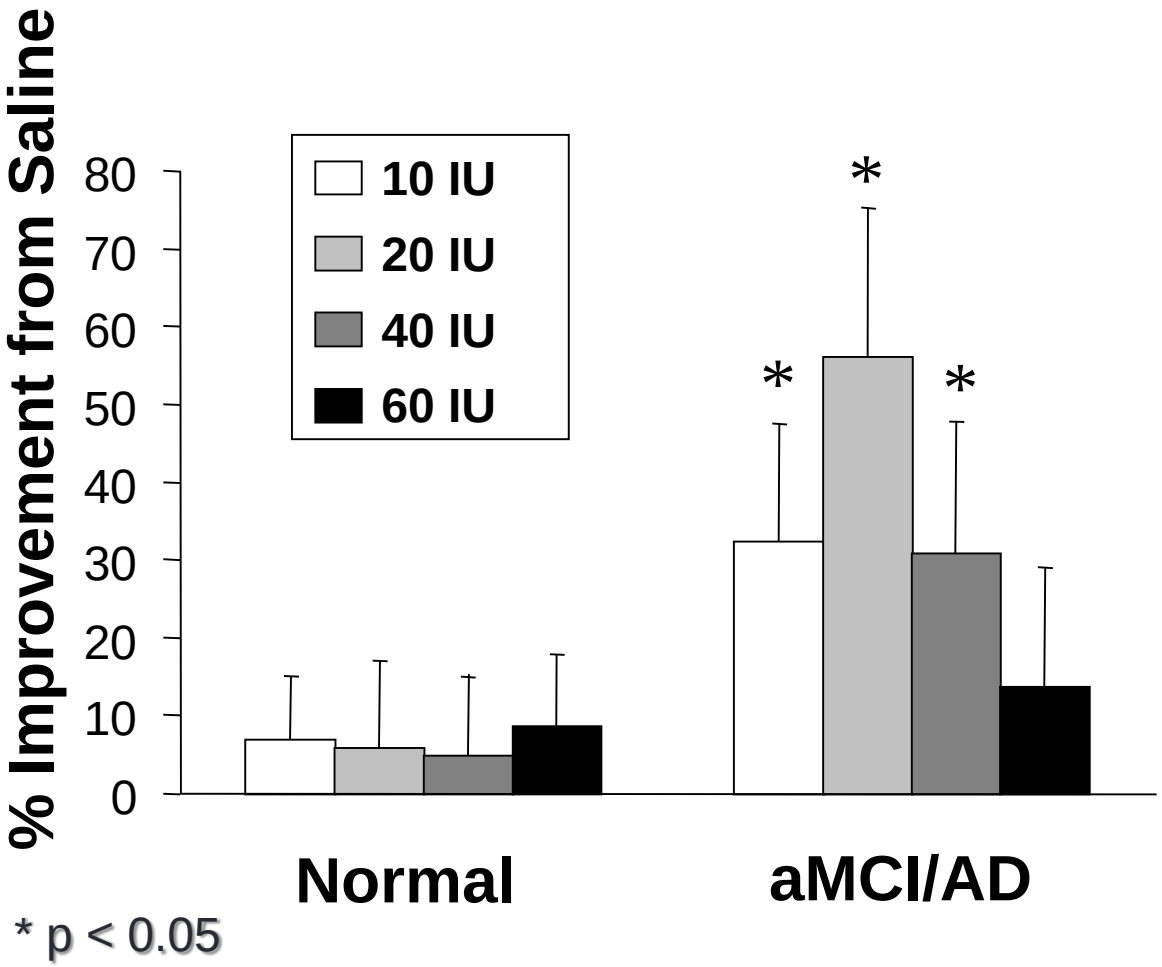
Mean (sd)	Normal	aMCI/AD
N	34	13
Age (yrs)	74 (6)	78 (7)
BMI (kg/m^2)	26 (4)	26 (6)
Dementia Rating Scale Score (max=144)	139 (4)	132 (8)



Reger et al. 2008

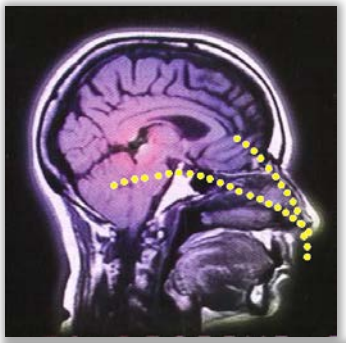
Results Delayed Story Recall





* $p < 0.05$

Effects of Intranasal Insulin in MCI and AD



104 Adults
With AD/aMCI

Intranasal
Insulin (10 or 20 IU)
2x daily 4 mos

Placebo

Baseline

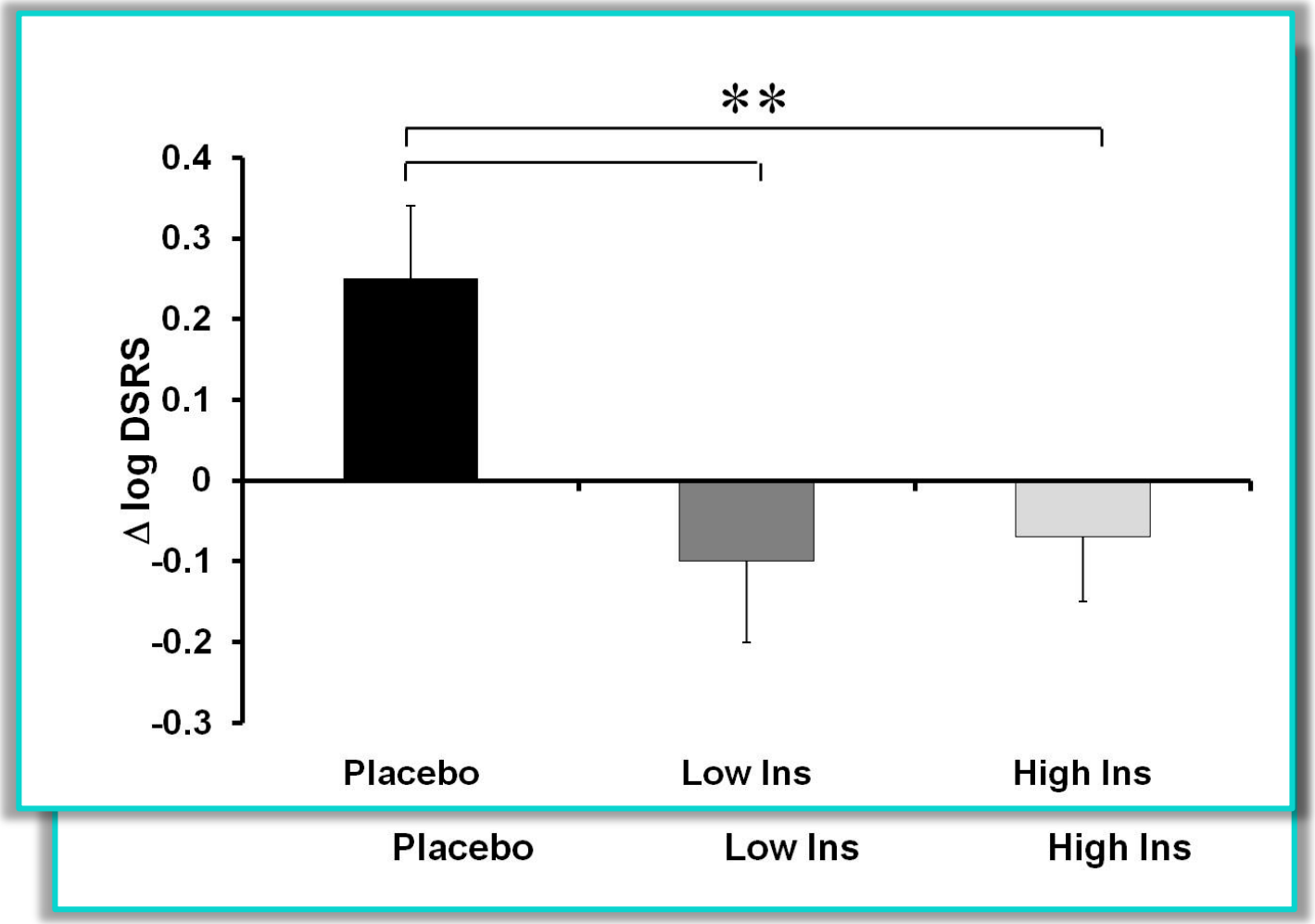
Month 4

Cognitive Function (Story Recall, ADAS-Cog)
Function (Dementia Severity Rating Scale)
FDG PET, CSF Biomarkers

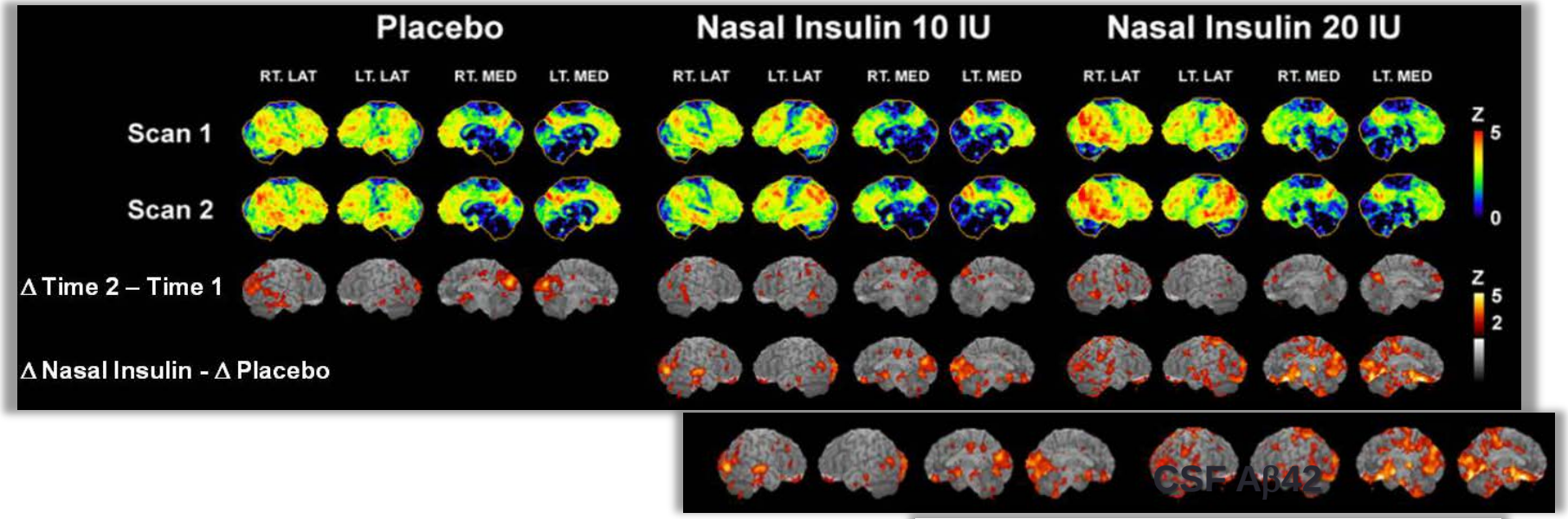
Craft et al. 2012

Results: Delayed Recall, Dementia Severity Rating Scale, ADAS-Cog

Change from Baseline to Month 4

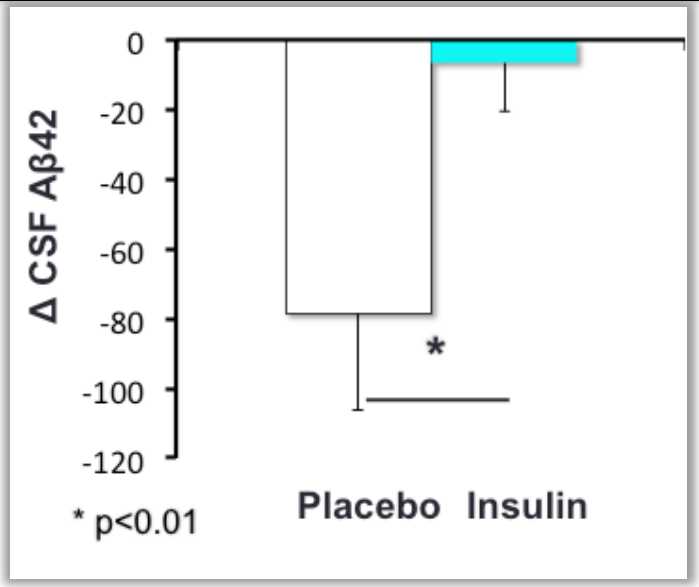


Results: FDG-PET and CSF Aβ42



Nasal Insulin 20 IU

Nasal Insulin 40 IU



Δ Nasal Insulin – Δ Placebo
'Hot' colors=hypometabolism in placebo group relative to insulin-tx group

Ongoing Phase II / III Trial

- Funded by 2012 NAPA funds
- Coordinated by ADCS (Paul Aisen, MD, Director)
- Trial Design
  - Randomized, double-blind, study of 12 m of regular INI vs placebo (40 IU), followed by 6 mos open label
  - 240 participants (aMCI, mild AD with MMSE ≥ 20)
  - ~25 ADCS Centers
  - Primary endpoint: ADAS-Cog12
  - Secondary endpoints: Other cog tests, CSF AD biomarkers, MRI
  - Safety and feasibility of intranasal administration, effectiveness of nasal delivery device
- Progress to date
  - 49 Ss enrolled
  - Excellent recruitment, retention and participant cooperation
  - Study enrollment temporarily paused while intranasal delivery device circuit board is modified to improve reliability

Summary & Conclusions

- **Growing evidence from basic science and preclinical models demonstrate:**
  - Insulin's role in synaptic function/viability, vascular function, amyloid/tau regulation, cerebral glucose metabolism, inflammation
  - Central insulin dysregulation in AD mice and human brain tissue
  - Therapeutic effects of intranasal insulin on synapses, amyloid, tau, and behavior in AD mice
- **Additional evidence of cognitive benefit suggests that INI may be a valuable tool in the AD therapeutic portfolio**
- **Assessment of INI effects on CSF and imaging biomarkers from ongoing trial, and further preclinical work needed to elucidate underlying mechanisms**

Collaborators

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