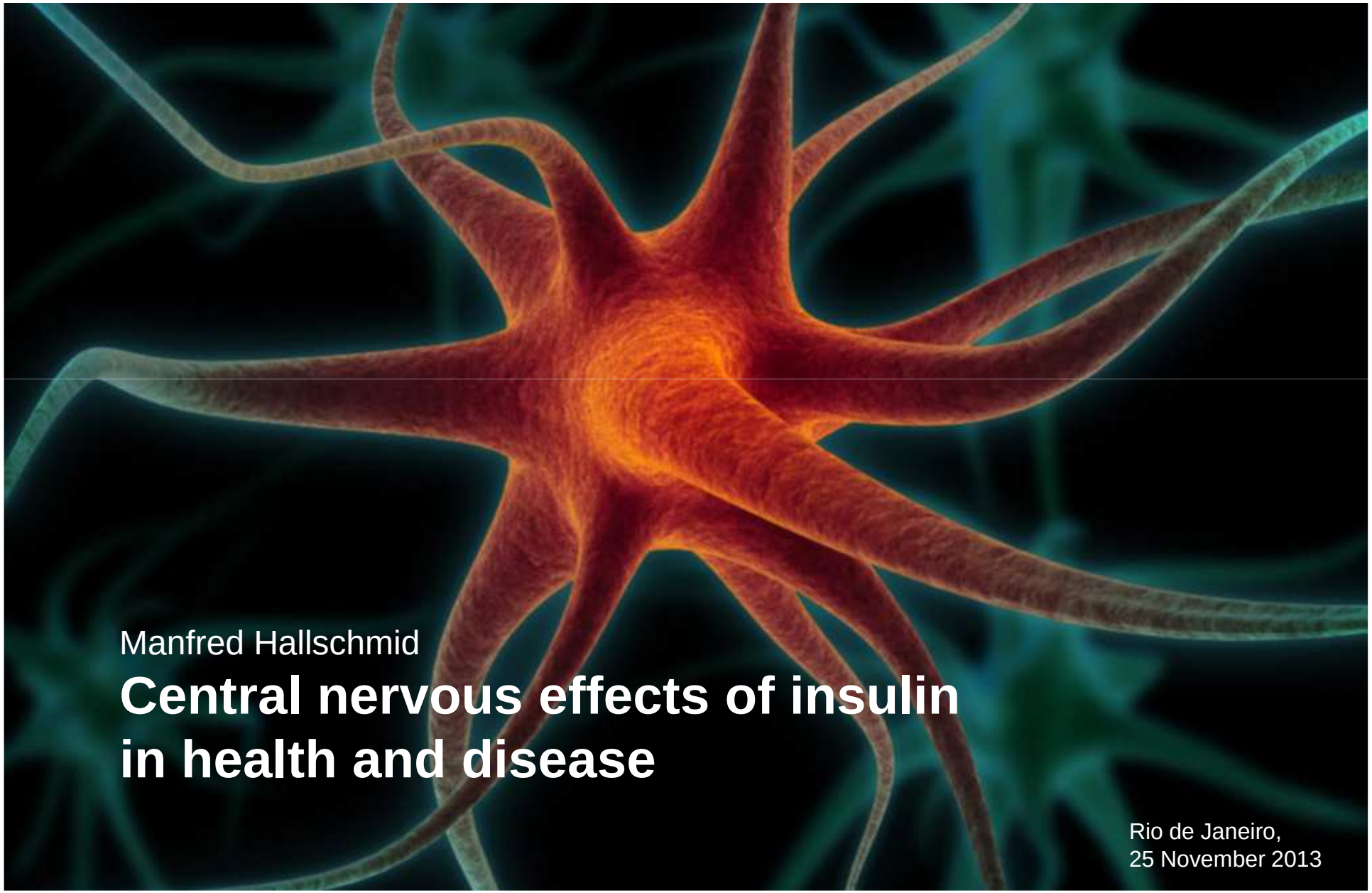
EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Department of Medical Psychology
and Behavioral Neurobiology

WORLD SCIENCE FORUM
RIO DE JANEIRO



Manfred Hallschmid

Central nervous effects of insulin in health and disease

Rio de Janeiro,
25 November 2013

Overview

- Diabetes, obesity and Alzheimer‘s disease: a fatal connection?
- Insulin in the brain, and the nose-brain pathway
- The role of central nervous insulin signaling in Alzheimer‘s disease
- Improving brain insulin signaling as a therapeutic perspective

Overview

- **Diabetes, obesity and Alzheimer‘s disease: a fatal connection?**
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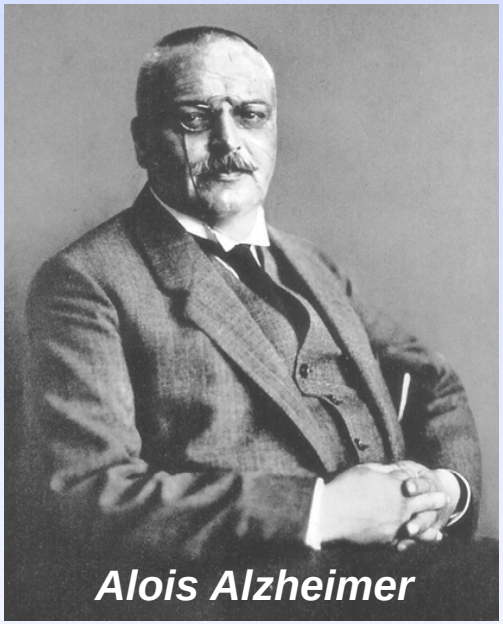
Alzheimer‘s disease

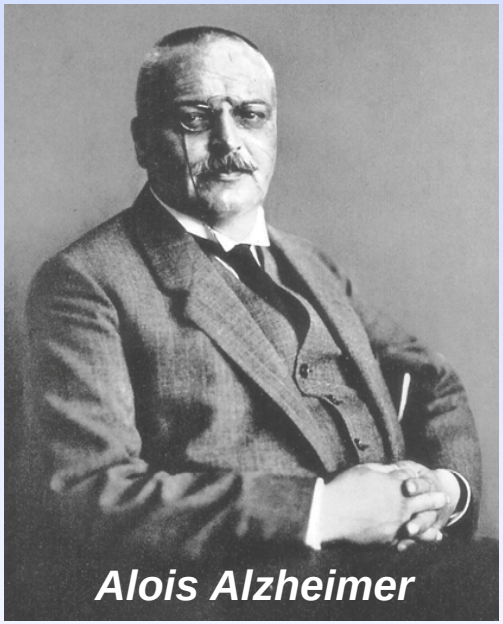
- Most common form of dementia in the elderly


Alois Alzheimer


Auguste Deter

Alzheimer‘s disease

- Most common form of dementia in the elderly



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Tübingen, Germany

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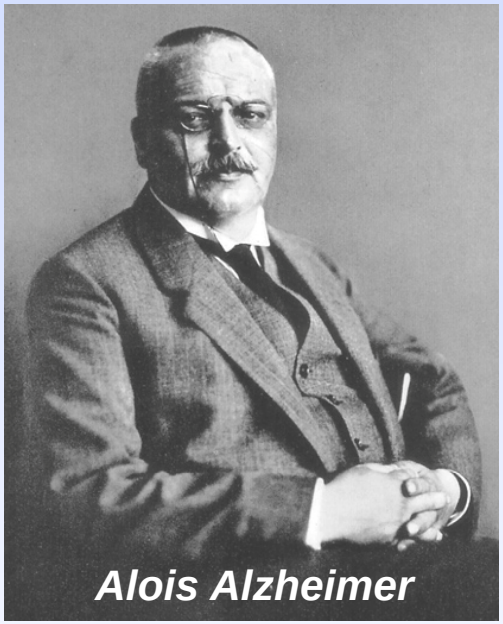
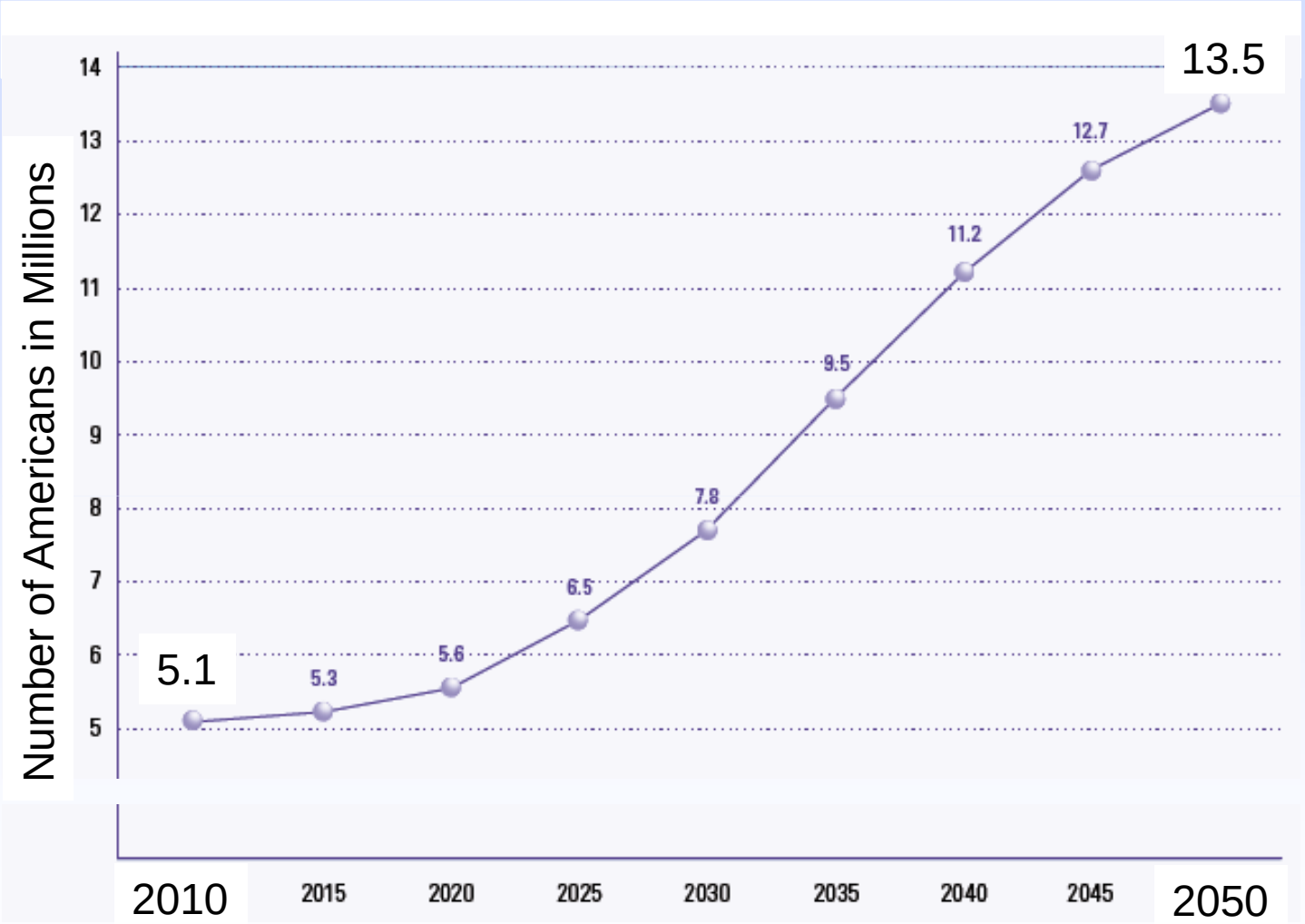


- No efficient treatments are available
- Estimated to affect more than 24 million individuals worldwide (Ballard et al., Lancet 2011)

Number of Americans >65 yrs with Alzheimer‘s disease



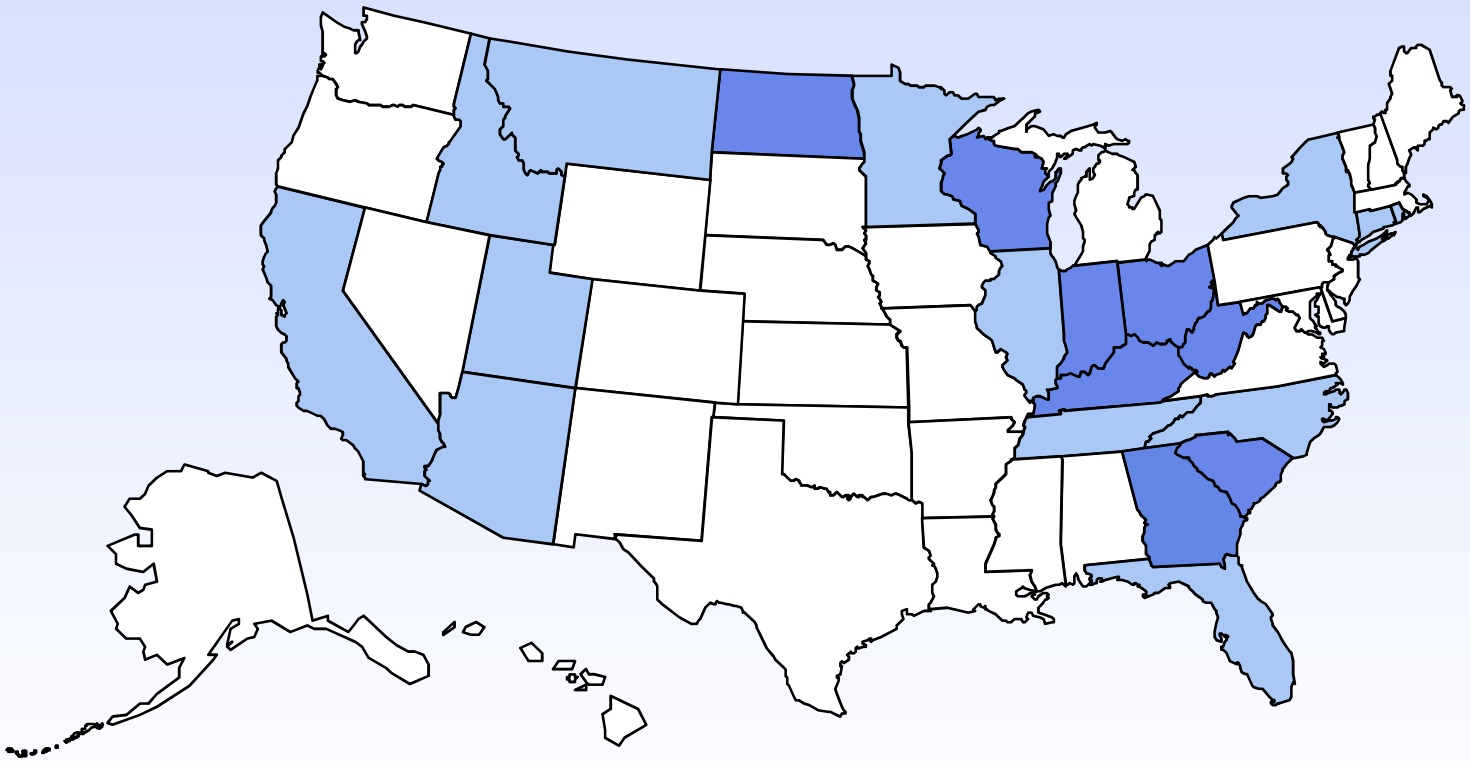
American Alzheimer’s Association 2010

Obesity

Ron Mueck, *Big Man* (2003)

Obesity (BMI ≥ 30) in US adults

1985

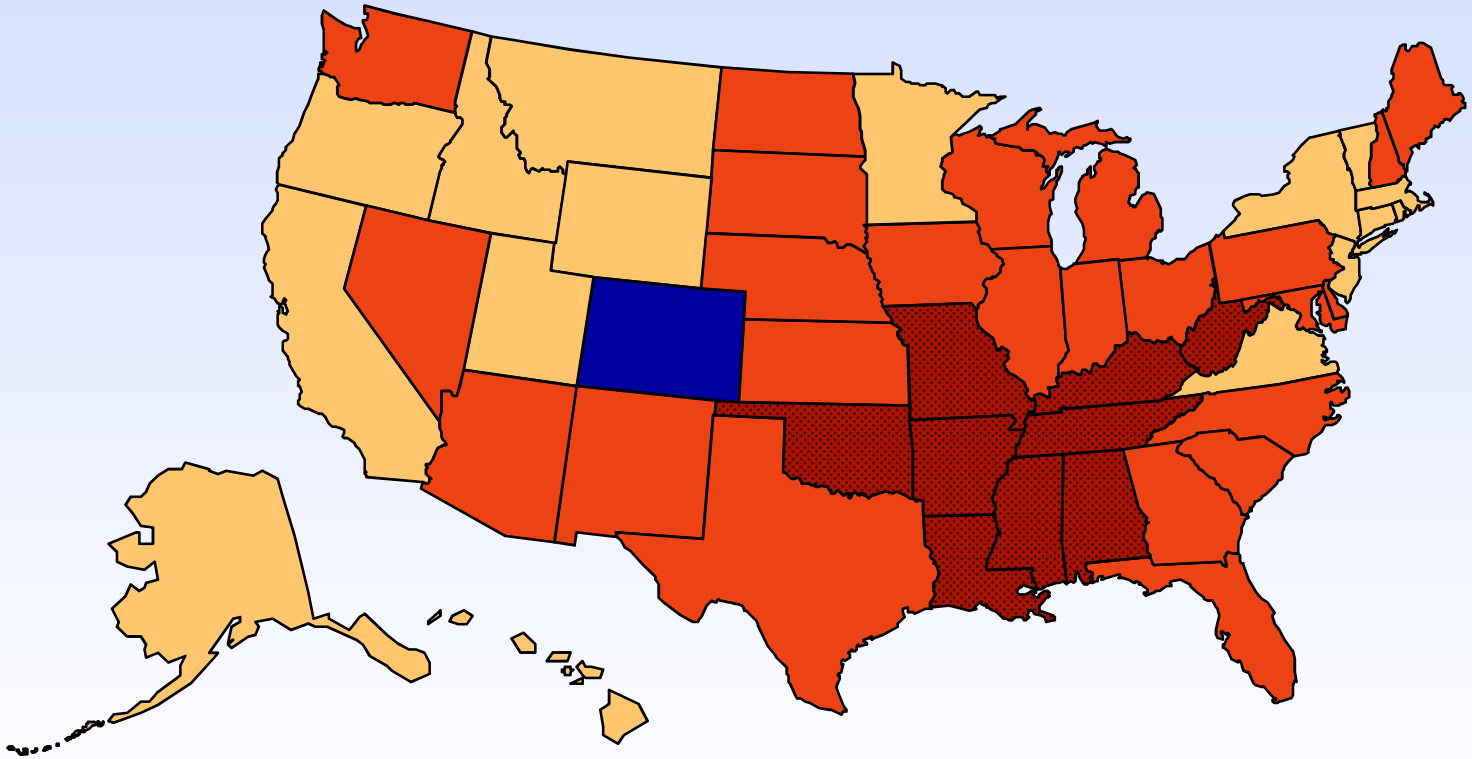


No Data | <10% | 10%–14%

Behavioral Risk Factor Surveillance System, CDC.

Obesity (BMI ≥ 30) in US adults

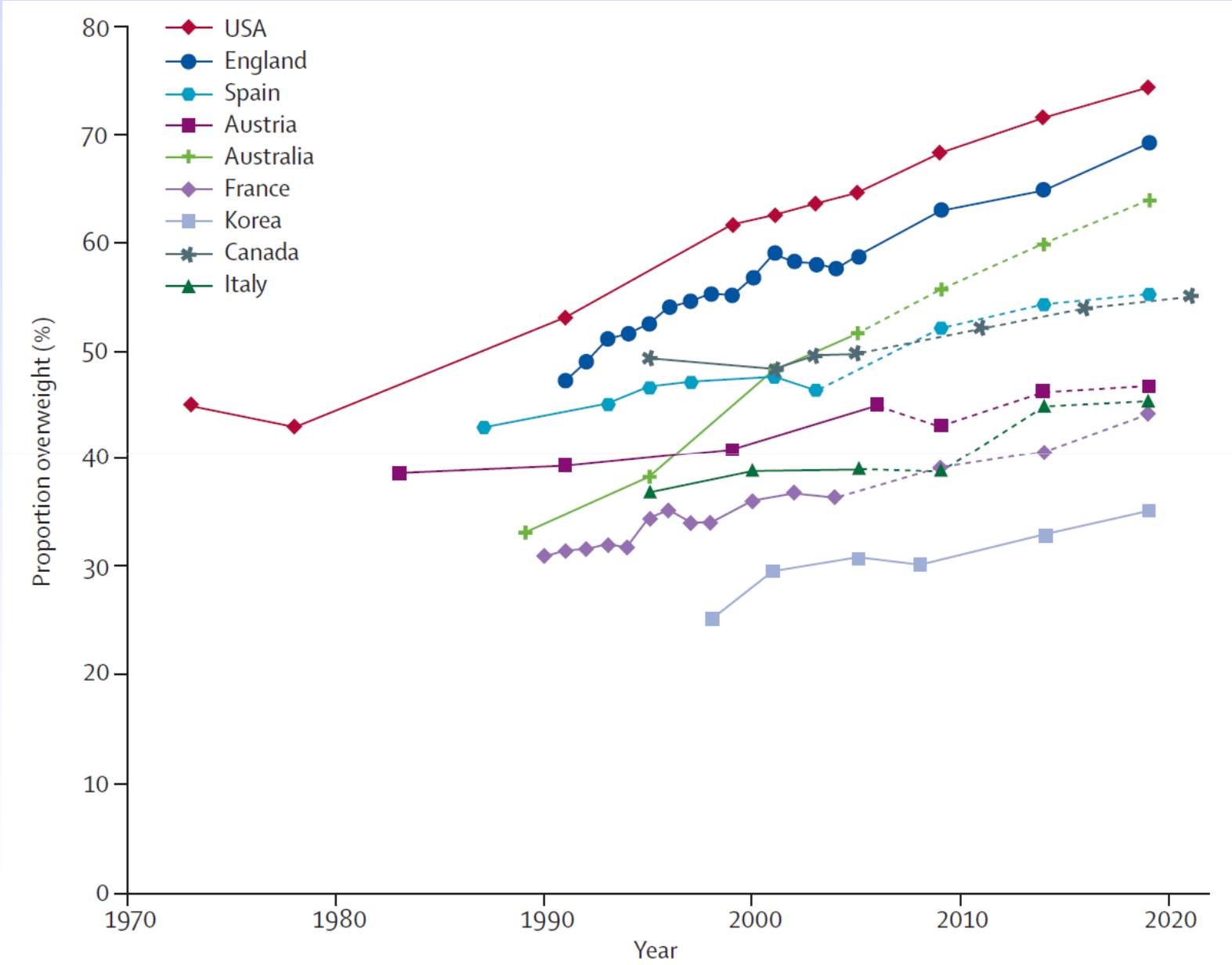
2009



No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥30%

Behavioral Risk Factor Surveillance System, CDC.

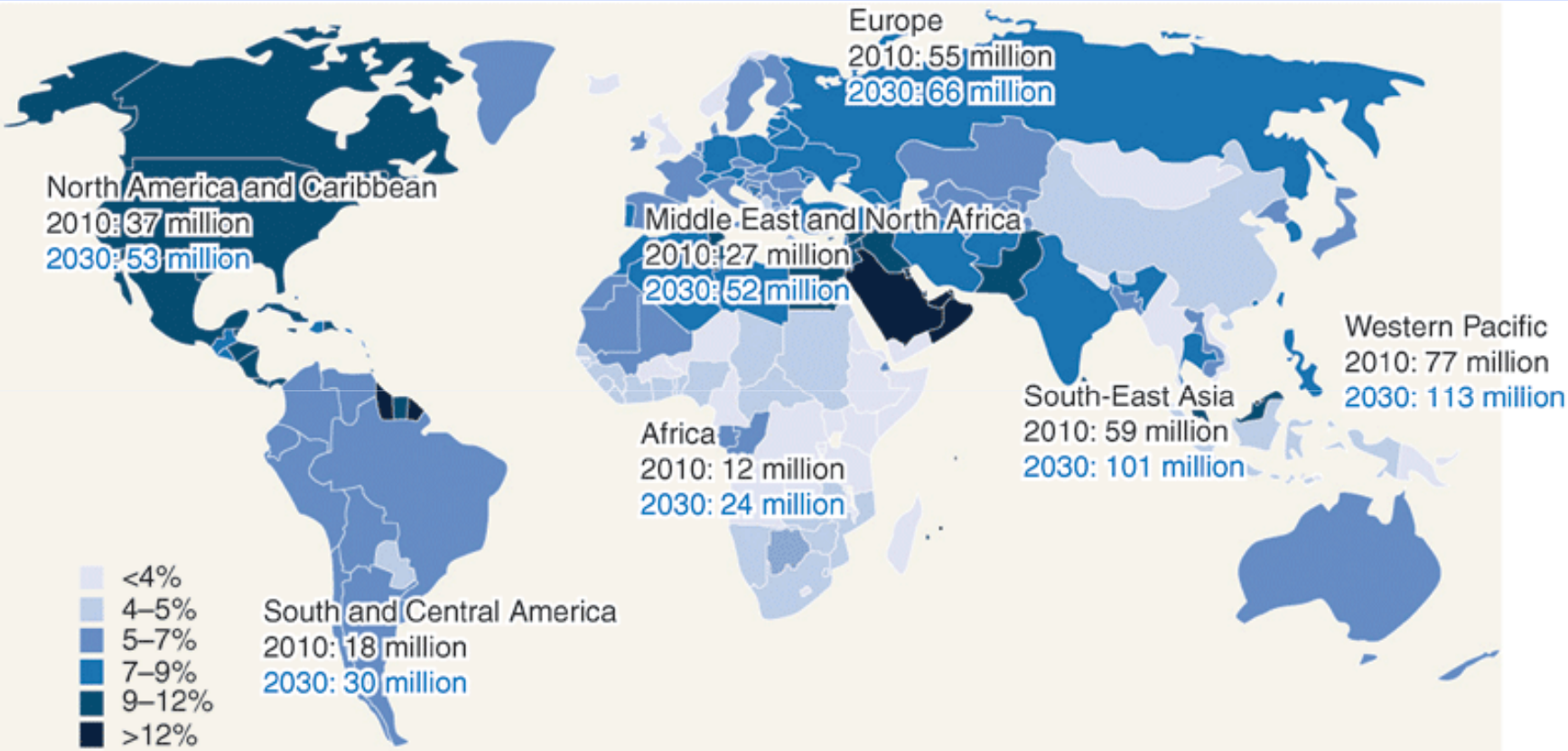
Projected prevalence of overweight (BMI ≥ 25)



Wang et al., Lancet 2011

Prevalence of type 2 diabetes

… currently estimated to affect more than 347 million people worldwide (Danaei et al., Lancet 2011)



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 18th Edition: www.accessmedicine.com

Obesity, diabetes and dementia: Epidemiological data

Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study

Rachel A Whitmer, Erica P Gunderson, Elizabeth Barrett-Connor, Charles P Quesenberry Jr, Kristine Yaffe

BMJ 330:1360-62, 2005

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BMJ 3

Relation between body mass index and cognitive function in healthy middle-aged men and women

M. Cournot, MD; J.-C. Marquié, PhD; D. Ansiau, PhD; C. Martinaud, MD; H. Fonds, MD; J. Ferrières, MD, MSc, FESC; and J.-B. Ruidavets, MD

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T. Cukierman · H. C. Gerstein · J. D. Williamson

Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies

Diabetologia (2005) 48: 2460–2469

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Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies

Diabetologia (2005) 48: 2

Neuro-cognitive Performance in Children with Type 1 Diabetes—A Meta-analysis

Justine M. Naguib,[1] BSc, MBBS, Elena Kulinskaya,[2] PhD, Claire L. Lomax,[3] PhD, and M. Elena Garralda,[4] MD

[1]School of medicine, [2]Statistical Advisory Service, Imperial College, [3]Department of Psychology, Institute of Psychiatry, Kings College, and [4]Academic Unit of Child and Adolescent Psychiatry, Imperial College

Journal of Pediatric Psychology 34(3) pp. 271–282, 2009

Diabetes and dementia: Epidemiological data

T. Cukierman · H. C. Gerstein · J. D. Williamson

Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies

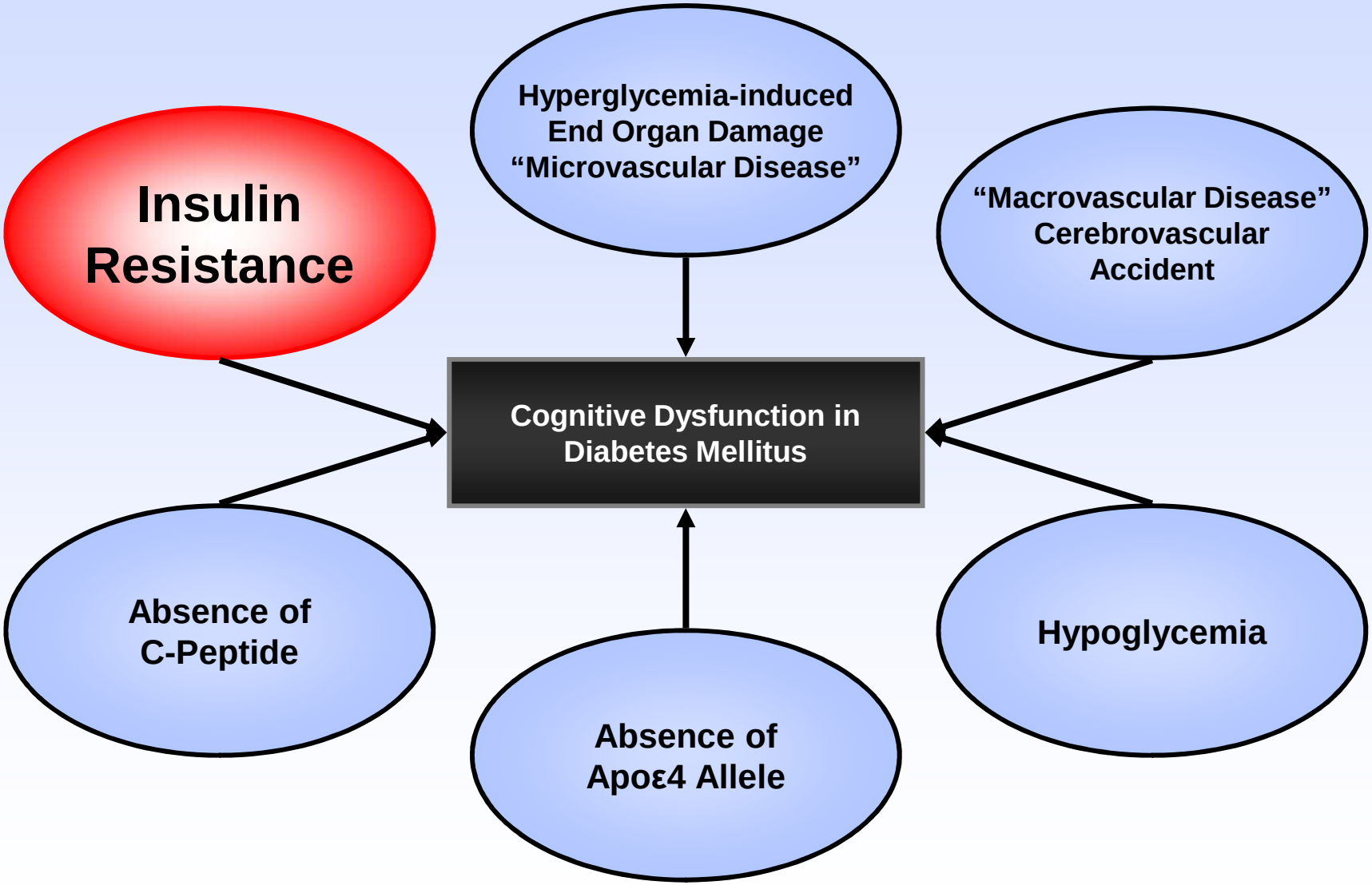
Diabetologia (2005) 48: 2460-2469

25 Studies, 8656 patients with type 2 diabetes, 2-18 yrs. follow up:

Diabetes increases the relative risk of future:

• cognitive decline	RR 1.7
• Alzheimer's disease	**RR 1.2-2.3**

Cognitive dysfunctions in diabetes mellitus: risk factors



Kodl & Seaquist, Endocrine Rev 2008

Overview

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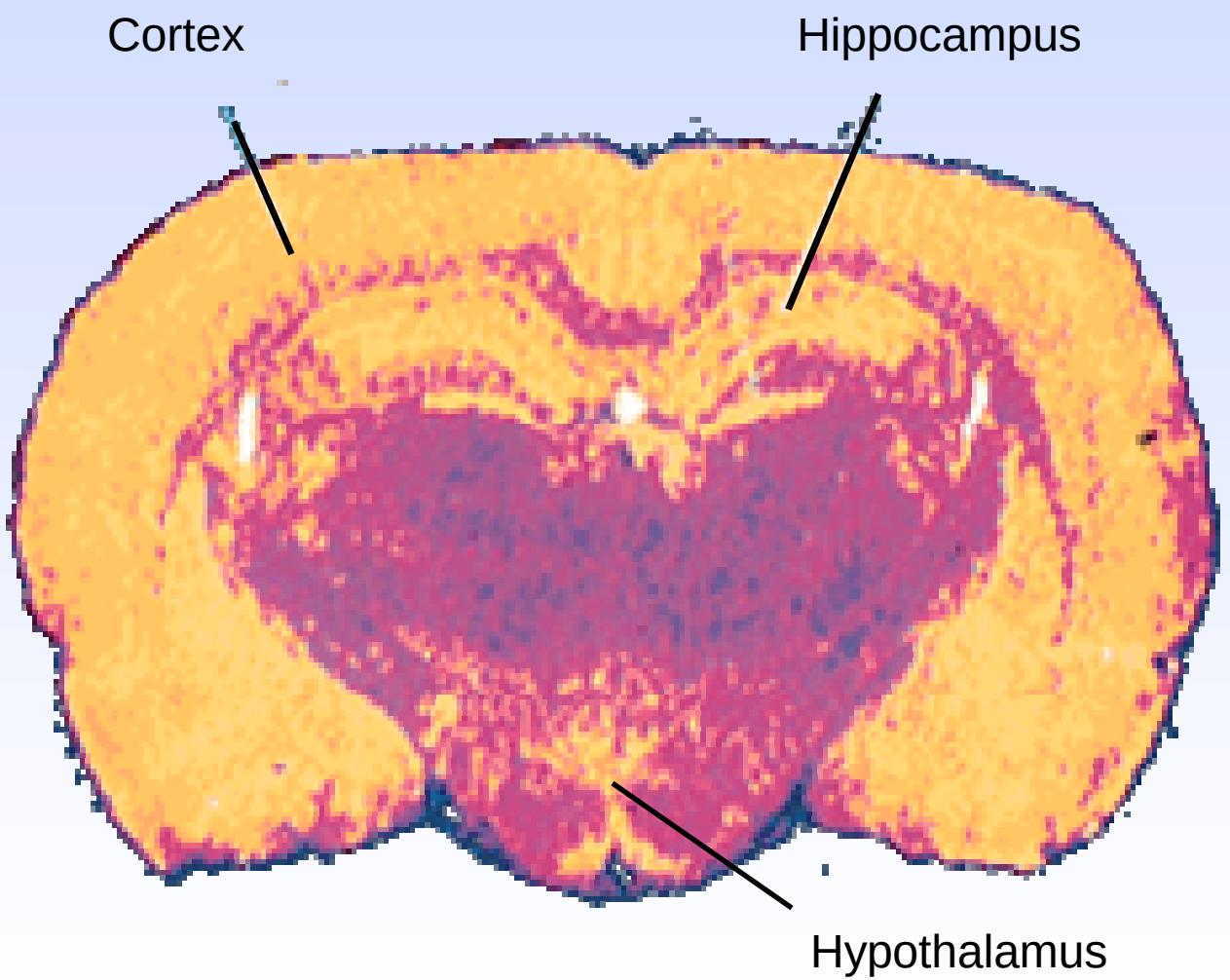
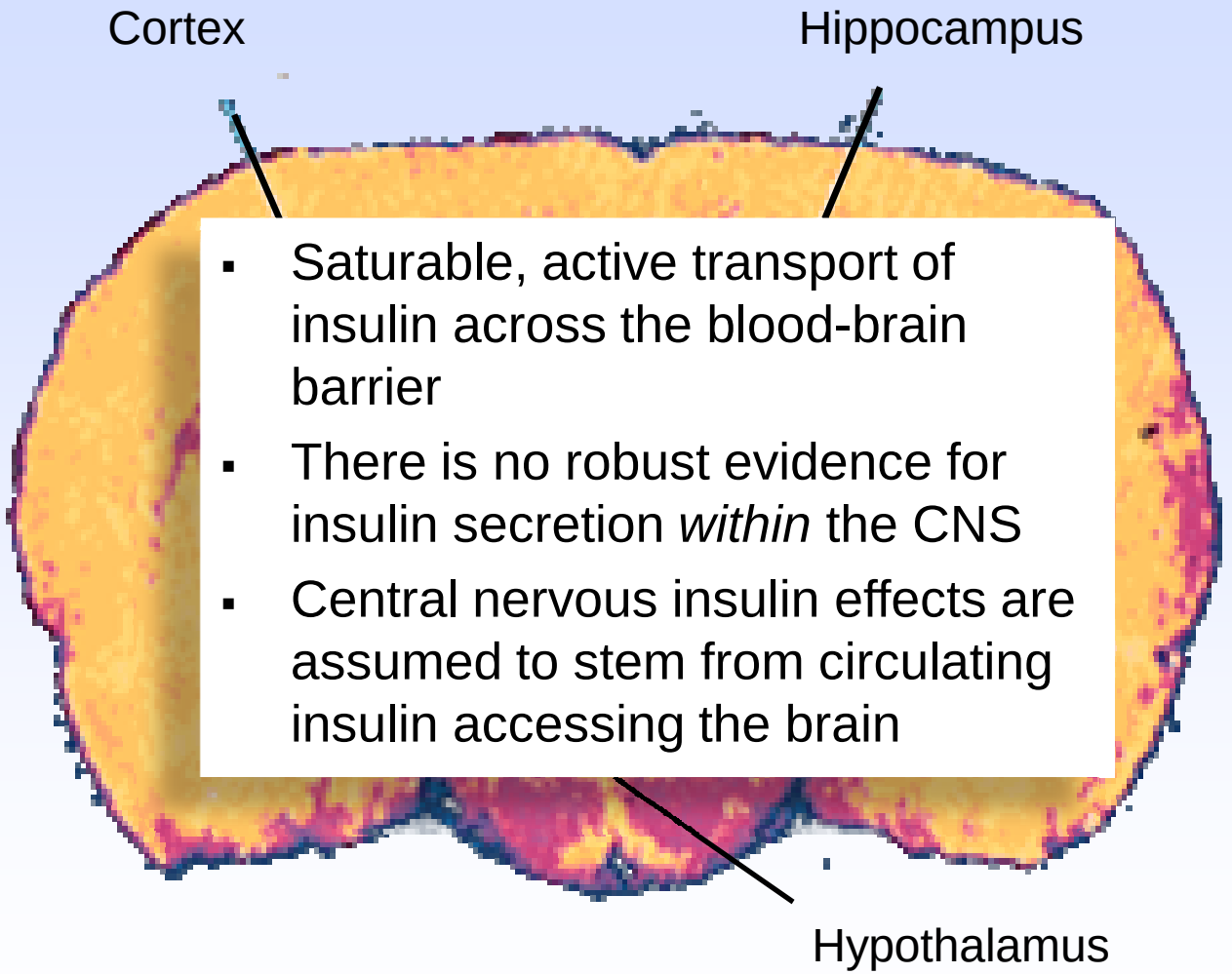
Insulin receptors in the brain



Wickelgren, Science 1998

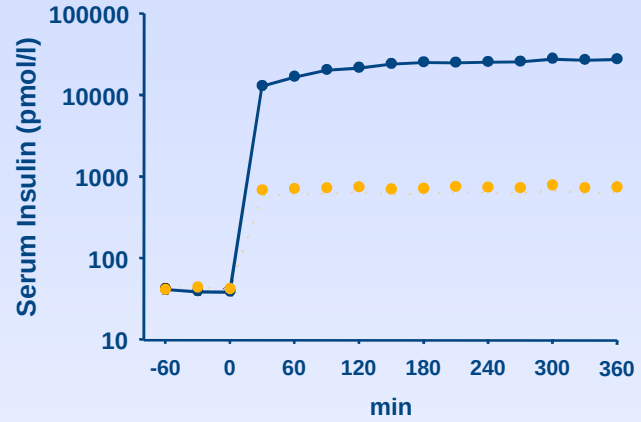
Insulin receptors in the brain

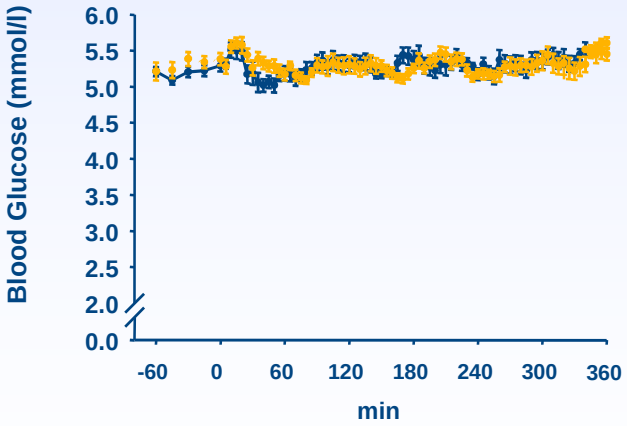


- Saturable, active transport of insulin across the blood-brain barrier
- There is no robust evidence for insulin secretion *within* the CNS
- Central nervous insulin effects are assumed to stem from circulating insulin accessing the brain

Wickelgren, Science 1998

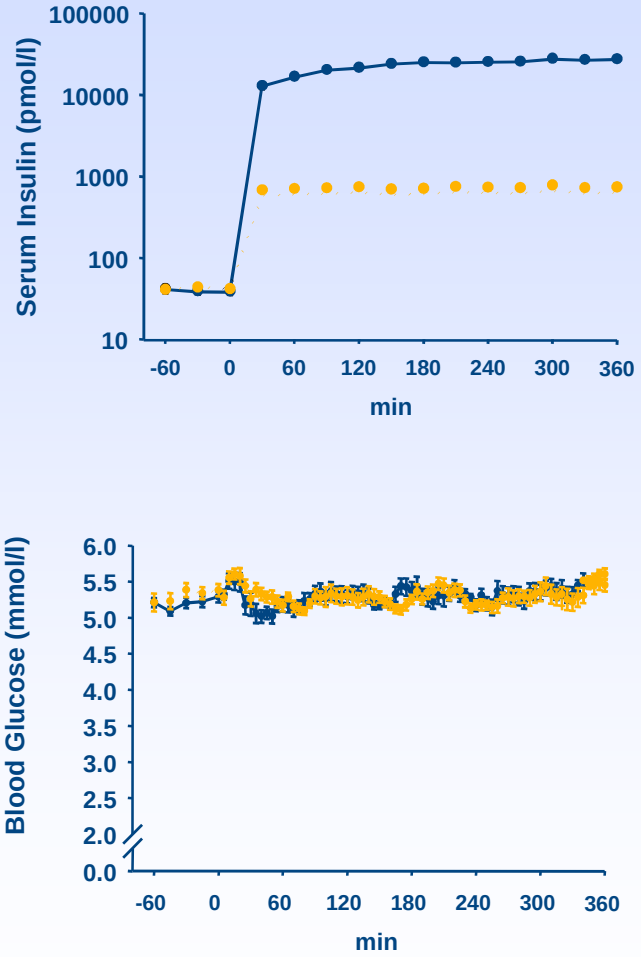
Euglycemic insulin infusion in humans

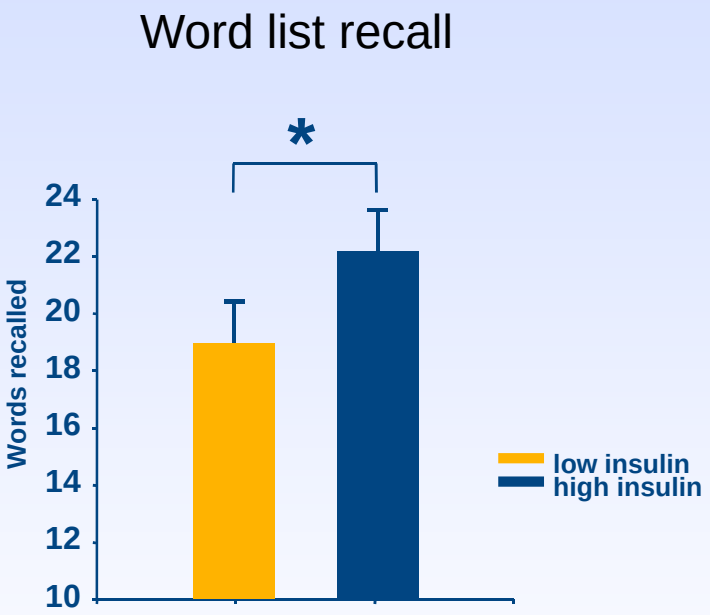




Kern et al., Neuroendocrinology 2001

Euglycemic insulin infusion in humans improves memory function





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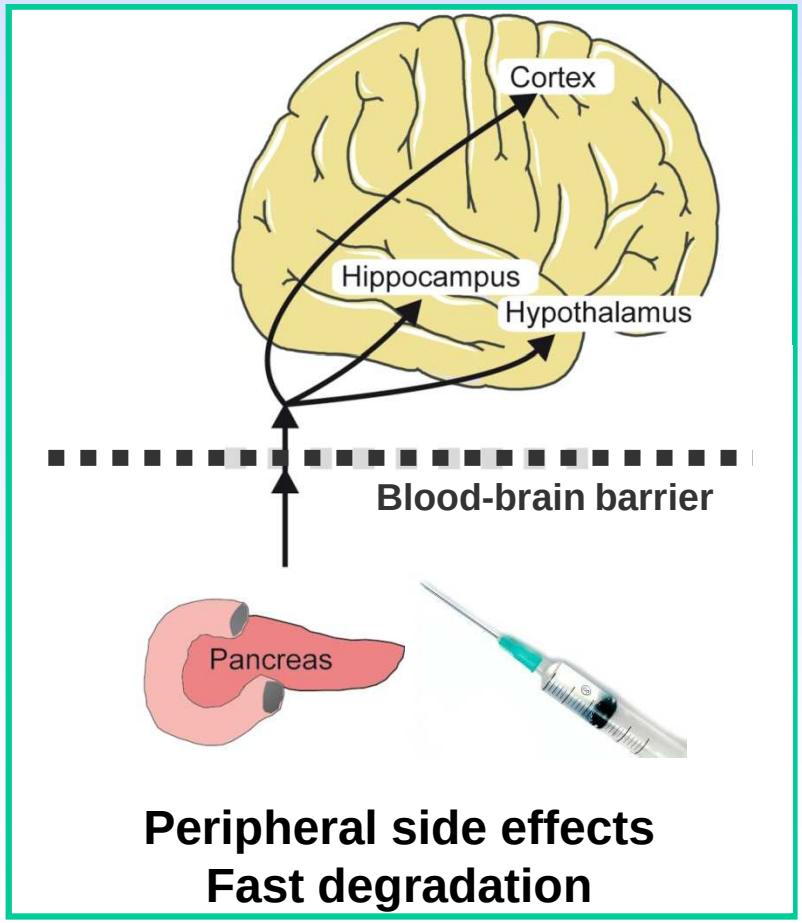
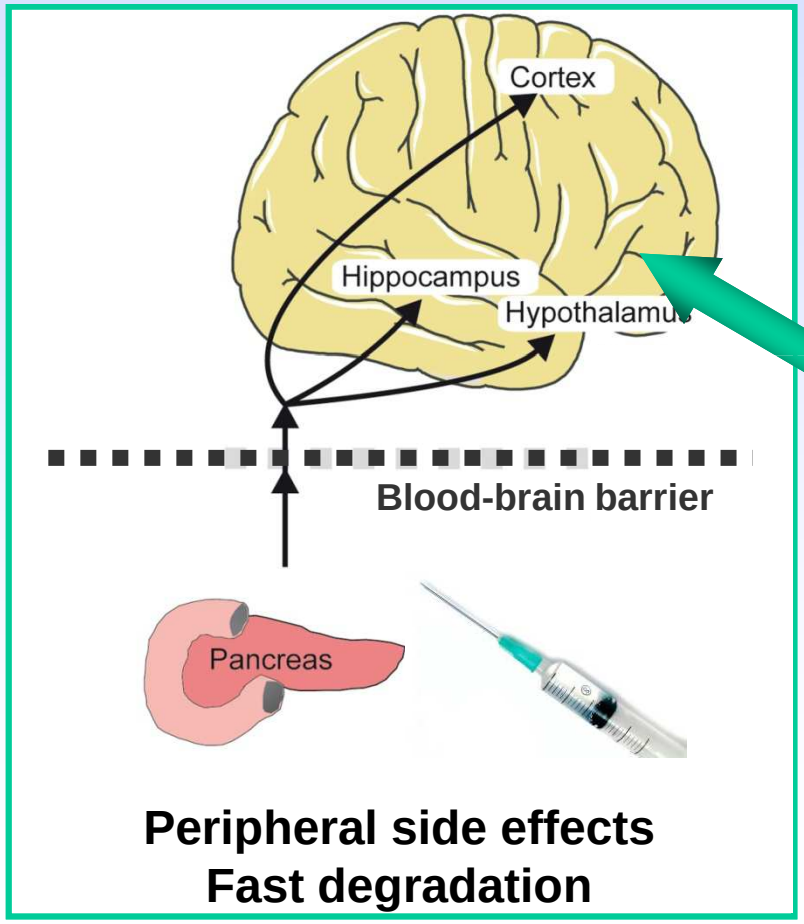


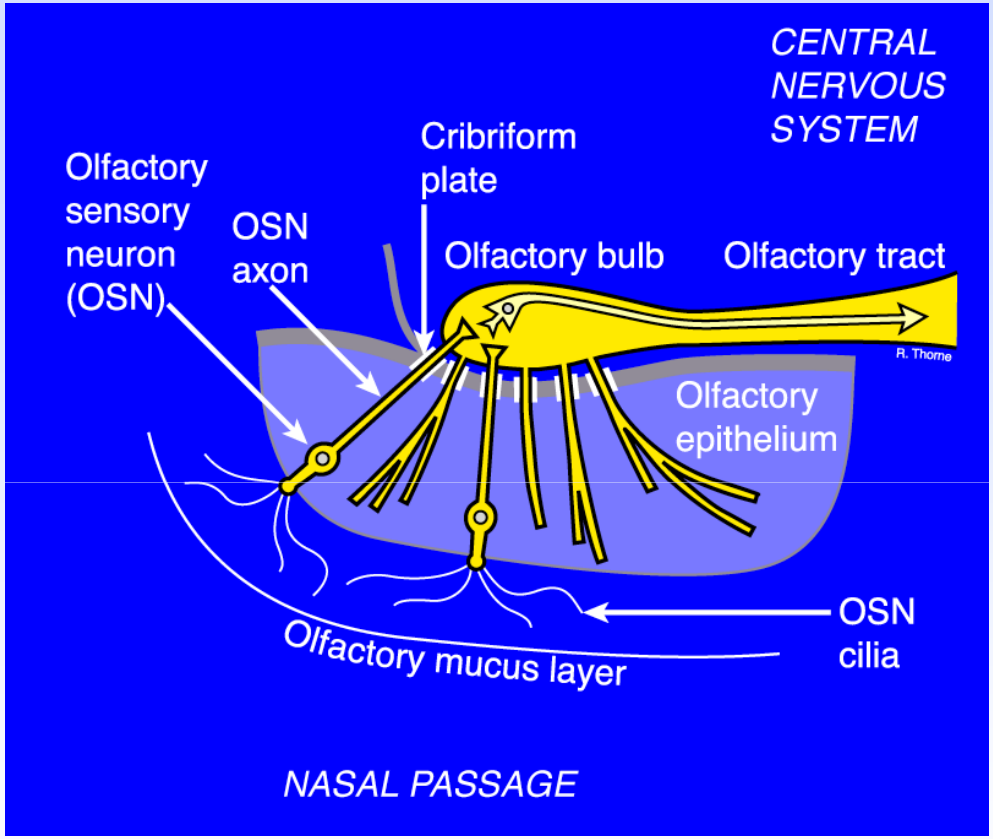
Peripheral side effects
Fast degradation

The nose-brain pathway



Peripheral side effects
Fast degradation

Extracellular delivery of intranasal substances to the CNS



© Thorne & Frey

William Frey II

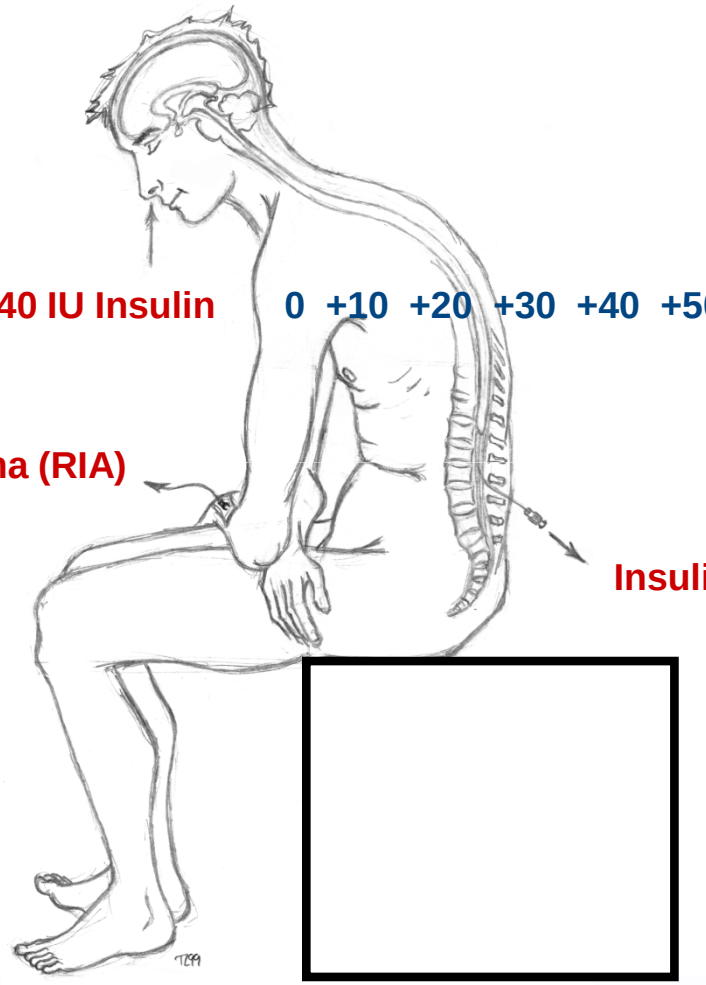
Intranasal insulin administration

Samples –10 40 IU Insulin 0 +10 +20 +30 +40 +50 +60 +70 Min

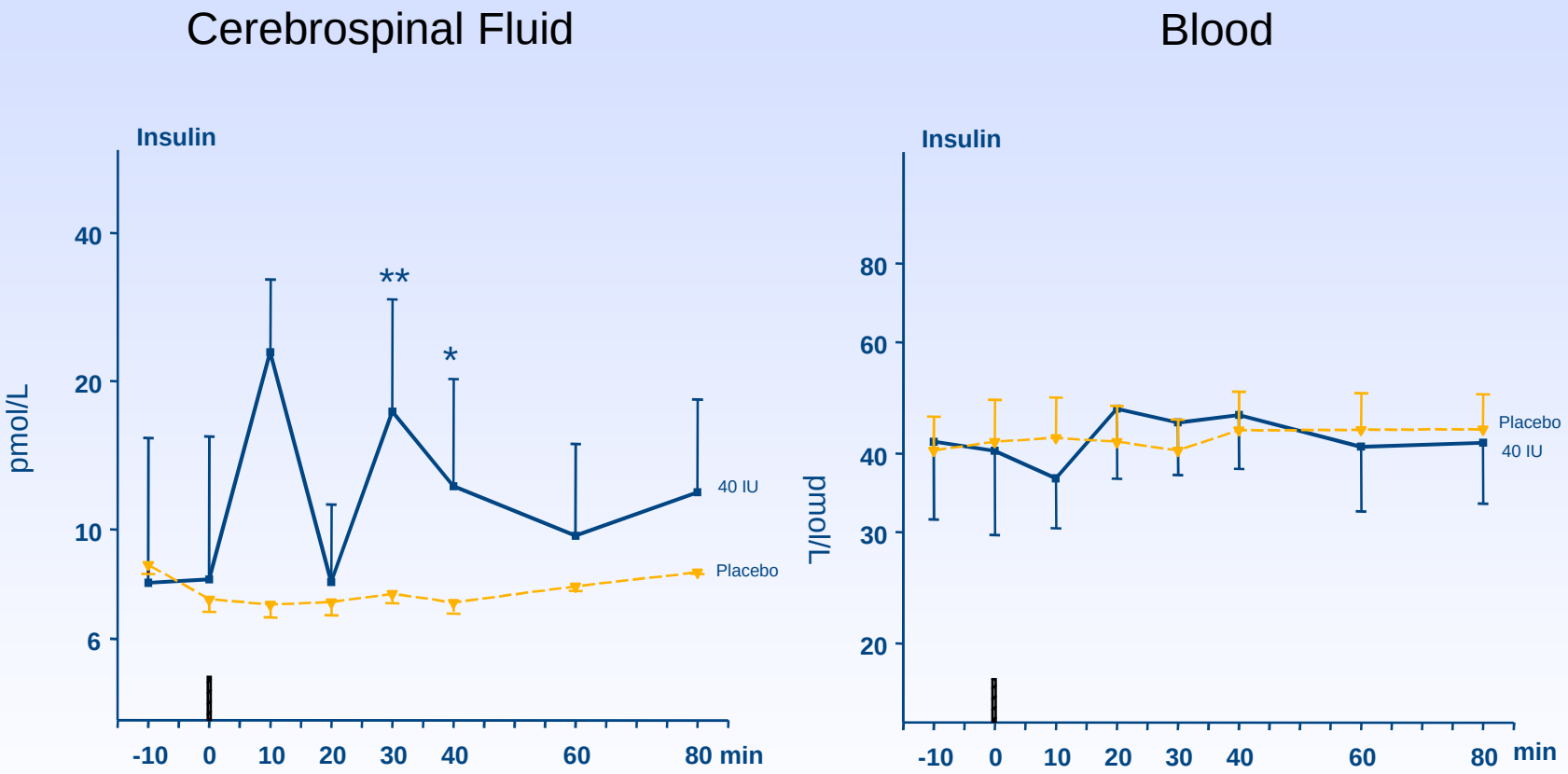
Insulin in plasma (RIA)

Insulin in cerebrospinal fluid (RIA)

5 Men
3 Women

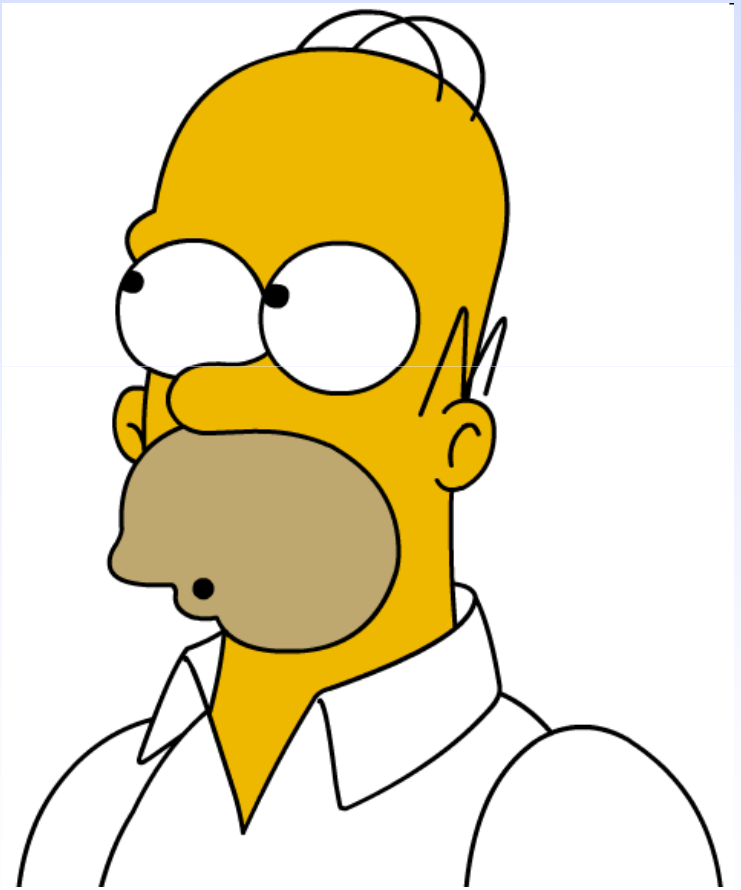


Intranasal insulin administration and CSF levels of insulin

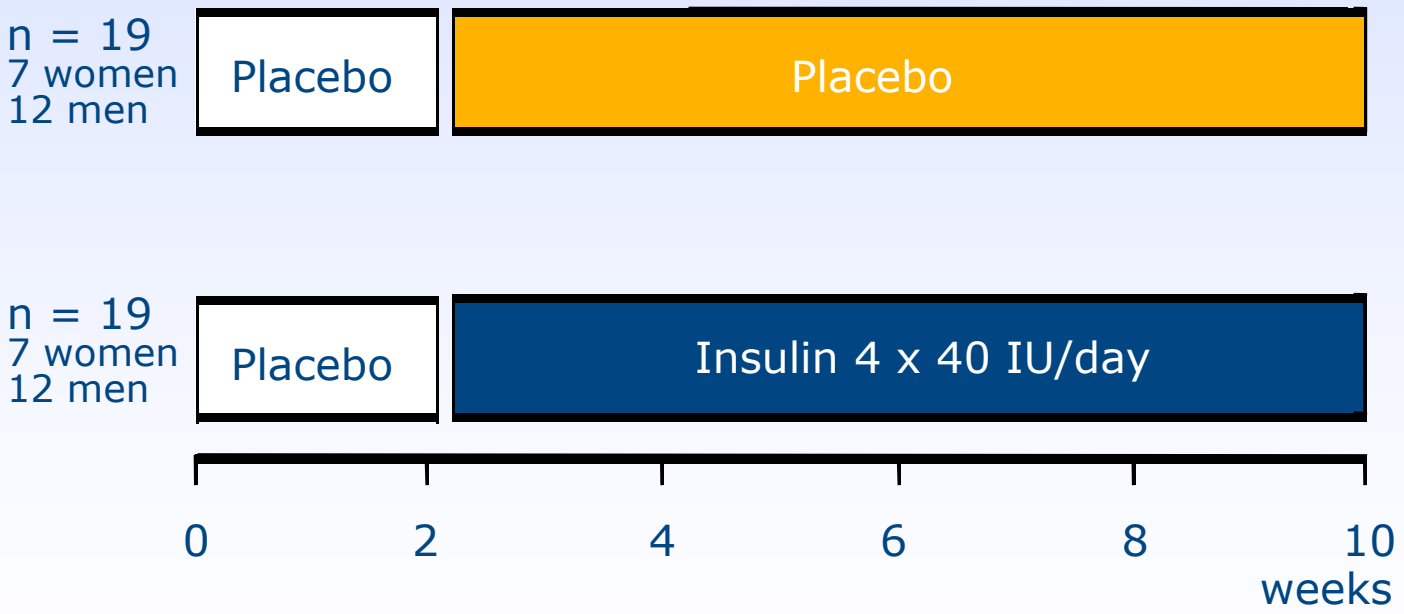


Born et al., Nat Neurosci 2002

Intranasal insulin: cognitive effects in healthy humans

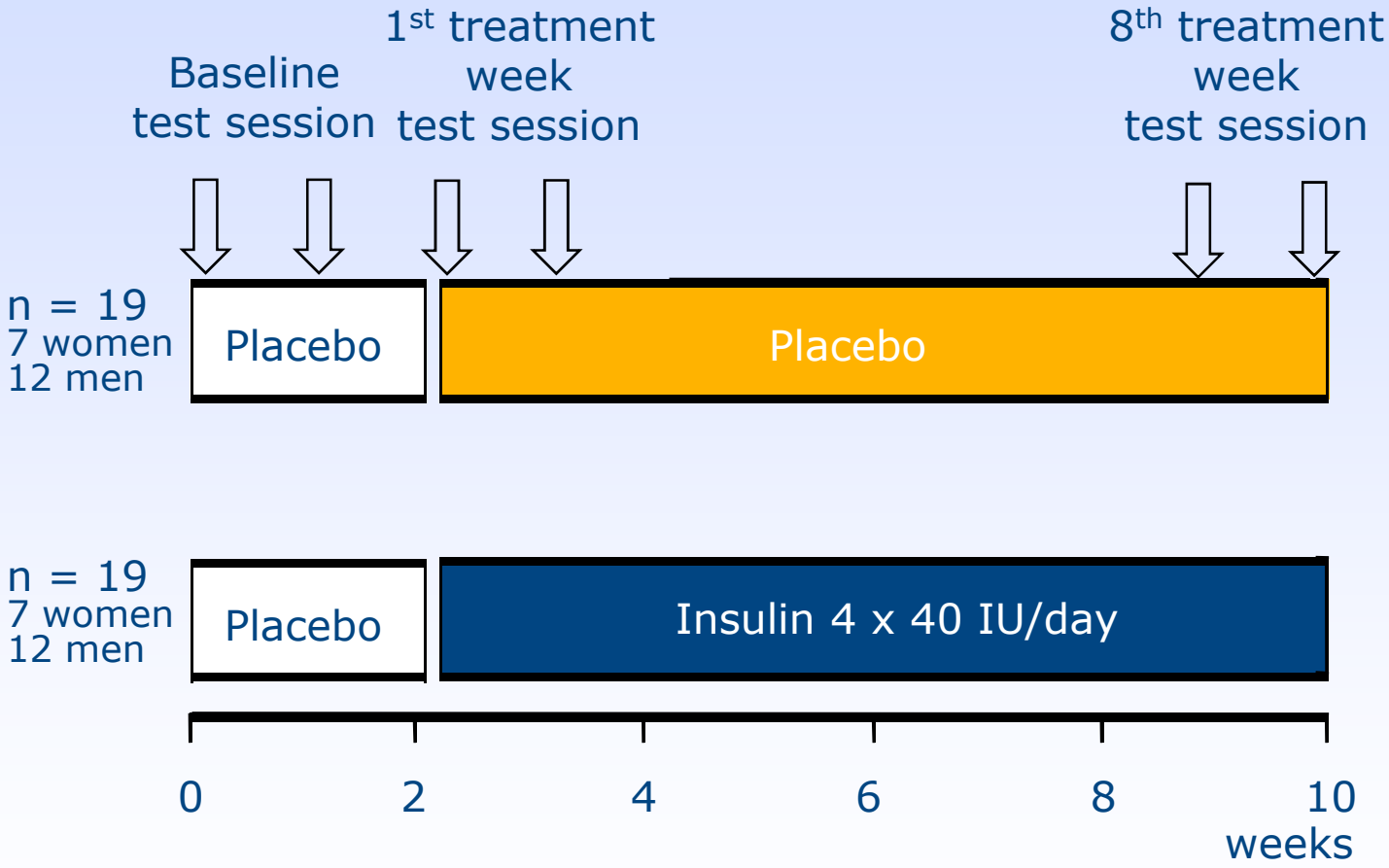


Longterm administration of i.n. insulin



Benedict et al., Psychoneuroendocrinology 2004

Longterm administration of i.n. insulin: Declarative memory



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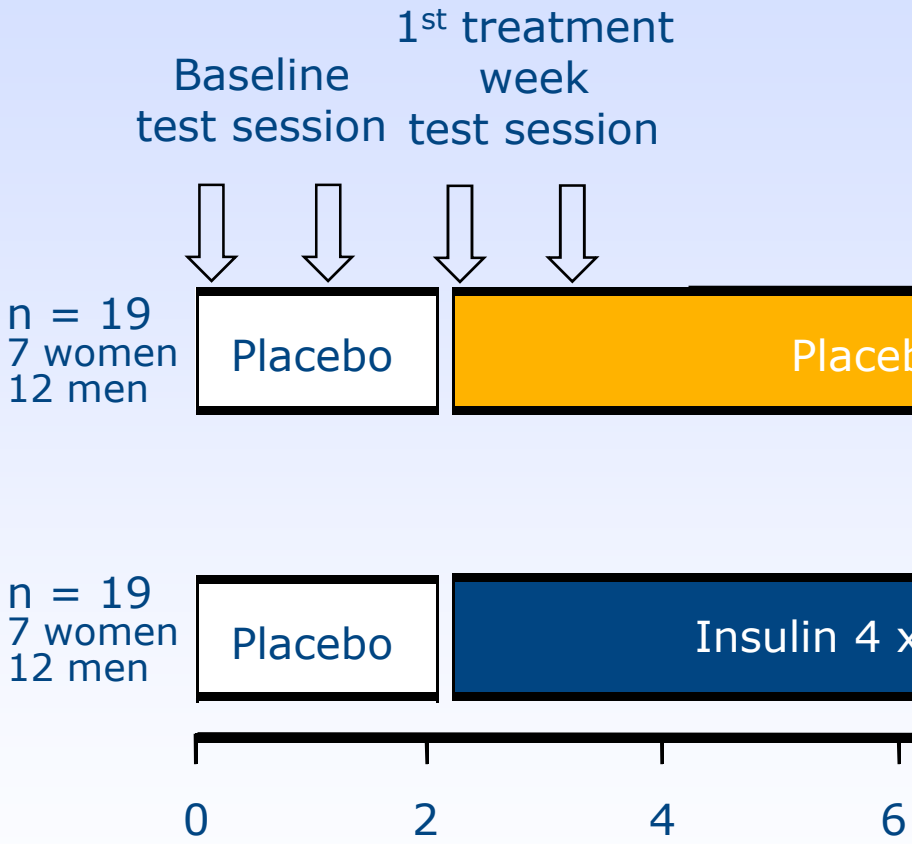


Schnitzel

Loneliness

Soup

Nipple

Flag

Ananas

Sun flower

Cheese

Sex

Wind

Salad

Girlfriend

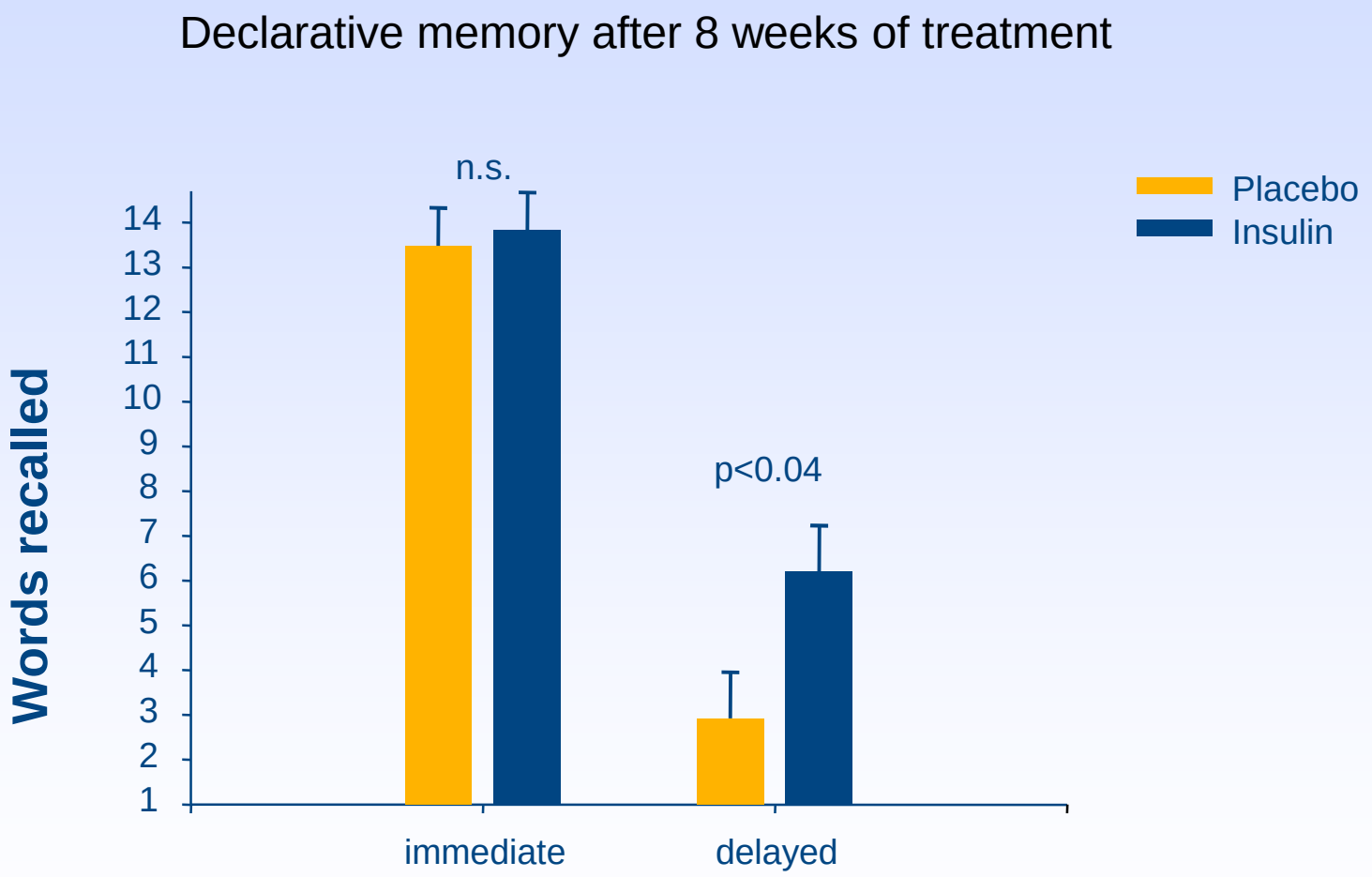
Fear

Bend

Rye field

Benedict et al., Psychoneuroendocrinology 2004

Longterm administration of i.n. insulin: Declarative memory



Benedict et al., Psychoneuroendocrinology 2004

Potential mechanisms of memory improvement by insulin

- Enhancement of local cerebral glucose utilization via GLUT-4/8

(Henneberg & Hoyer, Neurosci Lett 1994; Vannucci et al., Brain Res 1998; Schulingkamp et al., Neurosci Biobehav Rev 2000; Bingham et al., Diabetes 2002)

- Enhancement of cholinergic activity

(Figlewicz et al., Brain Res 1993; Messier & Destrade, Psychobiol 1994; Hajnal et al., Brain Res 1998; Kopf & Baratti, Neurobiol Learn Mem 1999)

- Modulation of synaptic activity via effects on NMDA and AMPA signaling in LTP

(Christie et al., J Neurochem 1999; Man et al., Neuron 2000; Skeberdis et al., PNAS 2001)

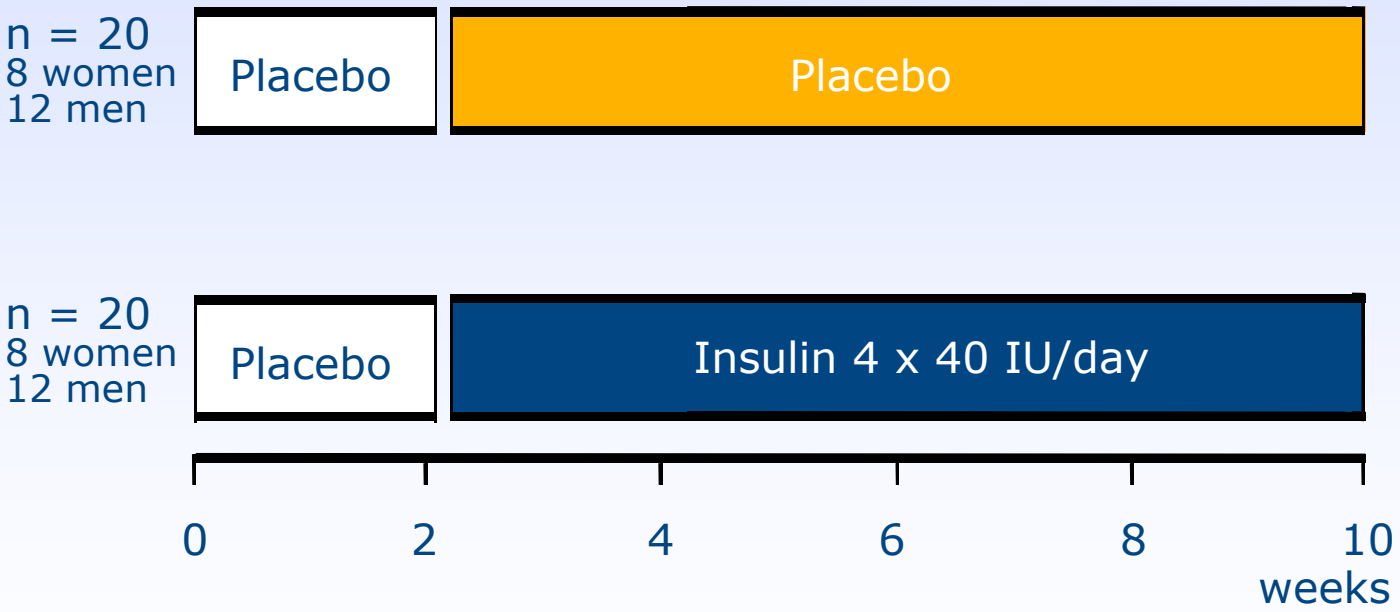
- Interaction with endocrine signals relevant to memory formation, e.g. glucocorticoids?

(Stranahan et al., Nat Neurosci 2008)

Intranasal insulin: Metabolic effects

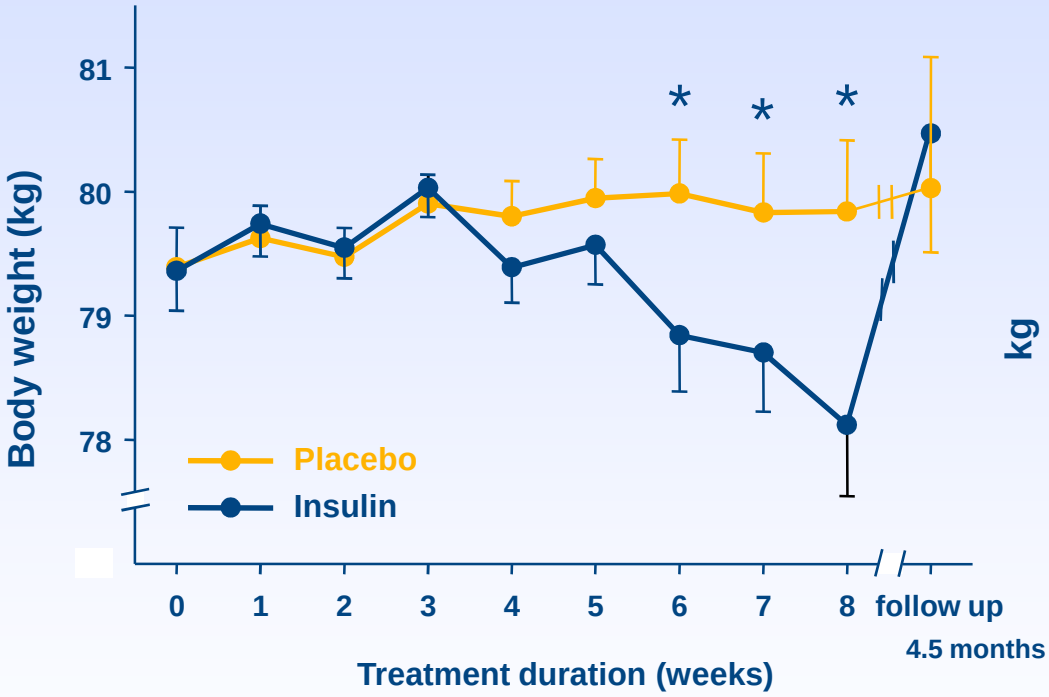
Longterm administration of i.n. insulin

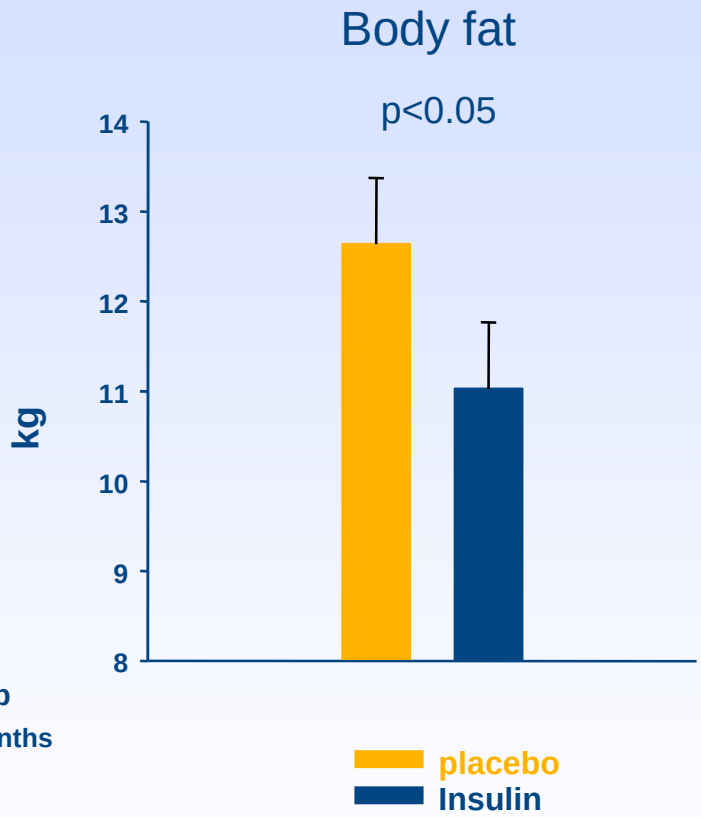
BMI < 25 kg/m^2



Hallschmid et al., Diabetes 53(11) 2004

Longterm administration of i.n. insulin decreases body fat





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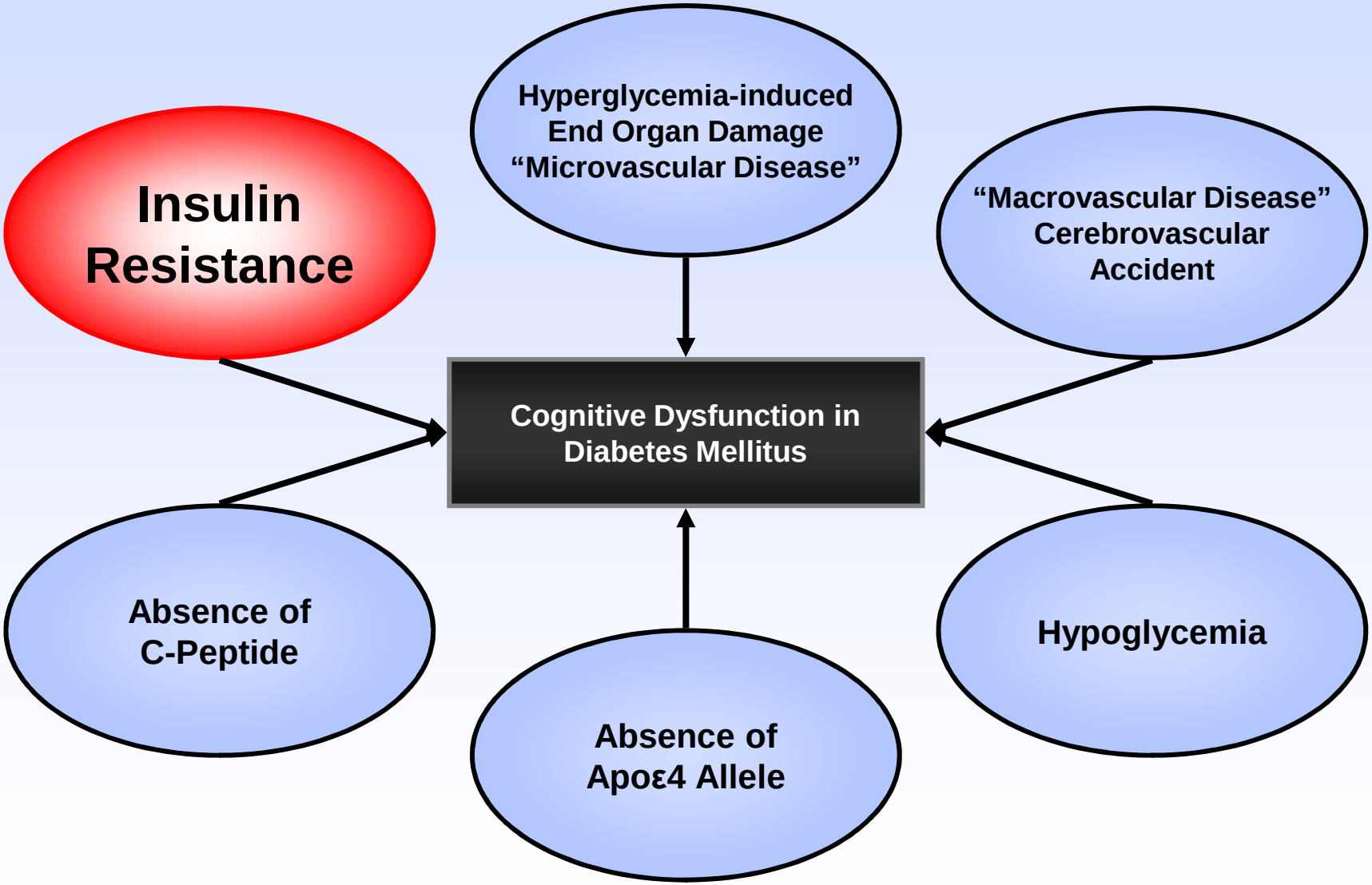
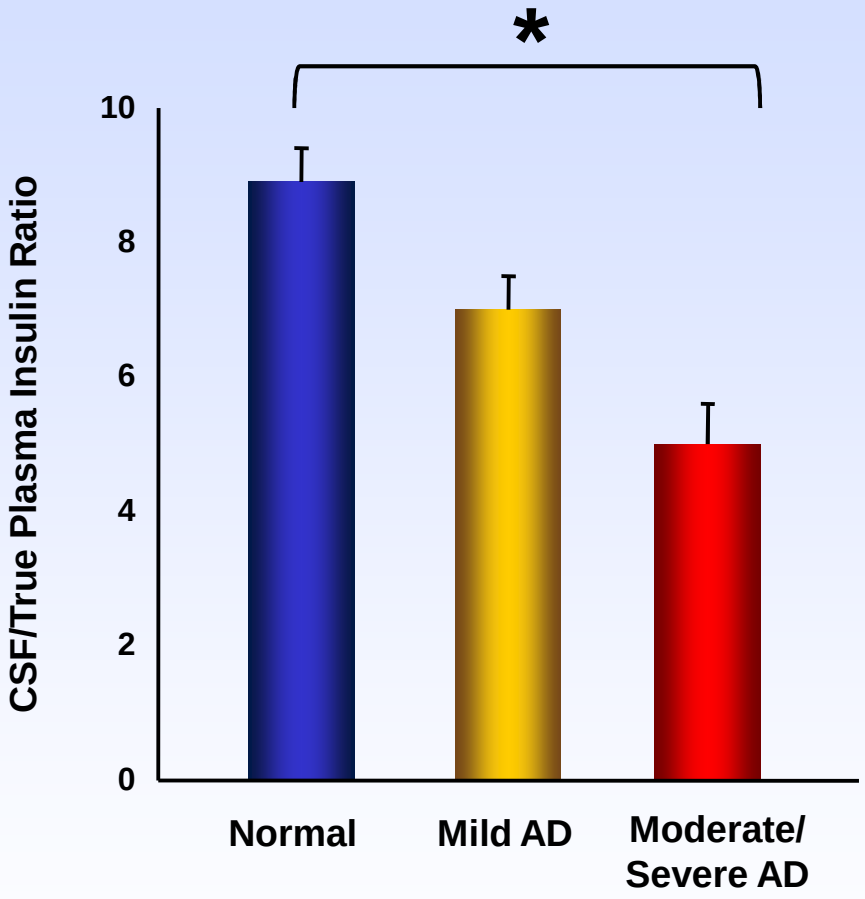


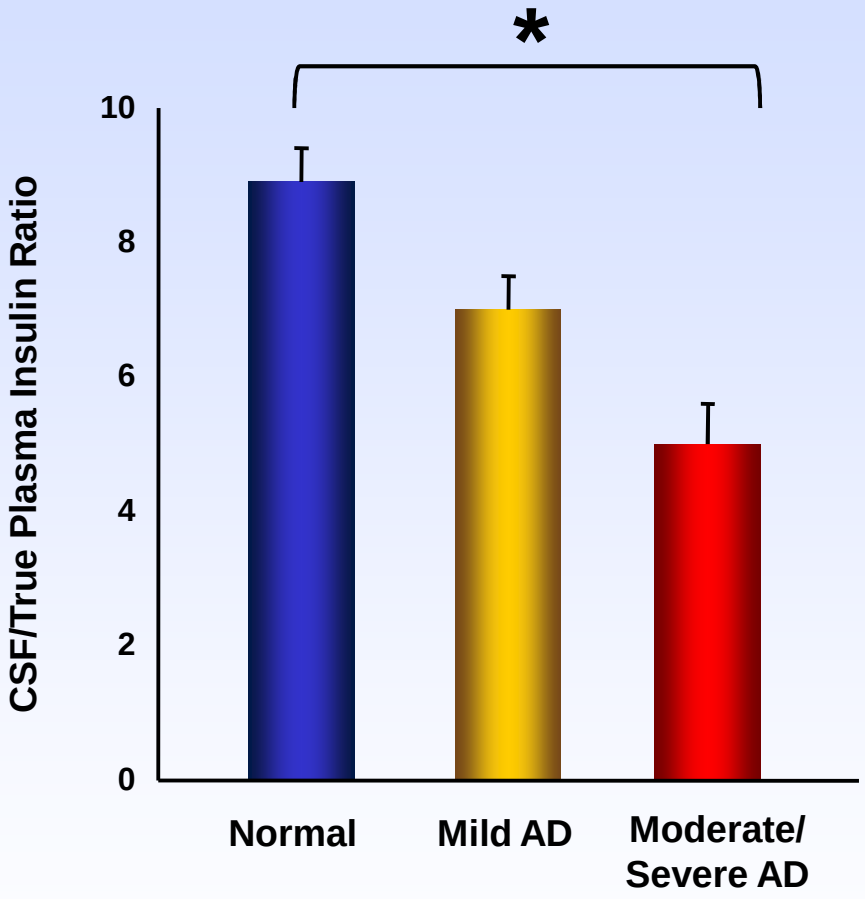
Kodl & Seaquist, Endocrine Rev 2008

Impaired brain insulin signaling in Alzheimer‘s disease



Craft et al., Neurology 1998

Impaired brain insulin signaling in Alzheimer‘s disease



- Reduction of insulin receptors and markers of insulin signaling in the brain of Alzheimer‘s patients (Frolich et al., J Neural Transm 1998)

Craft et al., Neurology 1998

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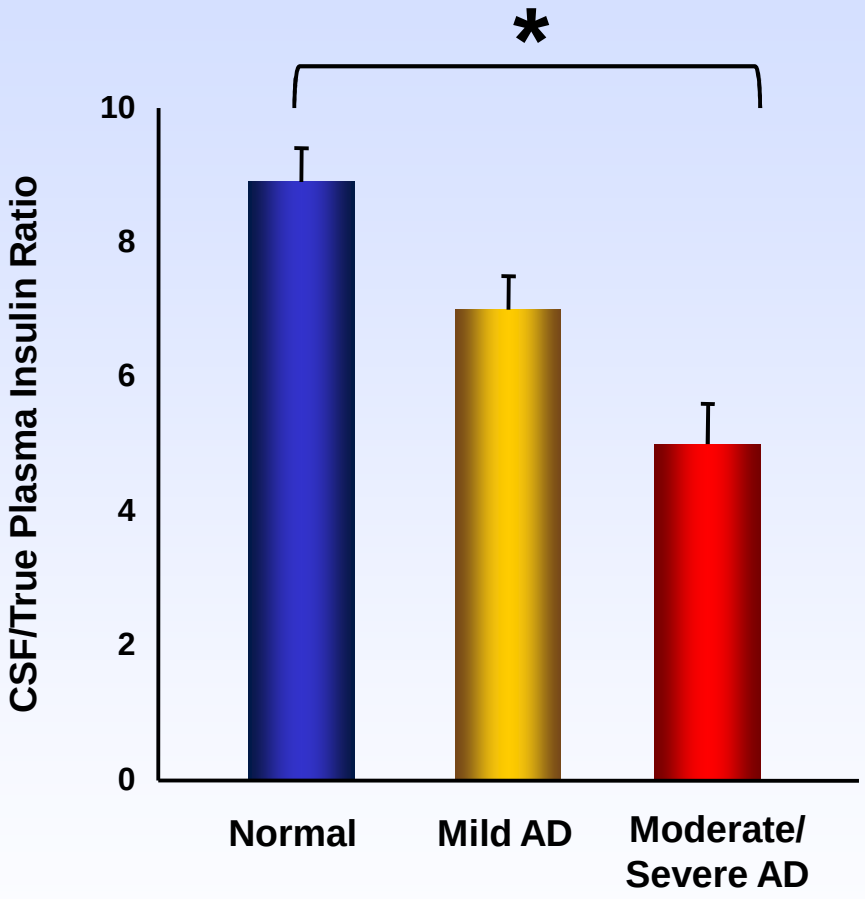
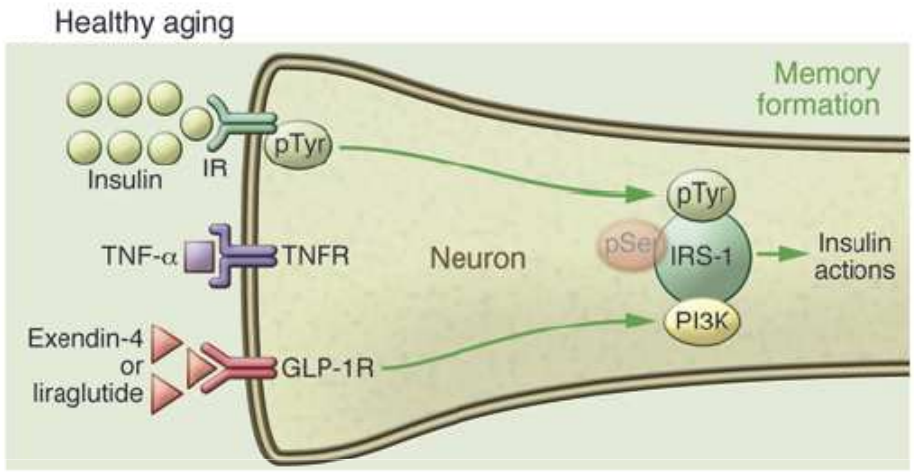


- Reduction of insulin receptors and markers of insulin signaling in the brain of Alzheimer‘s patients (Frolich et al., J Neural Transm 1998)
- Inducing peripheral insulin resistance via high fat/sucrose diets increases brain amyloid concentrations and impairs memory function in mouse models of Alzheimer’s disease (Cao et al., J Biol Chem 2007; Ho et al., FASEB J 2004).

Craft et al., Neurology 1998

Brain insulin signaling in healthy aging



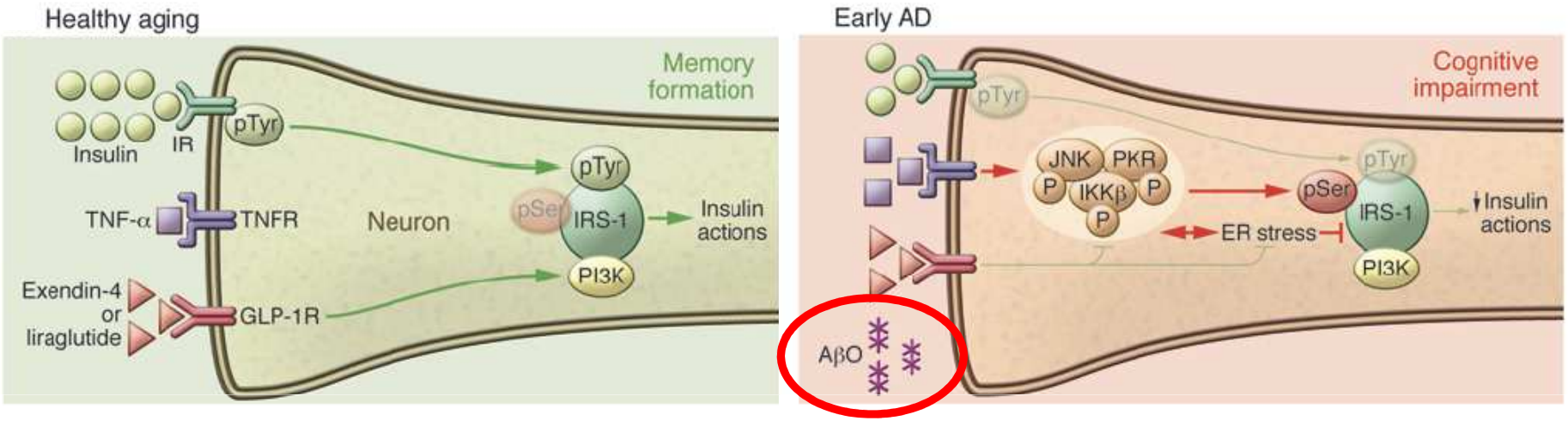
Science in medicine

Alzheimer's disease and insulin resistance: translating basic science into clinical applications

Fernanda G. De Felice

Institute of Medical Biochemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

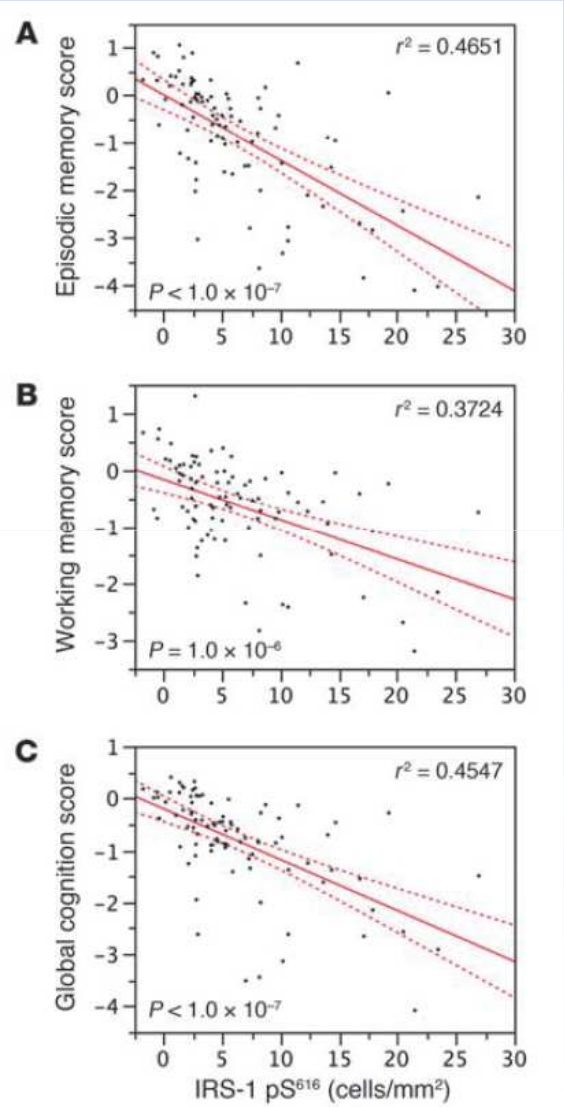
Impaired brain insulin signaling in early Alzheimer's disease



de Felice, JCI 2013

- Accumulation of amyloid β oligomers stimulates stress-sensitive kinase pathways, resulting in **serine phosphorylation of insulin receptor substrate protein-1 (IRS-1)**, which decreases downstream insulin signaling.

Alzheimer's disease symptoms and brain insulin signaling



Research article Related article, page 1191

Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline

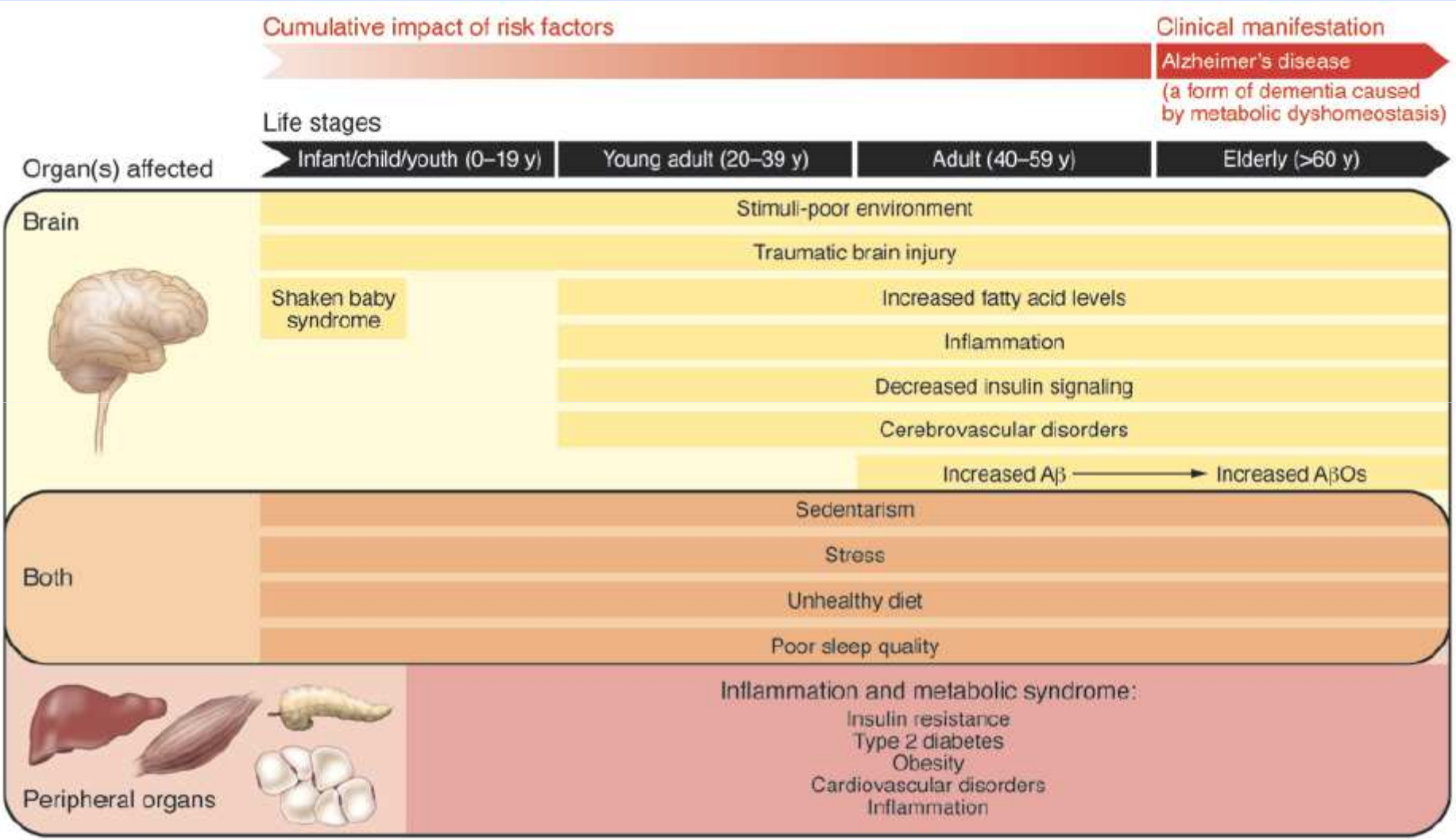
Konrad Talbot,[1] Hoau-Yan Wang,[2] Hala Kazi,[1] Li-Ying Han,[1] Kalindi P. Bakshi,[2] Andres Stucky,[2] Robert L. Fuino,[1] Krista R. Kawaguchi,[1] Andrew J. Samoyedny,[1] Robert S. Wilson,[3] Zoe Arvanitakis,[3] Julie A. Schneider,[3] Bryan A. Wolf,[4,5] David A. Bennett,[3] John Q. Trojanowski,[5] and Steven E. Arnold[1]

[1]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [2]Department of Physiology, Pharmacology, and Neuroscience, Sophie Davis School of Biomedical Education, City University of New York Medical School, New York, New York, USA. [3]Rush Alzheimer's Disease Center and Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA. [4]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA. [5]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

Talbot et al., JCI 2012

- The density of hippocampal CA1 neurons displaying **phosphorylation of IRS-1 at serine 616** was inversely associated with episodic memory, working memory, and global cognition in AD patients.

Fernanda de Felice: a “cumulative” hypothesis



JCI 2013

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Intranasal insulin in cognitive disorders: Suzanne Craft's work

Intranasal insulin improves cognition and modulates β-amyloid in early AD

M.A. Reger, PhD
G.S. Watson, PhD
P.S. Green, PhD
C.W. Wilkinson, PhD
L.D. Baker, PhD
B. Cholerton, PhD
M.A. Fishel, MD
S.R. Plymate, MD
J.C.S. Breitner, MD, MPH
W. DeGroodt, MS
P. Mehta, PhD
S. Craft, PhD

ABSTRACT

Background: Reduced brai
served in patients with Alz
administration improve me
bly by augmenting low bra
extracellular pathways to t

Objective: We tested the h
tion in patients with early
proportion of verbal inform
measure. Secondary outco
and plasma levels of insulir

Methods: Twenty-five part
20 IU BID intranasal insuli

ELSEVIER

Neurobiology of Aging xxx (2005) xxx–xxx

NEUROBIOLOGY OF AGING

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Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype

M.A. Reger[a,b], G.S. Watson[a,b], W.H. Frey II[f,g], L.D. Baker[a,b], B. Cholerton[a,b], M.L. Keeling[a,b], D.A. Belongia[a,b], M.A. Fishel[a,d], S.R. Plymate[a,c], G.D. Schellenberg[a,c,d,e], M.M. Cherrier[a,b], S. Craft[a,b,*]

CLINICA

SECTION EDITOR:

ONLINE FIRST

Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment

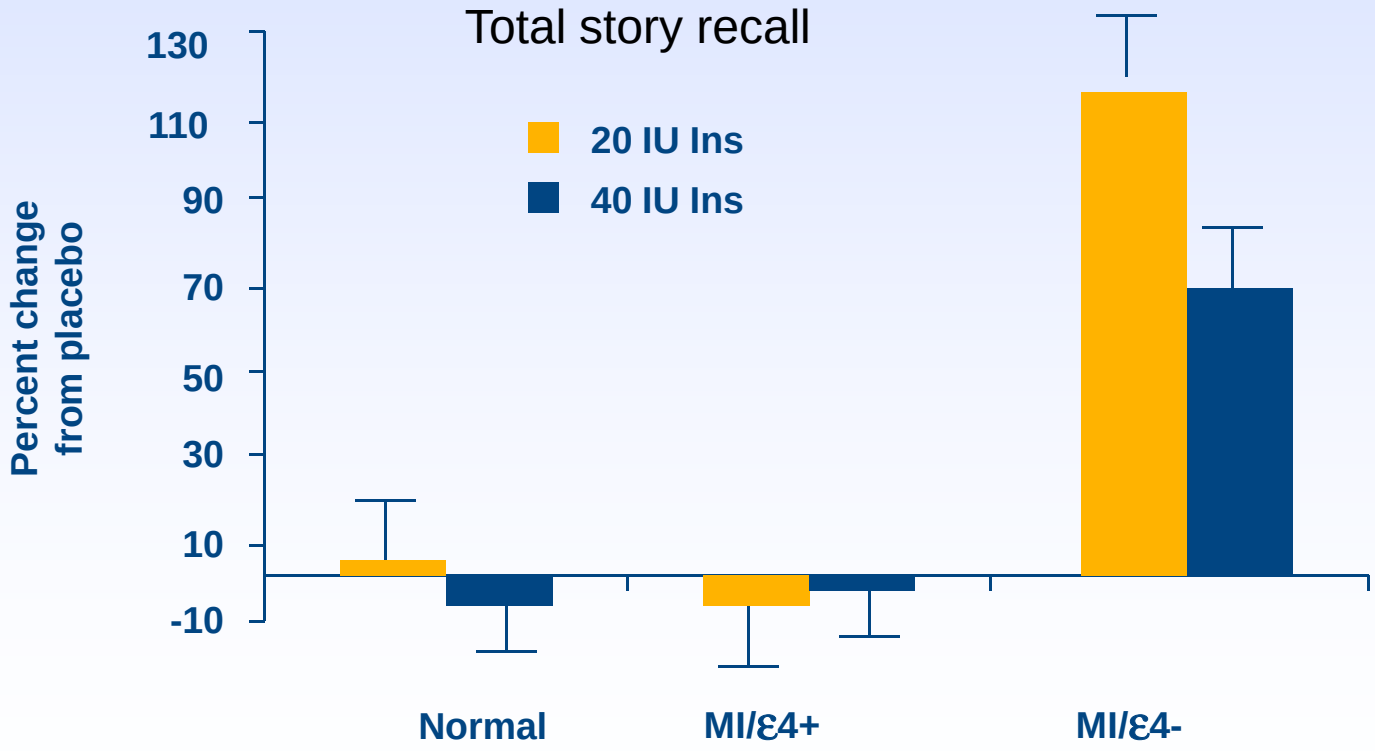
A Pilot Clinical Trial

Suzanne Craft, PhD; Laura D. Baker, PhD; Thomas J. Montine, MD, PhD; Satoshi Minoshima, MD, PhD; G. Stennis Watson, PhD; Amy Claxton, PhD; Matthew Arbuckle, BA; Maureen Callaghan, MD; Elaine Tsai, MD; Stephen R. Plymate, MD; Pattie S. Green, PhD; James Leverenz, MD; Donna Cross, PhD; Brooke Gerton, MD

Intranasal insulin acutely improves memory in older adults

Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype

M.A. Reger[a,b], G.S. Watson[a,b], W.H. Frey II[f,g], L.D. Baker[a,b], B. Cholerton[a,b], M.L. Keeling[a,b], D.A. Belongia[a,b], M.A. Fishel[a,d], S.R. Plymate[a,c], G.D. Schellenberg[a,c,d,e], M.M. Cherrier[a,b], S. Craft[a,b,*]



Reger et al., Neurobiol Aging 2006

Intranasal insulin improves memory in early Alzheimer patients

Intranasal insulin improves cognition and modulates β-amyloid in early AD

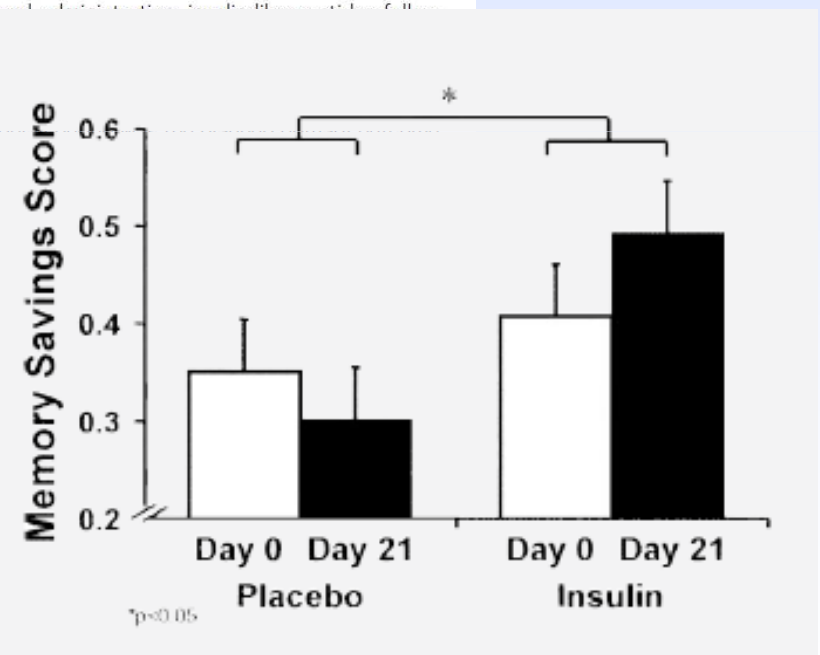
M.A. Reger, PhD
G.S. Watson, PhD
P.S. Green, PhD
C.W. Wilkinson, PhD
L.D. Baker, PhD
B. Cholerton, PhD
M.A. Fishel, MD
S.R. Plymate, MD
J.C.S. Breitner, MD, MPH
W. DeGroodt, MS
P. Mehta, PhD
S. Craft, PhD

ABSTRACT

Background: Reduced brain insulin signaling and low CSF-to-plasma insulin ratios have been observed in patients with Alzheimer disease (AD). Furthermore, intracerebroventricular or IV insulin administration improve memory, alter evoked potentials, and modulate neurotransmitters, possibly by augmenting low brain levels. After intrana
extracellular pathways to the brain within 15 minu

Objective: We tested the hypothesis that daily intr
tion in patients with early AD or its prodrome, a
proportion of verbal information retained after a
measure. Secondary outcome measures included
and plasma levels of insulin, glucose, β-amyloid, a

Methods: Twenty-five participants were randomly
20 IU BID intranasal insulin treatment (n = 13) us



Reger et al., Neurology 2008

Four months of in. insulin treatment in patients with mild AD

CLINICAL TRIALS

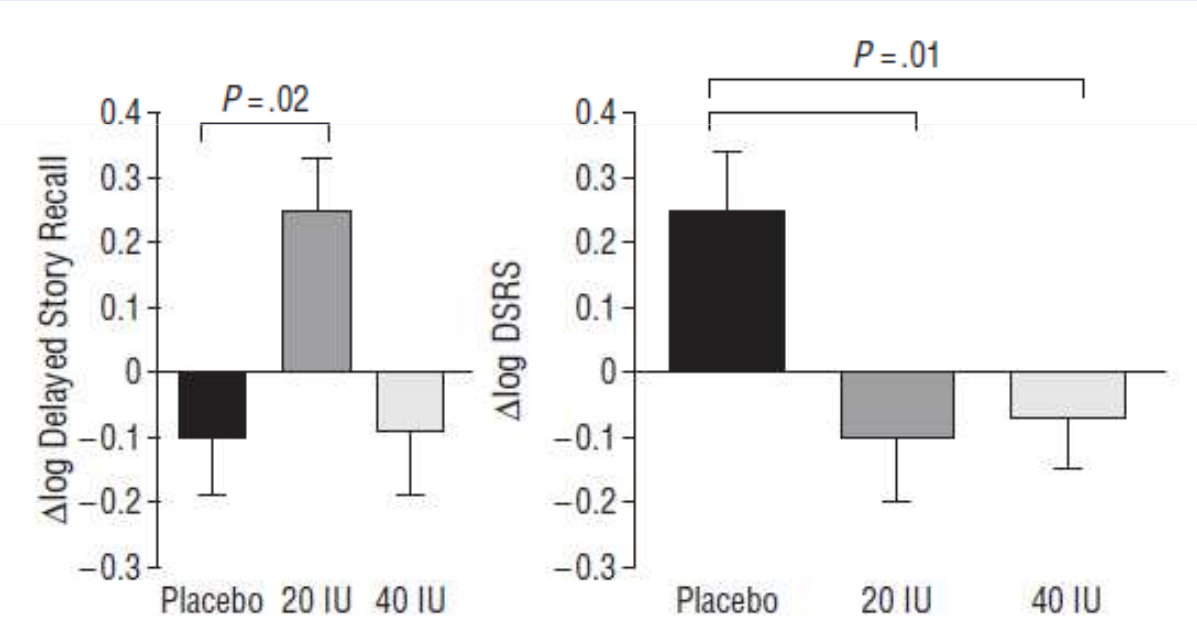
SECTION EDITOR: IRA SHOULSON, MD

ONLINE FIRST

Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment

A Pilot Clinical Trial

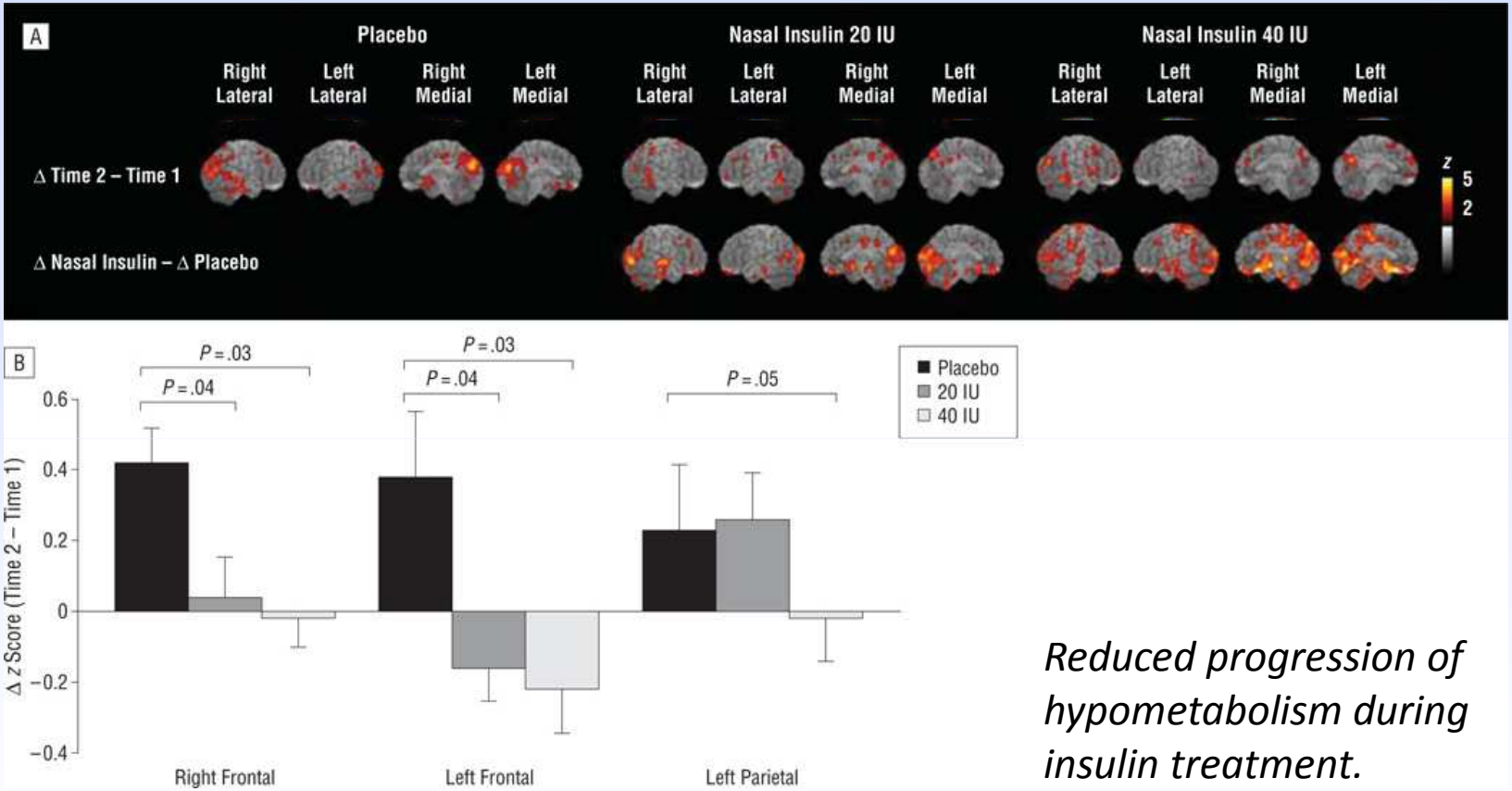
Suzanne Craft, PhD; Laura D. Baker, PhD; Thomas J. Montine, MD, PhD; Satoshi Minoshima, MD, PhD; G. Stennis Watson, PhD; Amy Claxton, PhD; Matthew Arbuckle, BA; Maureen Callaghan, MD; Elaine Tsai, MD; Stephen R. Plymate, MD; Pattie S. Green, PhD; James Leverenz, MD; Donna Cross, PhD; Brooke Gerton, MD



Delayed story recall **Dementia Severity Rating Scale**

Craft et al., Arch Neurology 2011

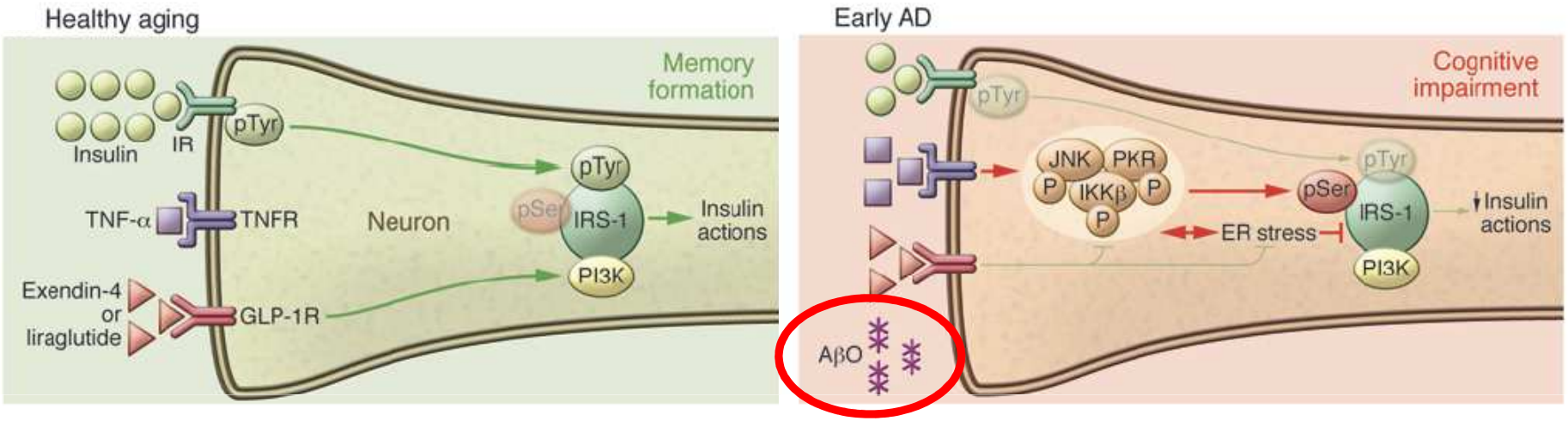
Four months of in. insulin treatment in patients with mild AD

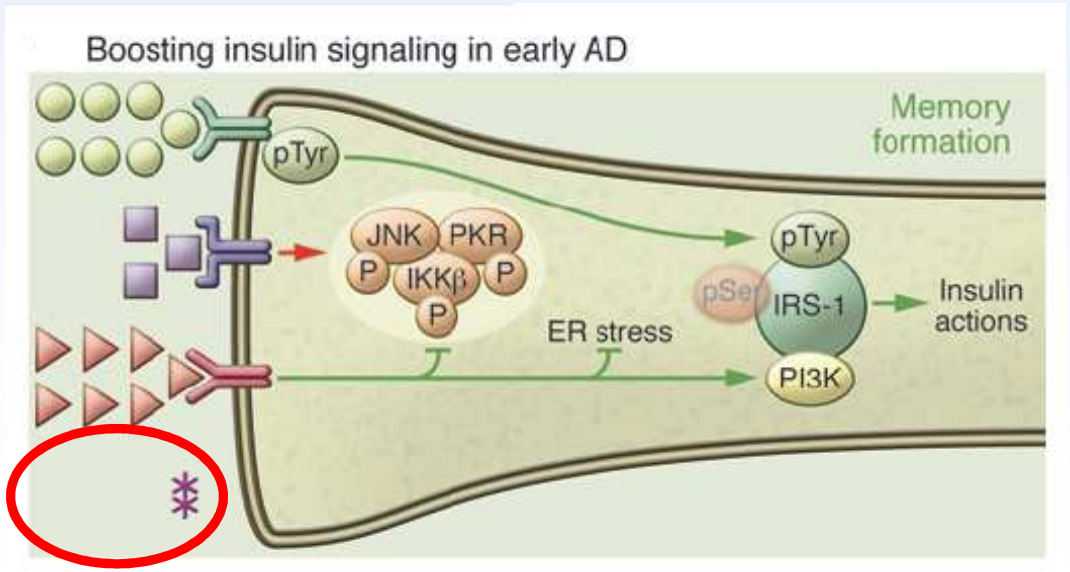


Reduced progression of hypometabolism during insulin treatment.

Craft et al., Arch Neurology 2011

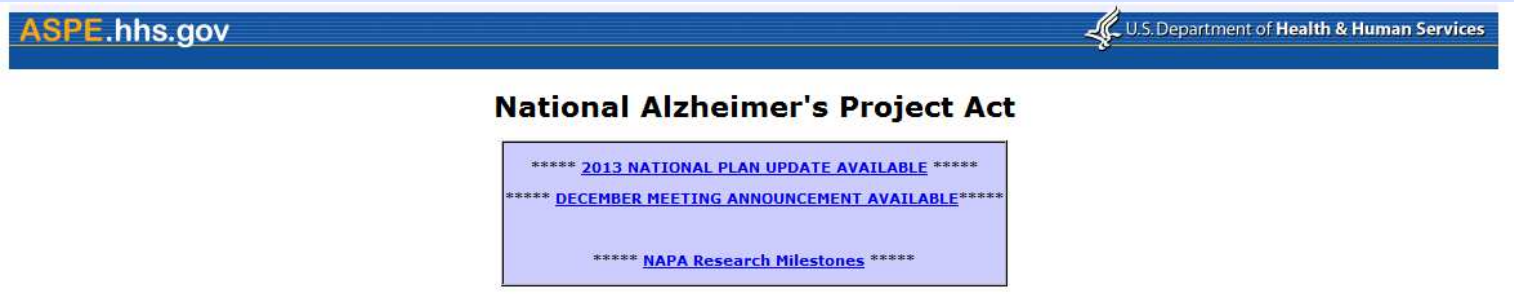
Boosting brain insulin signaling in early Alzheimer's disease





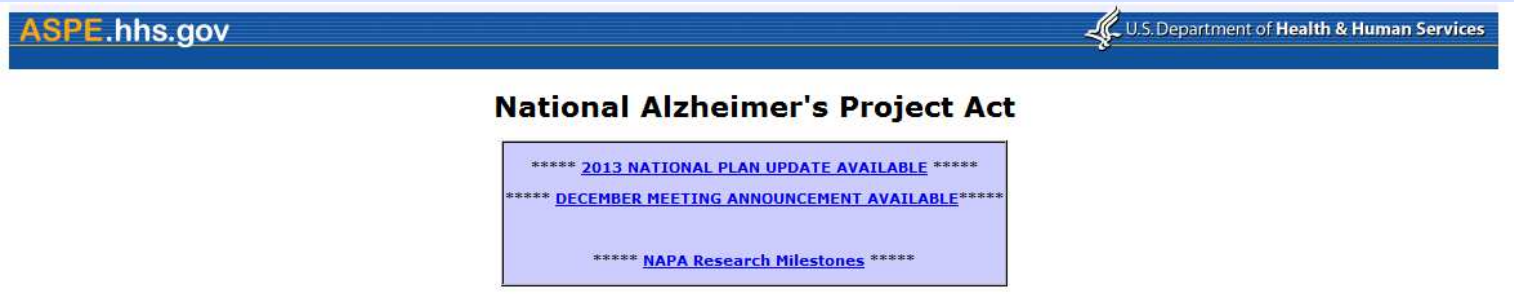
de Felice, JCI 2013

National plan to address Alzheimer‘s disease



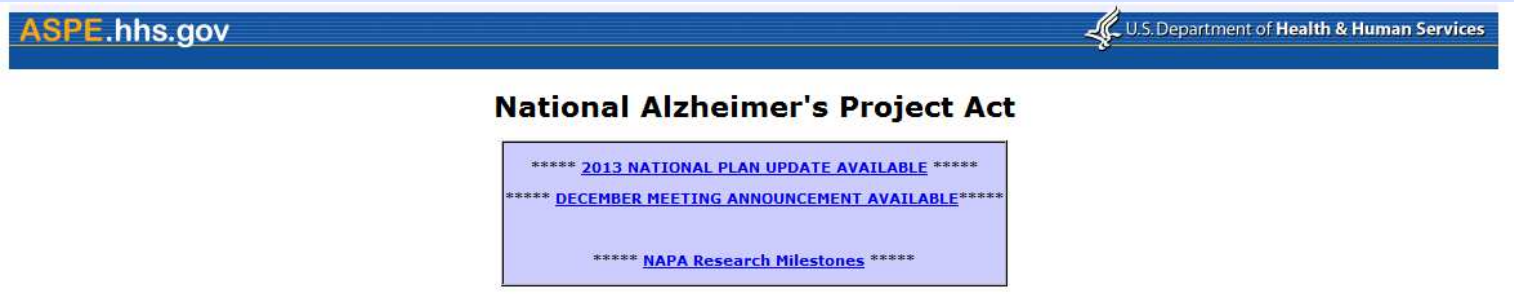
- Development of effective prevention and treatment approaches for Alzheimer’s disease and related dementias by 2025

National plan to address Alzheimer‘s disease



- Development of effective prevention and treatment approaches for Alzheimer’s disease and related dementias by 2025
- Funding of two major clinical trials
- $16 million for the first prevention trial in people at the highest risk for the disease

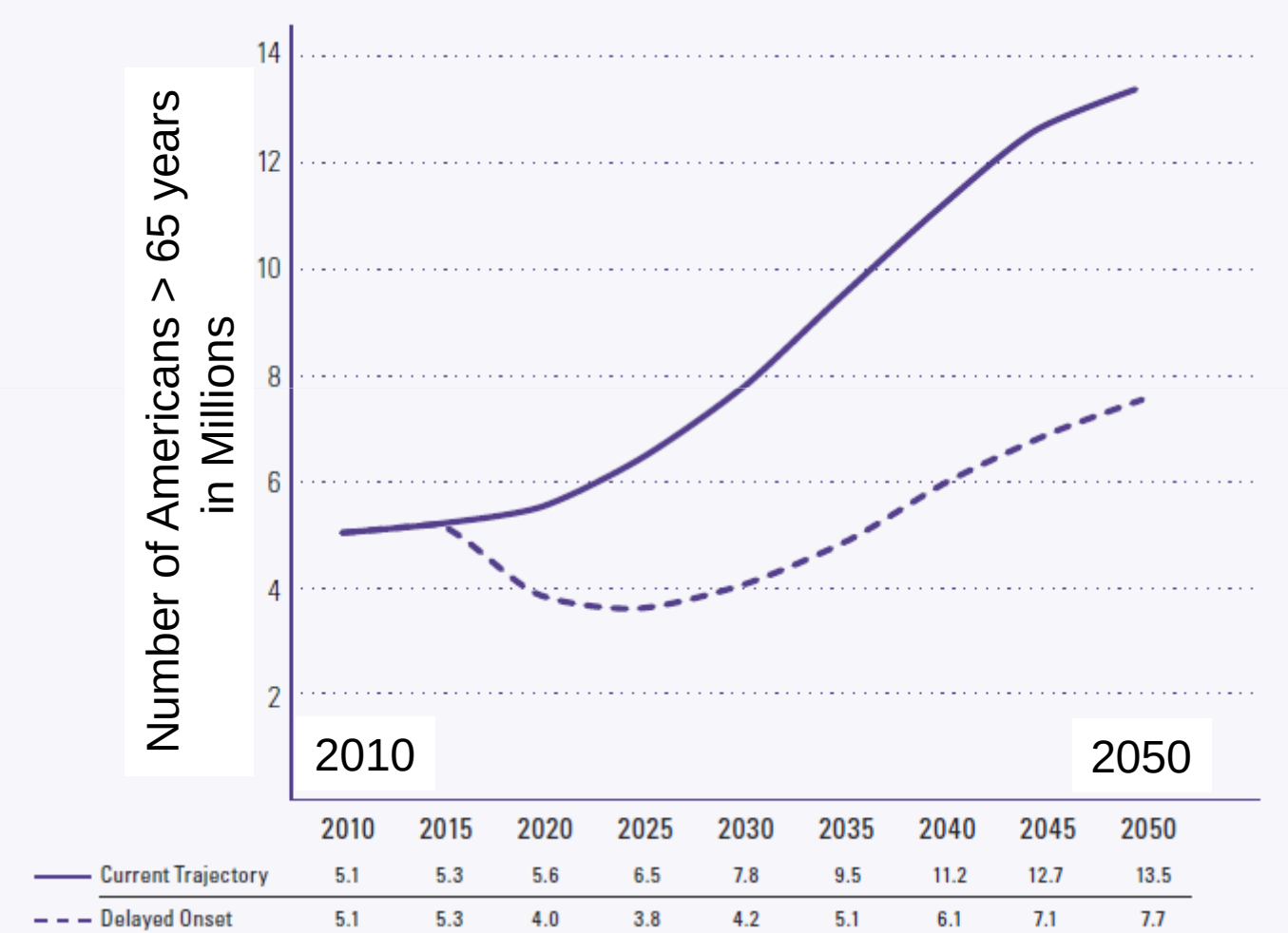
National plan to address Alzheimer‘s disease



- Development of effective prevention and treatment approaches for Alzheimer’s disease and related dementias by 2025
- Funding of two major clinical trials
- $16 million for the first prevention trial in people at the highest risk for the disease
- $7.9 million to test an **insulin nasal spray** for treating Alzheimer’s disease: 240 volunteers participate in a year-long treatment trial at multiple sites across the U.S. that is coordinated by **Suzanne Craft**

“Changing the trajectory of Alzheimer’s disease”

Assuming that the onset of Alzheimer‘s disease can be delayed by five years due to a novel treatment available from 2015 on…



	2010	2015	2020	2025	2030	2035	2040	2045	2050
Current Trajectory	5.1	5.3	5.6	6.5	7.8	9.5	11.2	12.7	13.5
Delayed Onset	5.1	5.3	4.0	3.8	4.2	5.1	6.1	7.1	7.7

American Alzheimer‘s Association, 2010

Thank you

Jan Born
Christian Benedict
Susanne Diekelmann
Horst-Lorenz Fehm
Stefan Fischer
Graham Finlayson
William H. Frey II
Fabian Griebe
Sabine Groch
Suzanne Higgs
Werner Kern
Rosi Krug
Hendrik Lehnert
Felix Machleidt
Lisa Marshall
Matthias Mölle
Anja Niepelt
Anja Otterbein
Bernd Schultes
Ullrich Wagner
Ines Wilhelm

Dpt. of Neuroendocrinology and Medical Clinic I, University of Lübeck, Germany
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Dpt. of Neuroscience, Uppsala University, Sweden
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School of Psychology, University of Birmingham, UK
Inst. of Psychological Sciences, University of Leeds, UK
Alzheimer's Research Center at Region's Hospital, St. Paul, MN, USA

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Alzheimer's Research Center at Region's Hospital, St. Paul, MN, USA

Thank you for your attention!

Obesity and dementia: Epidemiological data

Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study

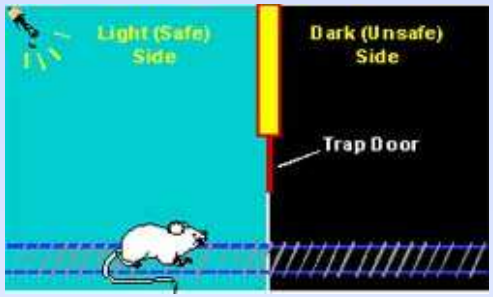
Rachel A Whitmer, Erica P Gunderson, Elizabeth Barrett-Connor, Charles P Quesenberry Jr, Kristine Yaffe

BMJ 330:1360-62, 2005

- 10 276 men and women, age 40-45 yrs, 27 yrs follow up
- Overweight increased the risk of future dementia by **35%**
- Obesity increased the risk of future dementia by **74%**

Insulin i.c.v. improves memory in rats

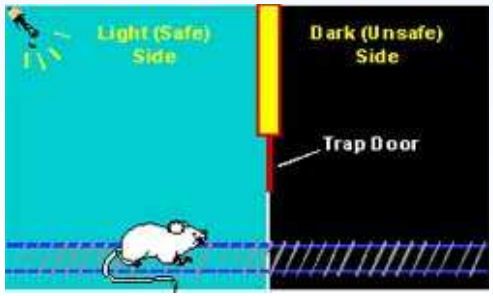
Training

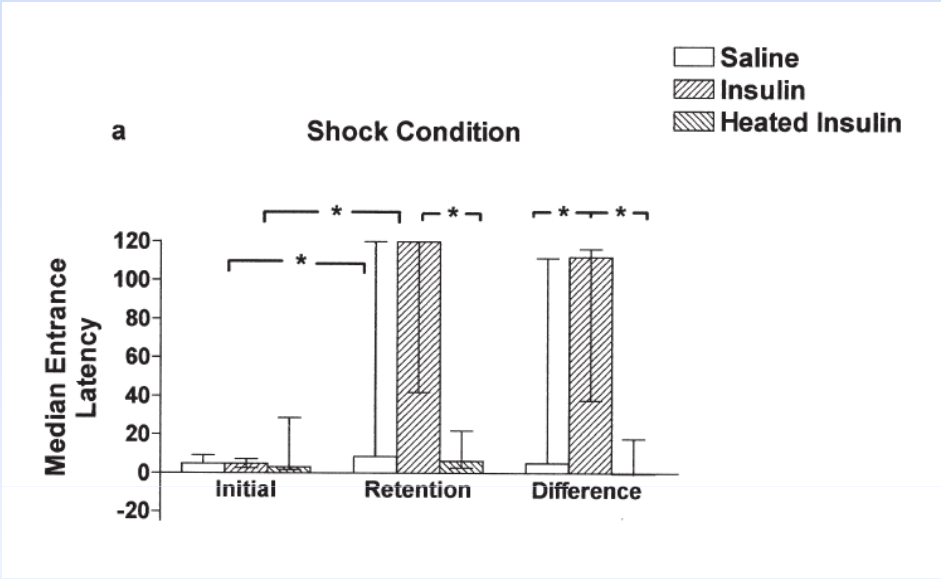


ICV: 4 mU insulin, heat-deactivated insulin or saline vehicle

24-h retention interval

Recall





Park et al., Physiol Behav 2000

The nose-brain pathway: Animal studies

Drugs: Cocaine, Albumin, Apomorphine, L-Dopa, Dextran, Dihydroergotamine

Antibiotics: Cephalexin, Sulfonamides, Zidovudine

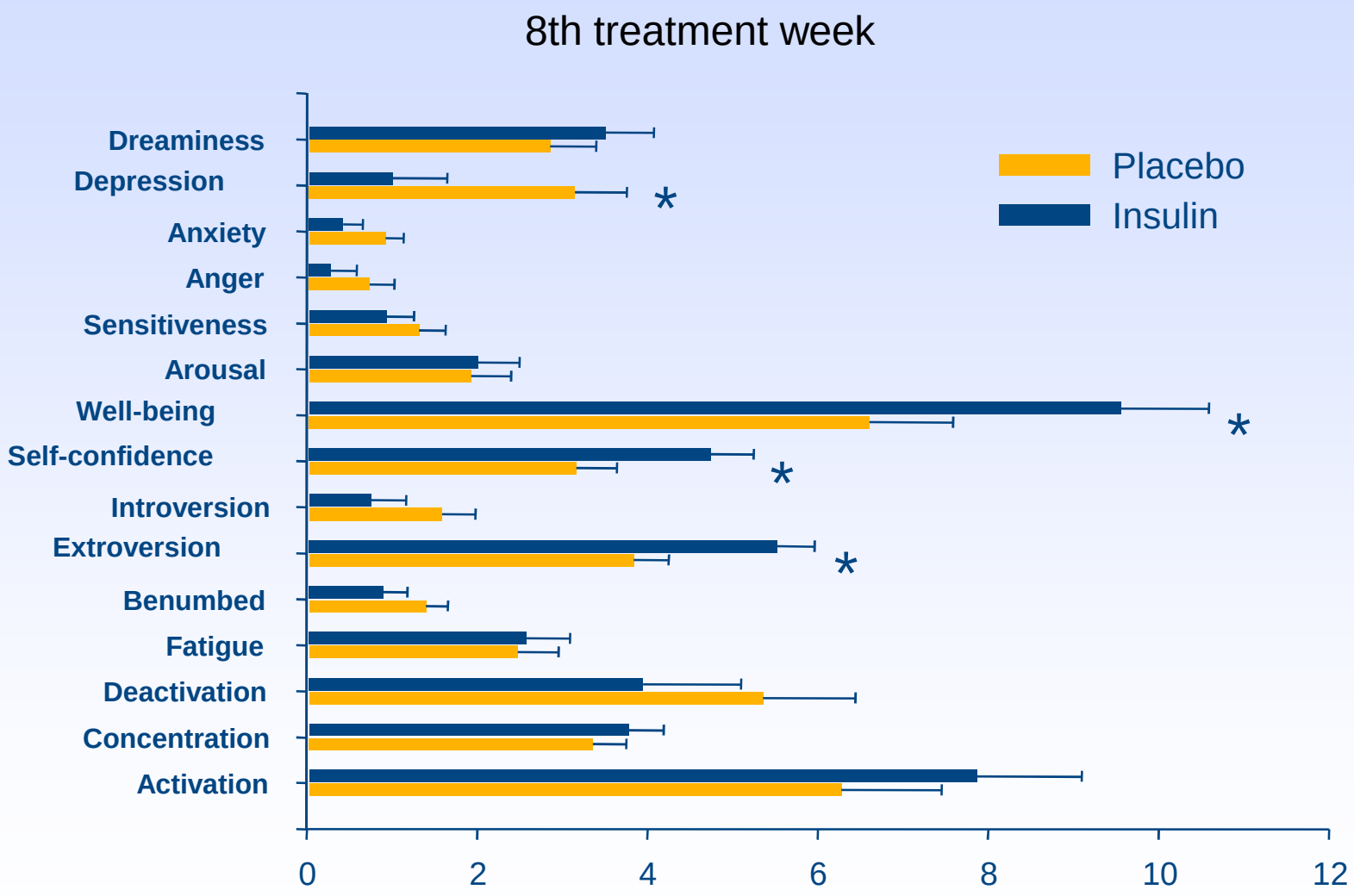
Metals: Cadmium, Aluminium, Mercury, Magnesium, Gold

Hormones: IGF-1, Insulin, Estradiol, Progesterone

Viruses/Microorganisms: Rabies, Pneumococci, Borna, Salmonella enteritidis, Corona, Bazillus piliformis, Amebie, Equine encephalo-myelitis, Hepatitis, Herpes simplex, Influenca, Mice encephalitis, Poliomyelitis, Pseudorabies, Vaccinia, Yellow fever

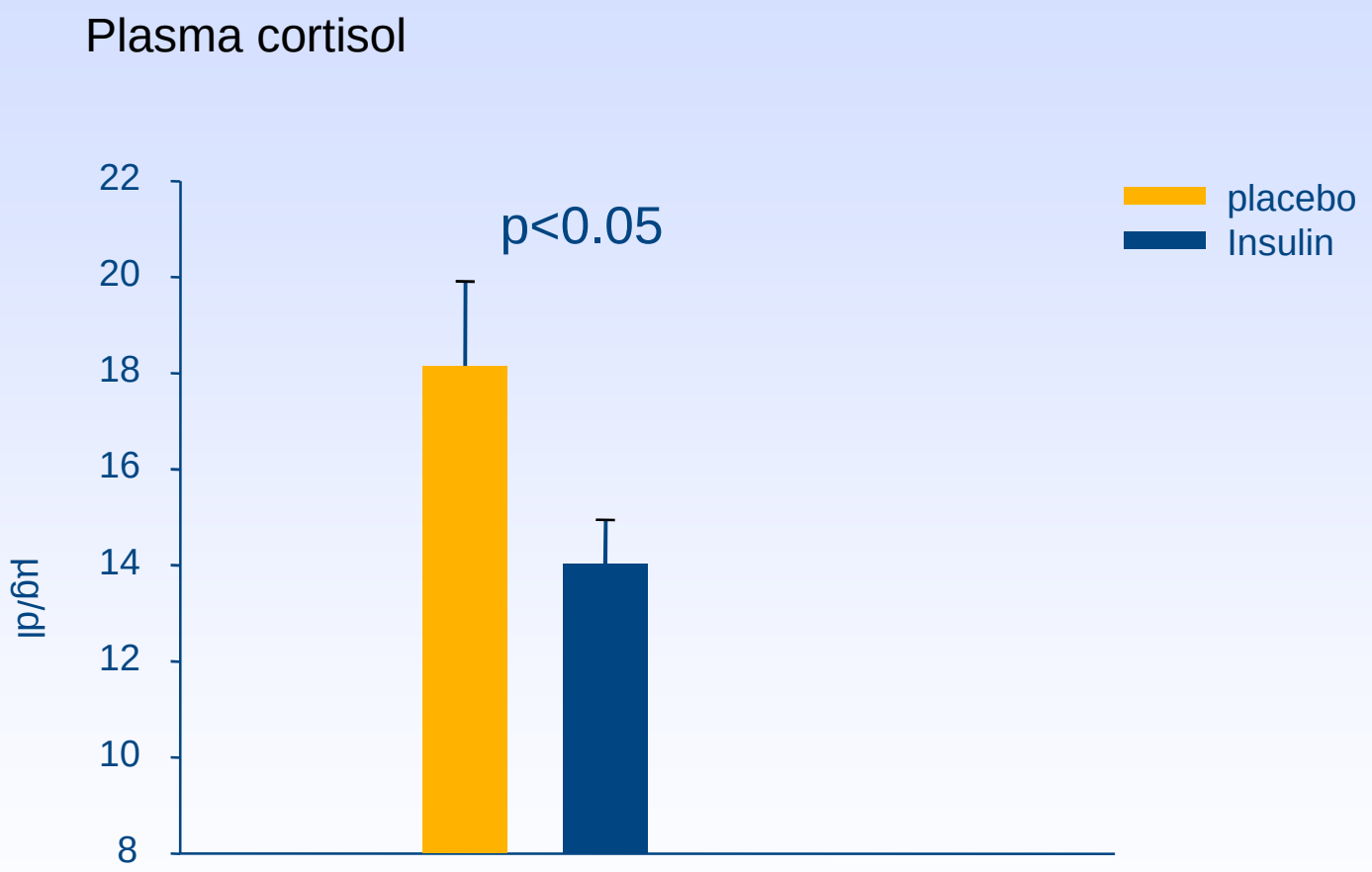
Misc.: Leucine, Nerve growth factor, Horseradish peroxidase, wheat germ agglutinine

Longterm administration of i.n. insulin: Mood



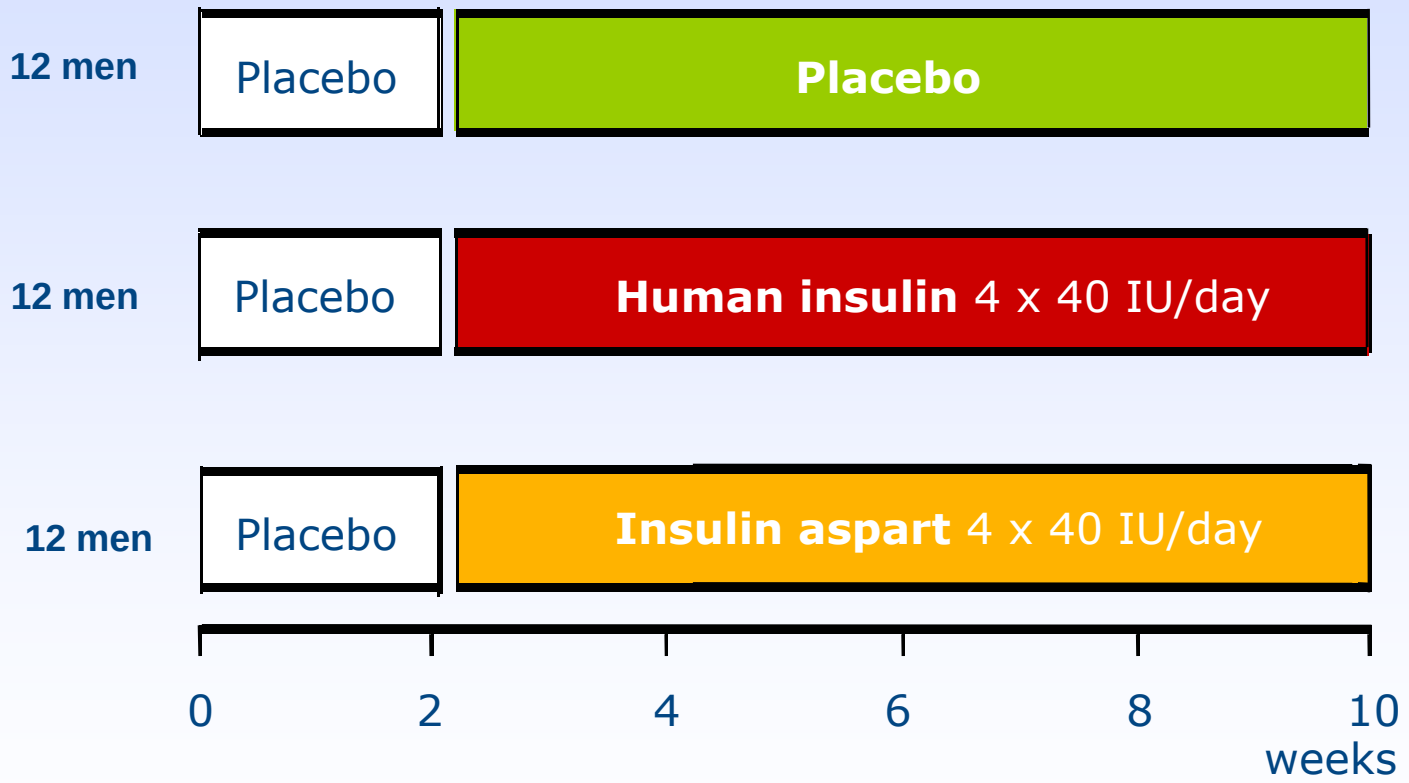
Benedict et al., Psychoneuroendocrinology 2004

Longterm administration of i.n. insulin: Cortisol concentrations

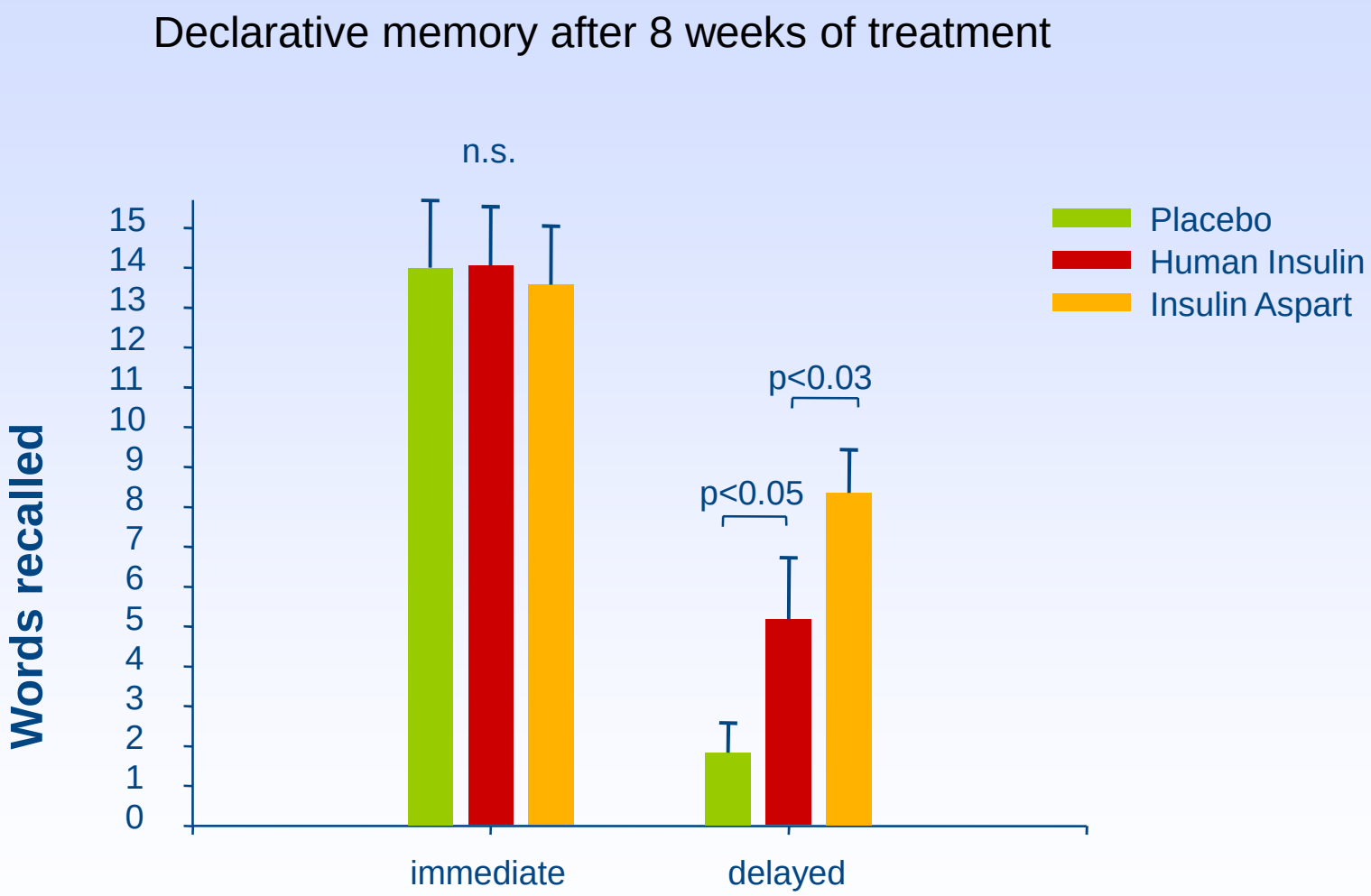


Benedict et al., Psychoneuroendocrinology 2004

Longterm administration of i.n. insulin aspart



Longterm administration of i.n. insulin aspart

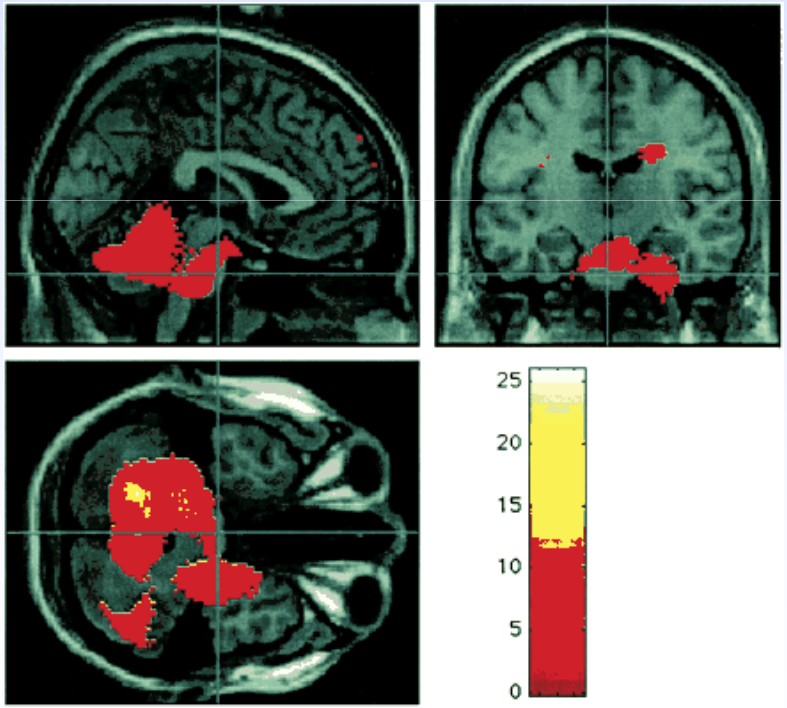


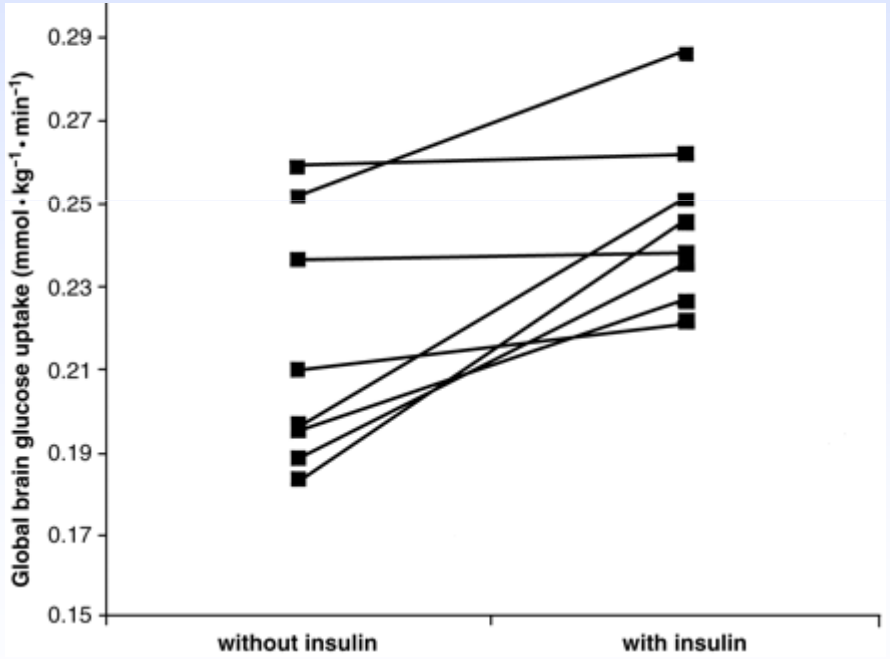
Benedict et al., Neuropsychopharmacology 2007

Potential mechanisms of memory improvement by insulin

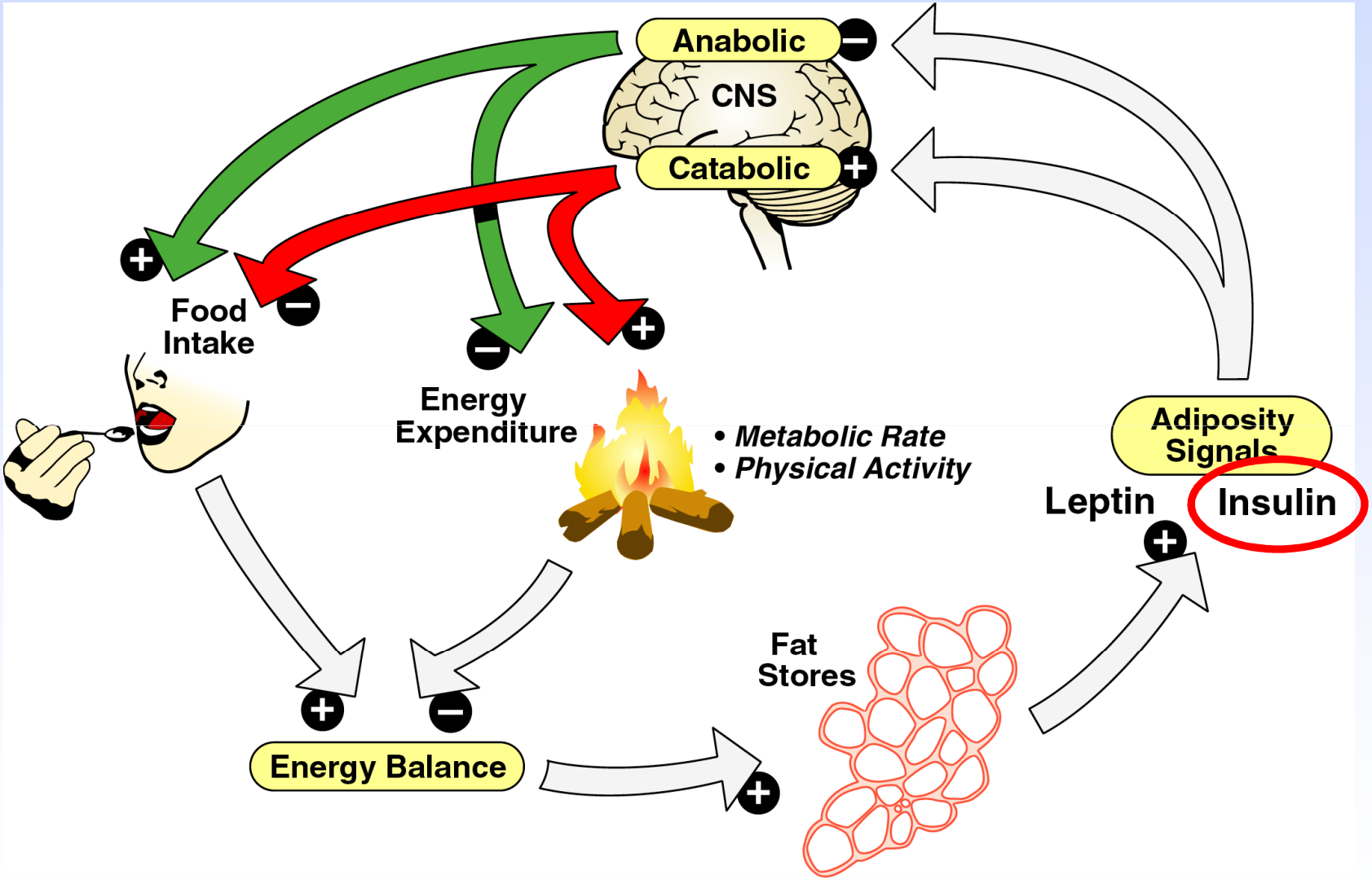
➢ Enhancement of local cerebral glucose utilization via GLUT-4/8

(Henneberg & Hoyer, Neurosci Lett 1994; Vannucci et al., Brain Res 1998; Schulingkamp et al., Neurosci Biobehav Rev 2000; **Bingham et al., Diabetes 2002**)



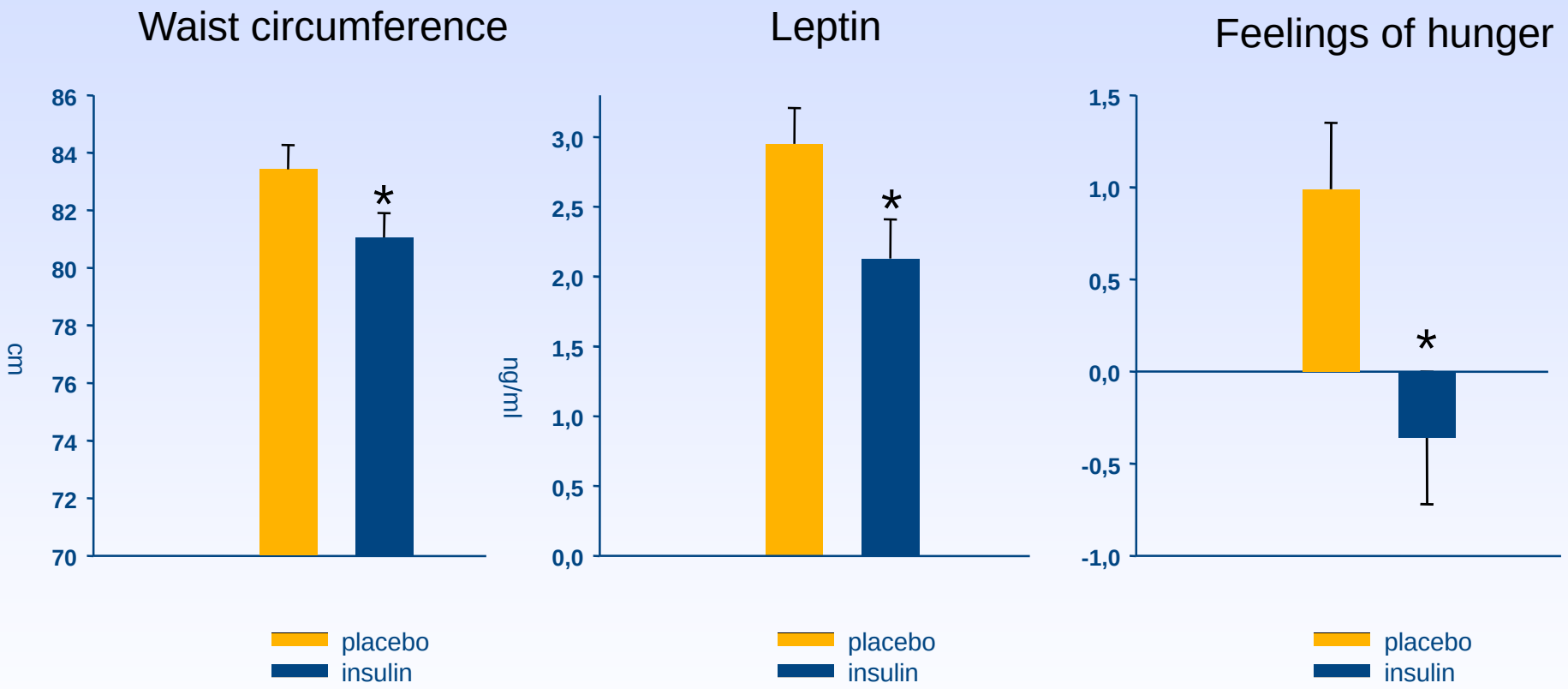


Regulation of energy balance by adiposity signals



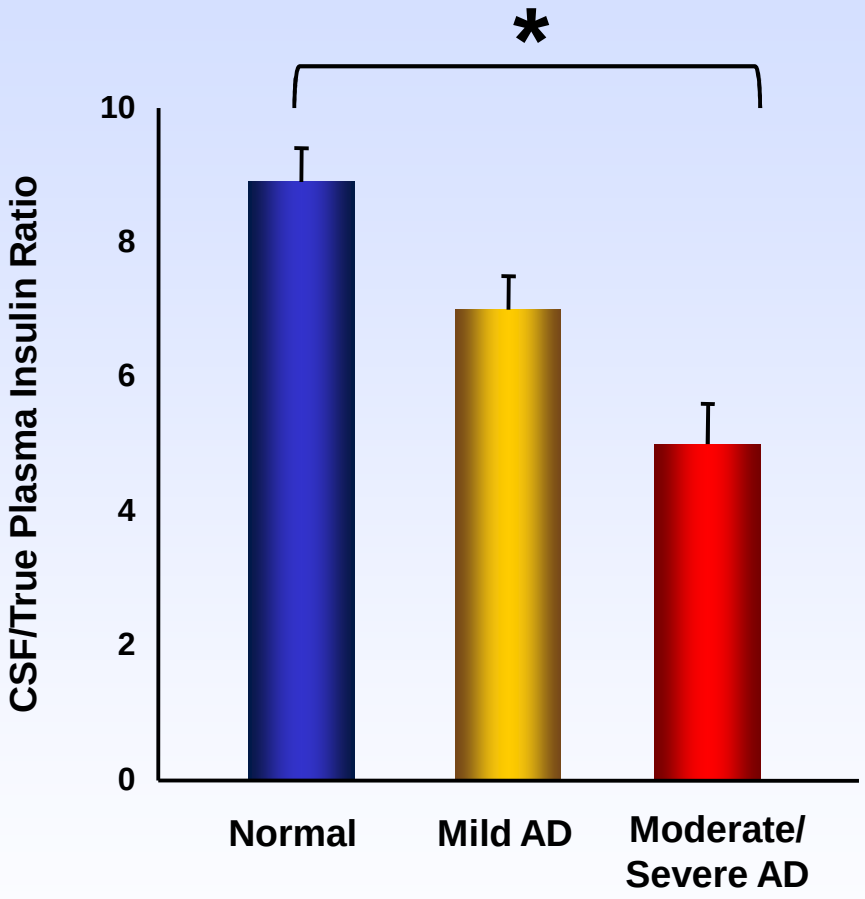
Schwartz et al., Diabetes 2003

Longterm administration of i.n. insulin decreases body fat

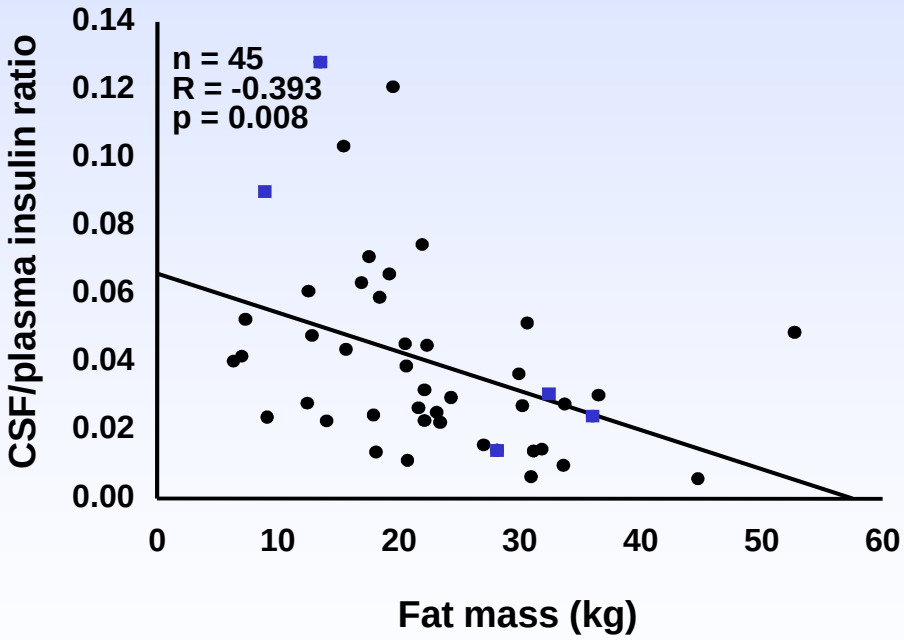


Hallschmid et al., Diabetes 53(11) 2004

Decreased CSF insulin concentrations in Alzheimer‘s *and* obesity



Craft et al., Neurology 1998



Kern et al., Diabetologia 2006

Central nervous insulin resistance in obesity: MEG studies

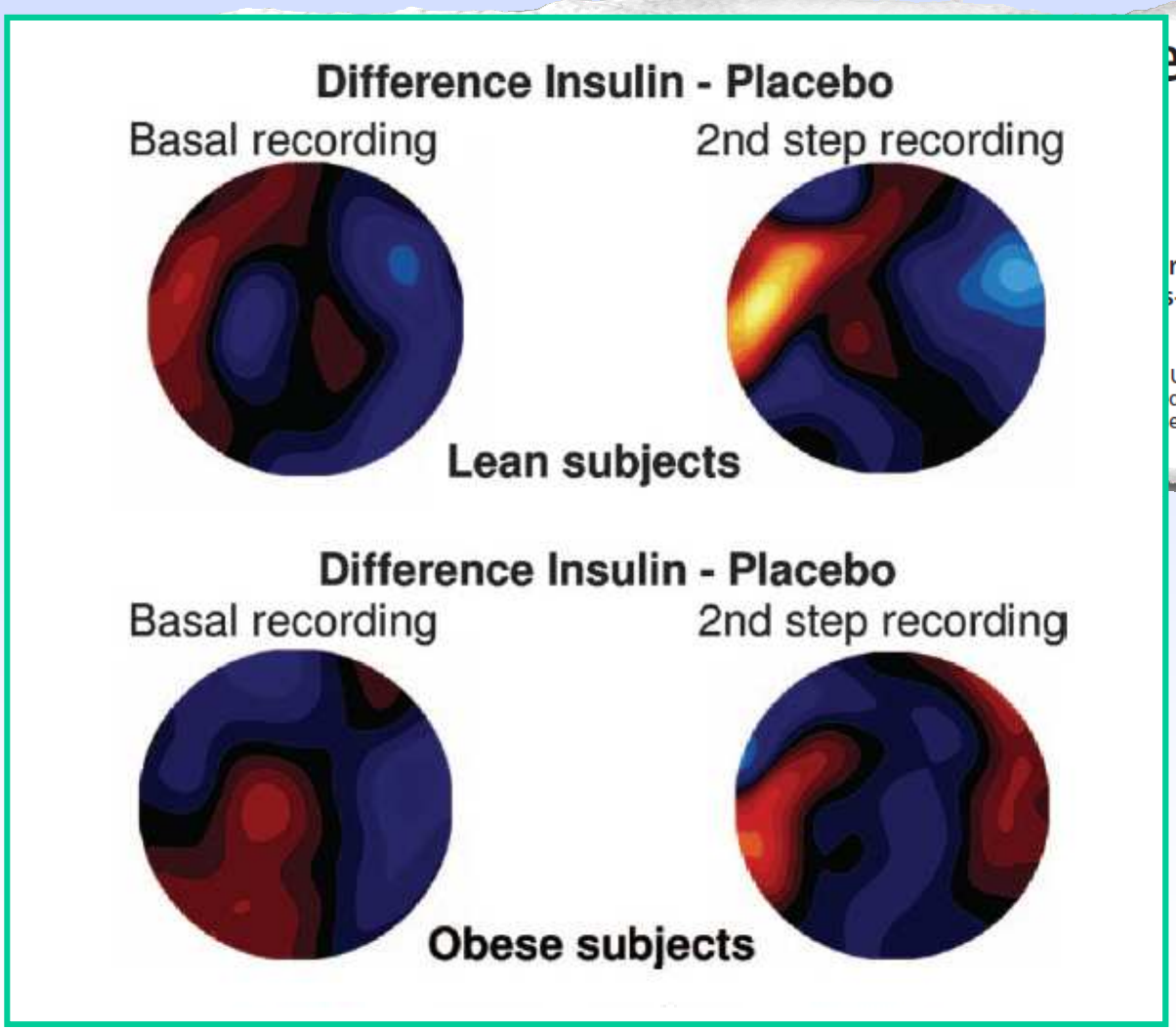
The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: A magnetoencephalographic study

Otto Tschritter*†, Hubert Preissl†‡§, Anita M. Hennige*, Michael Stumvoll*¶, Katarina Porubska‡, Rebekka Frost*, Hannah Marx*, Benjamin Klösel*, Werner Lutzenberger‡, Niels Birbaumer‡‖, Hans-Ulrich Häring*,**, and Andreas Fritsche*

*Medizinische Klinik der Universität and ‡Institute of Medical Psychology and Behavioural Neurobiology, University of Tübingen, 72076 Tübingen, Germany; §Department of Obstetrics and Gynecology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 72205; ¶Medical Department III, University of Leipzig, 04103 Leipzig, Germany; and ‖Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH), Bethesda, MD 20892

Tschritter et al., PNAS 2006

Central nervous insulin resistance in obesity: MEG studies



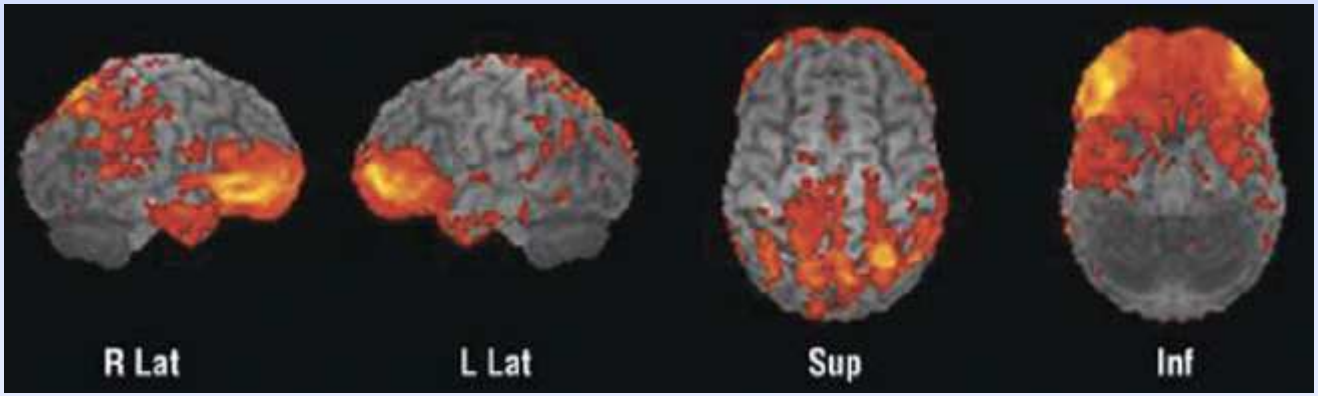
erinsulinemia

rina Porubska‡, Rebekka Frost*,
s-Ulrich Häring*,**,

University of Tübingen, 72076 Tübingen,
dical Sciences, Little Rock, AR 72205;
ection, National Institute

Tschritter et al., PNAS 2006

Peripheral insulin resistance impairs brain glucose metabolism



- Insulin-resistant adults display hypometabolism in default mode network regions such as the posterior cingulate/precuneus (in fluorodeoxyglucose positron emission tomography, FDG-PET).
- Reduced metabolism was associated with subtle reductions in memory encoding.

Baker et al., Arch Neurol 2011

Acute intranasal insulin administration to memory-impaired patients

Subjects

Mean (sd)	Normal Controls	AD ε4-	AD ε4+
N	35	14	12
Age (yrs)	75 (6)	77 (6)	77 (5)
Education	15 (2)	14 (2)	15 (2)
BMI (kg/m^2)	26 (3)	25 (3)	25 (3)
DRS (max=144)	140 (4)	127 (10)	125 (11)

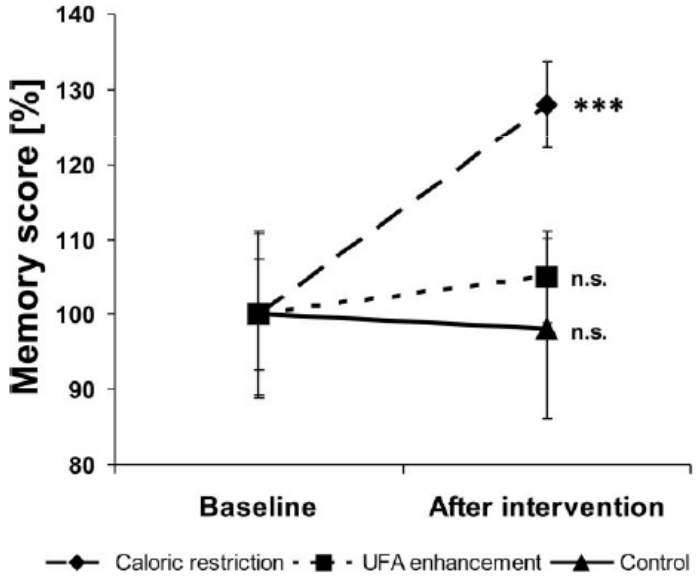
Reger et al., Neurobiol Aging 2006

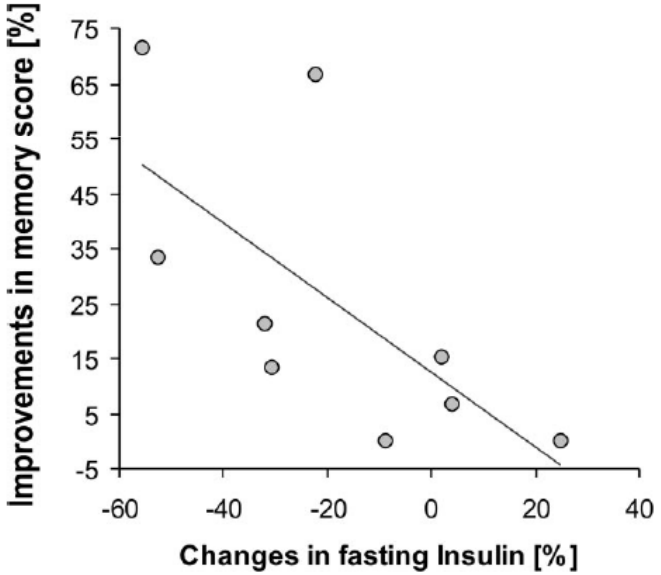
Dieting to improve insulin sensitivity and memory

Caloric restriction improves memory in elderly humans

A. V. Witte[a], M. Fobker[b], R. Gellner[c], S. Knecht[a], and A. Flöel[a,d,1]

Departments of [a]Neurology and [c]Internal Medicine, [b]Center for Laboratory Medicine, and [d]Interdisciplinary Center of Clinical Research, University of Münster, Albert-Schweitzer-Strasse 33, 48149 Münster, Germany





Witte et al., PNAS 2009