Hormesis and Exercise: Support for an Inverted-U Response to Acute and Chronic Work

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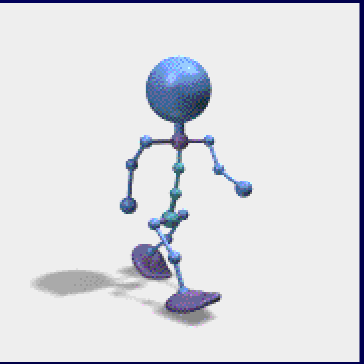
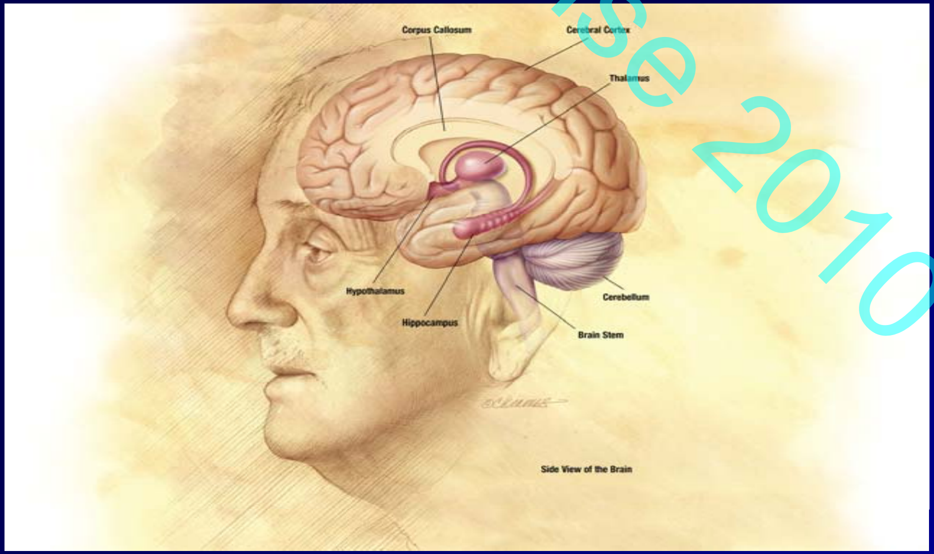
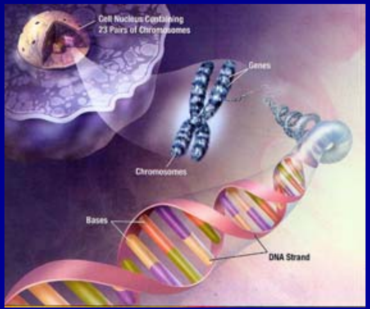
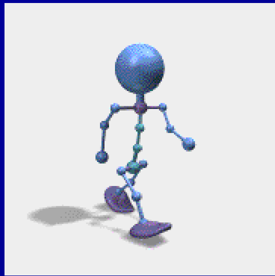
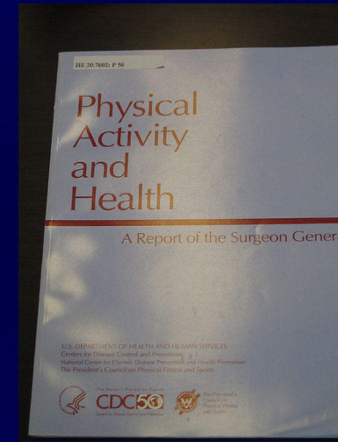








A Report of the Surgeon General, <u>1996</u>



"Physical Activity Reduces Risk of Premature Mortality in General, and of Coronary Heart Disease, Hypertension, Colon Cancer, and Diabetes Mellitus in Particular."

***-mental health and cognitive benefits* (pp. 135-141)**

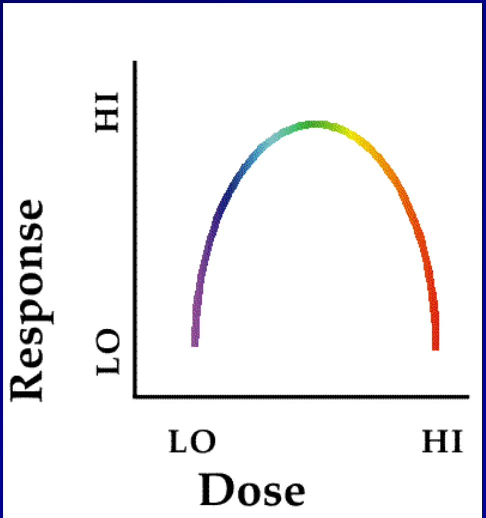
Institute of Medicine Report, 2007

Bottom line: <u>there is documented evidence of significant health benefits of physical activity</u>

But, can we get too much physical activity?

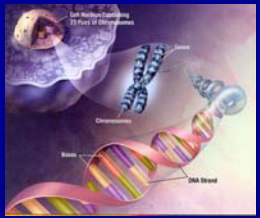
What is the dose-response relationship between the volume / intensity of work negotiated over time and cell aging?

Any evidence of hormesis?



To address this question -

Relationship between Physical activity level, Telomere length, and Telomerase activity



Ludlow, Zimmerman, Witkowski, Hearn, Hatfield & Roth
***Medicine & Science in Sports and Exercise*, 2008**

Telomeres are DNA-protein complexes that cap chromosomal ends and promote chromosomal stability - *telomeres shorten with every replication of the cell*

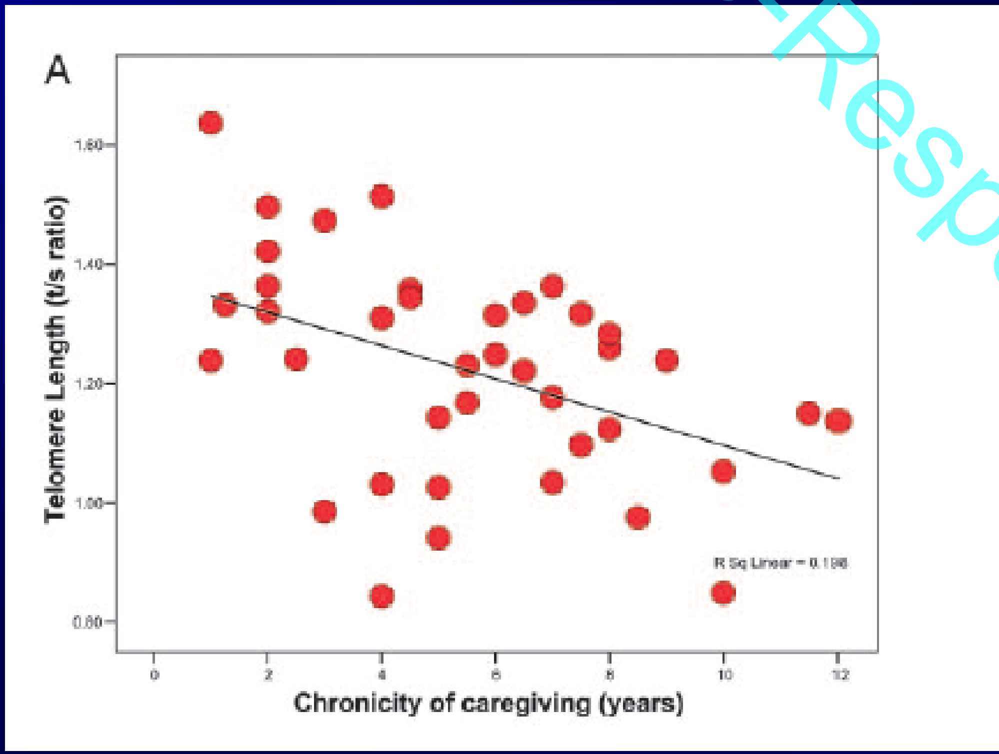
Telomerase status and telomere length are well established indices of cellular health and longevity (PROLIFERATIVE VIABILITY - potential for further division)

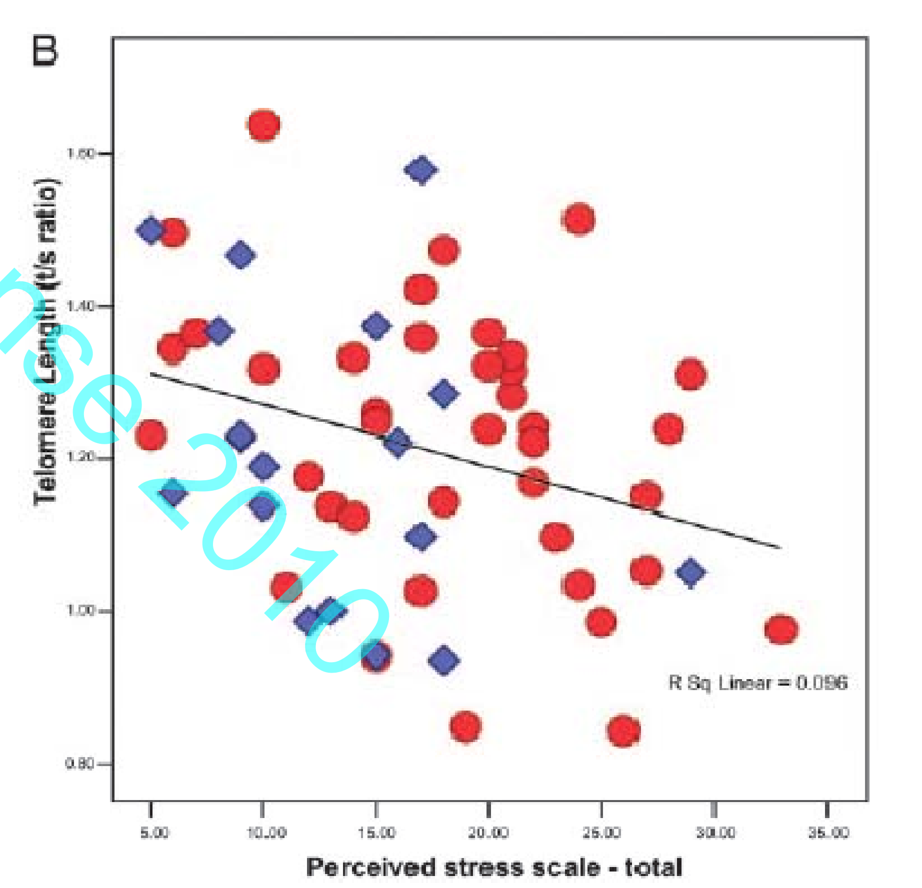
Background

Participants: 58 premenopausal mothers of healthy *and* chronically ill children (age-controlled)

Epel et al., *PNAS* 2004

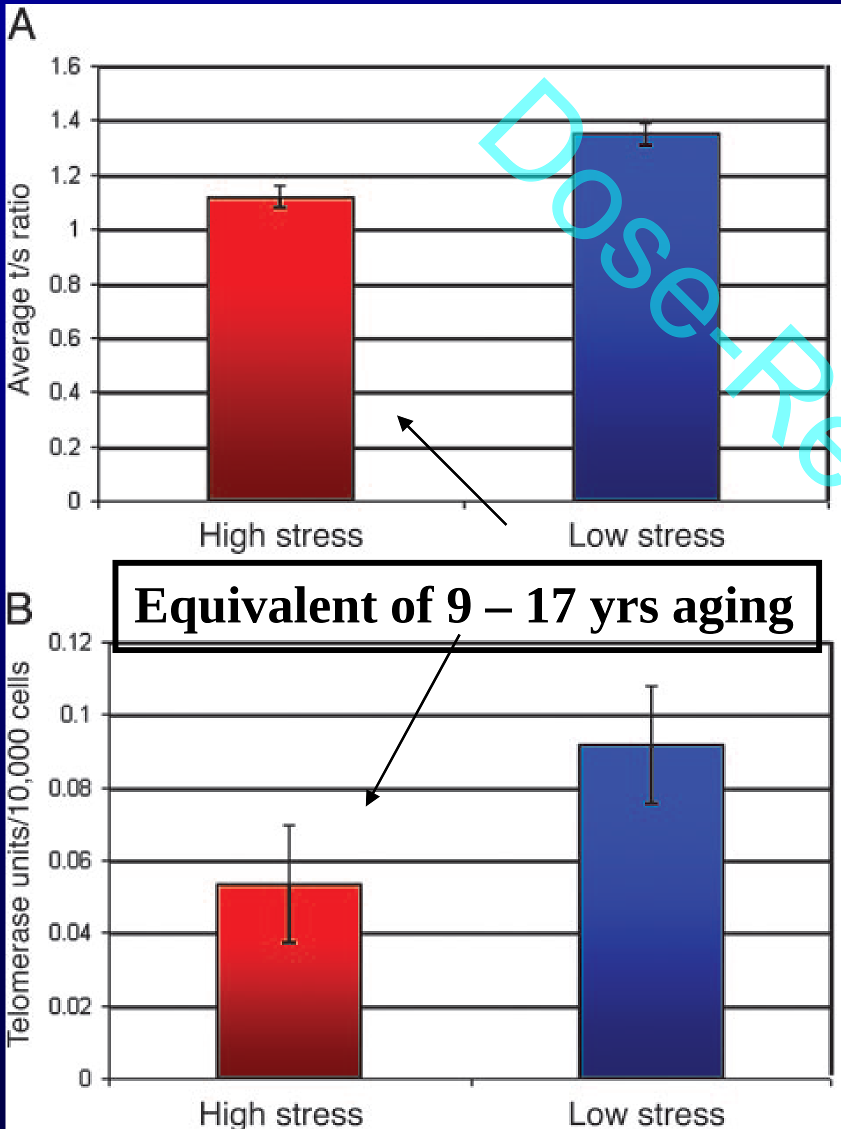
<u>Accelerated telomere shortening in response to life stress</u>





Telomeres measured in PBMC

Highest vs lowest quartiles



Epel et al., PNAS 2004

Exercise is a stressor

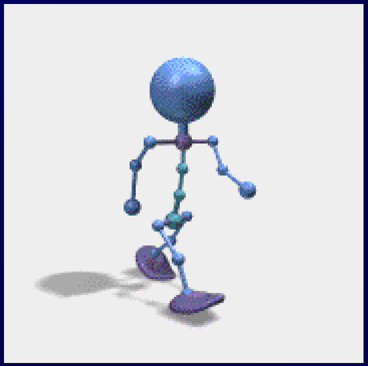
Mild – Moderate - Severe

Back to Ludlow et al.

70 men and women between the ages of 50 and 70

Yale Physical Activity Survey

Medical screening



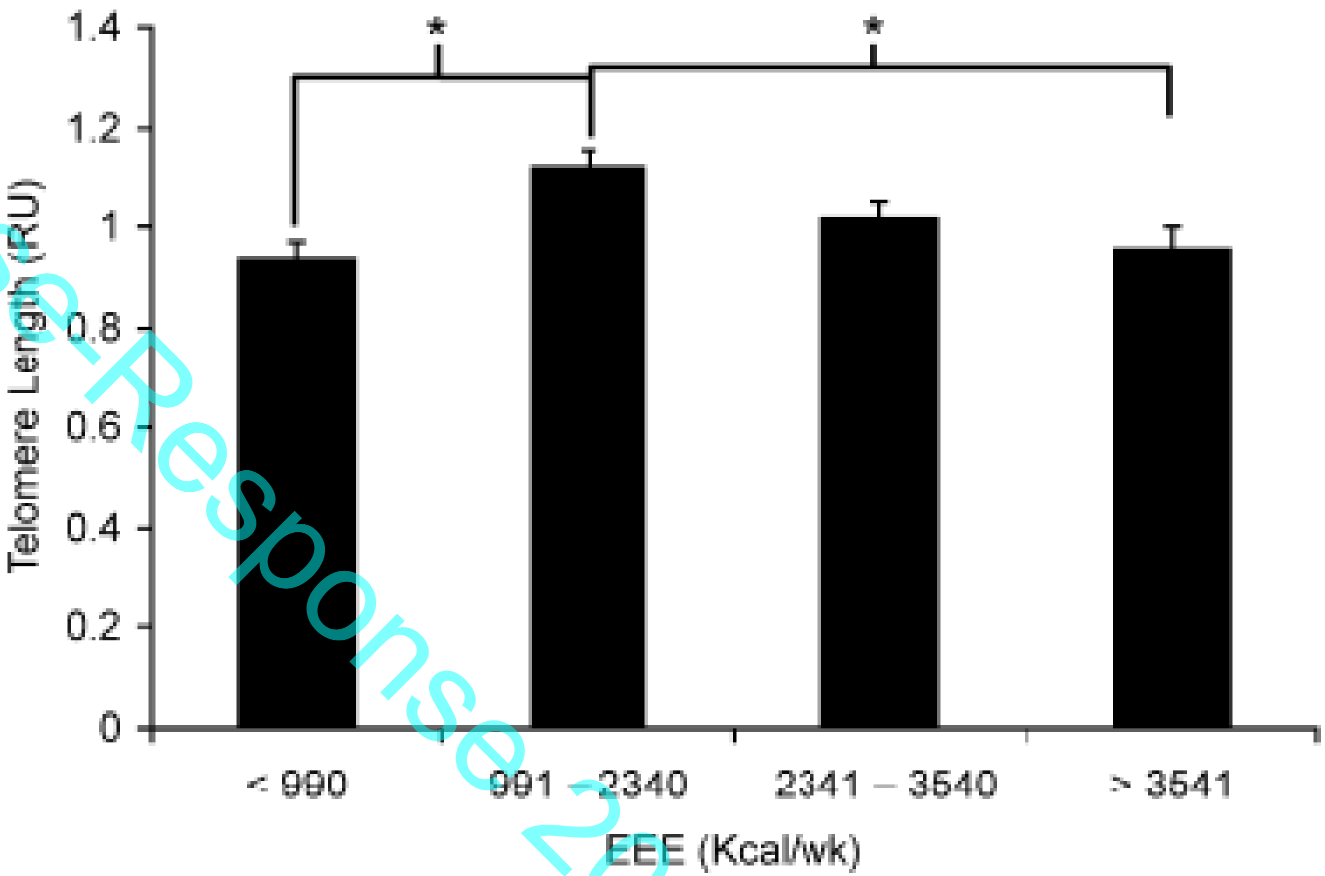
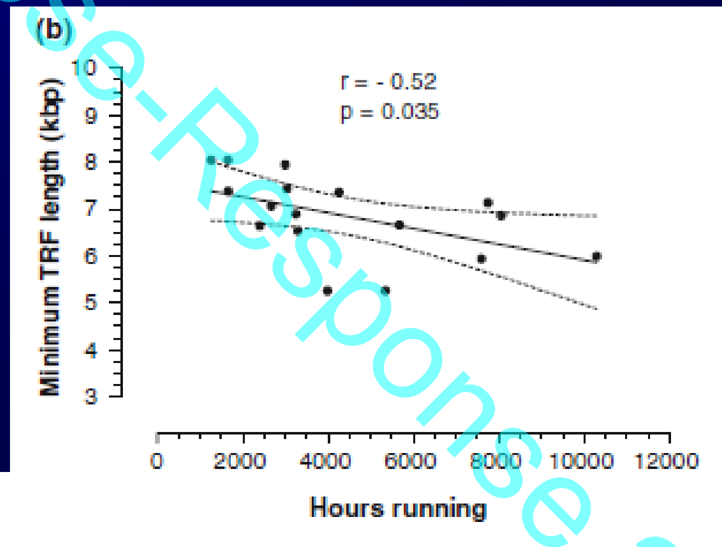
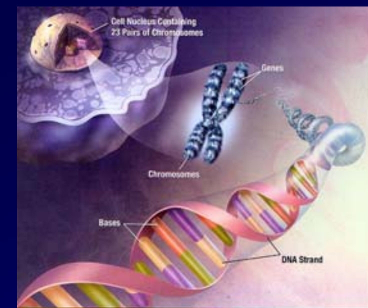


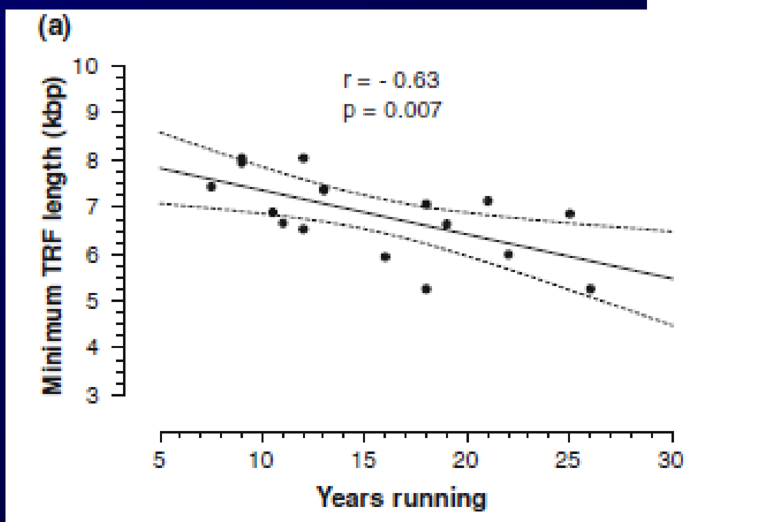
FIGURE 1—PBMC telomere length (relative telomere units, RU) is shown by EEE quartile (kcal·wk^{-1}). *Significantly different from the second EEE quartile ($P < 0.05$). The second EEE quartile exhibited significantly longer telomere lengths (1.12 ± 0.03 RU) than both the first and fourth EEE quartiles (0.94 ± 0.03 and 0.96 ± 0.03 RU, respectively; $P < 0.05$) but was not different from the third quartile.

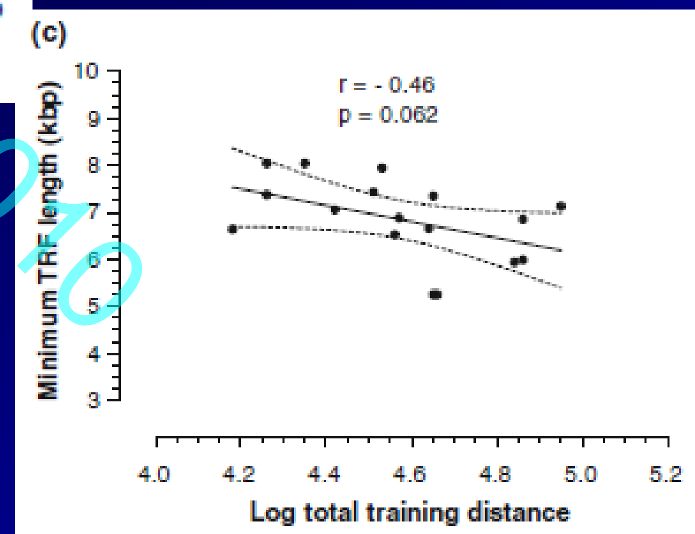
Rae et al., *EJAP* (2010)

Skeletal muscle telomere length in healthy, experienced, endurance runners







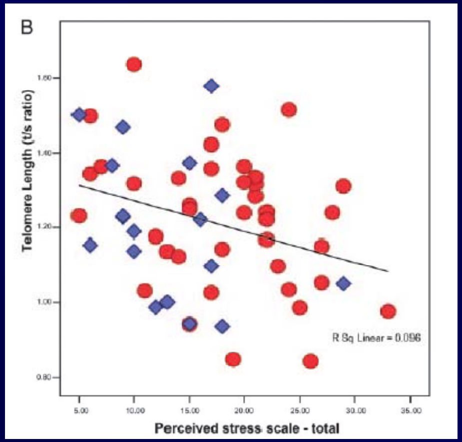


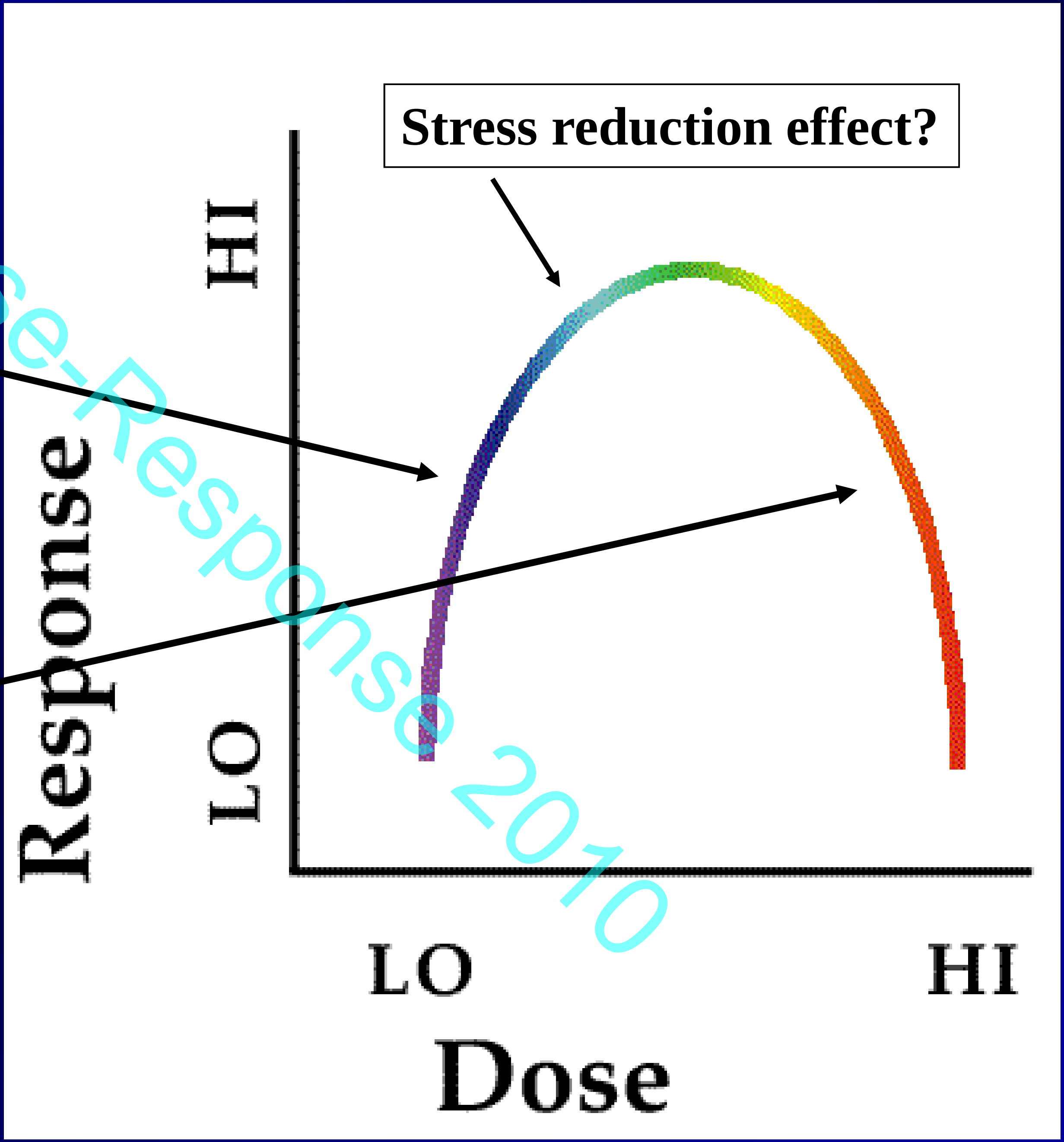
Evidence for hormesis in *cell aging*

Cherkas et al., 2006
Aging Cell

Ludlow et al., 2008

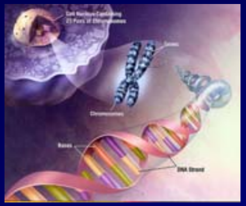
Rae et al., 2010





Individual differences in Physical Activity and *cognitive aging* – an illustration of gene x environment interaction in dose-response

The NIH Cognitive and Emotional Health Project (CEHP)



The goal of CEHP is to identify the demographic, biological, and psychosocial factors that can help people maintain or enhance their cognitive and emotional health *as they grow older* - a major public health goal for the United States **(Hendrie et al. 2006)**

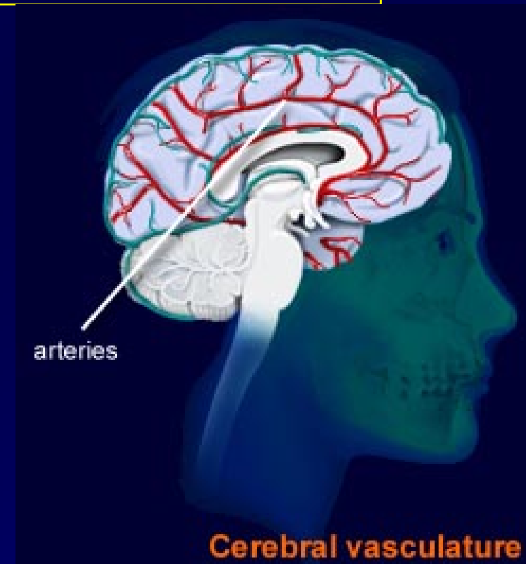
Alzheimer's & Disease

What factors are protective?

The protective factors for cognitive health that were most consistently reported in these large-scale high-quality studies included (1) higher education levels, (2) higher SES, (3) emotional support, (4) mastery, (5) better baseline cognitive function, (6) better lung capacity, (7) *<u>more physical exercise</u>*, (8) moderate alcohol use, and (9) use of vitamin supplements.

Why might this be so?

1. The oxygenation hypothesis (cerebral circulation)
   Swain et al., 2003, *Neuroscience*; Rogers, 1990, *J Cer Bloodflow*



2. The neurotransmitter hypothesis (catecholamines & serotonin)
   Spirduso, 1983, *RQES*; Meeusen, 2001, Sports Medicine.

3. Attenuation of glucocorticoids

4. The neurotrophic effect - (BDNF)
   Neeper, Gomez, Choi & Cotman, 1995, *Nature*

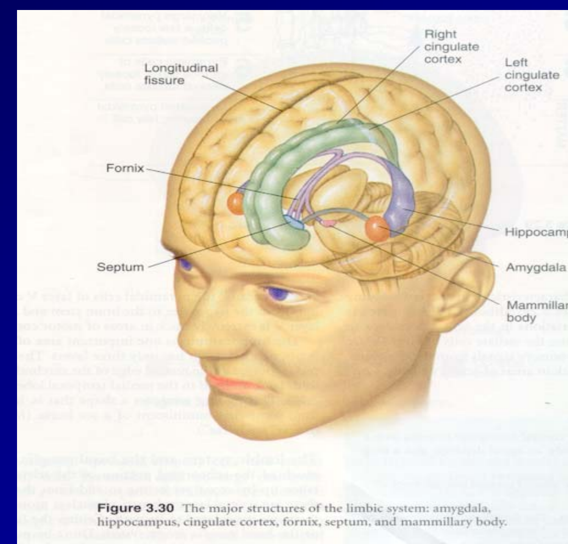
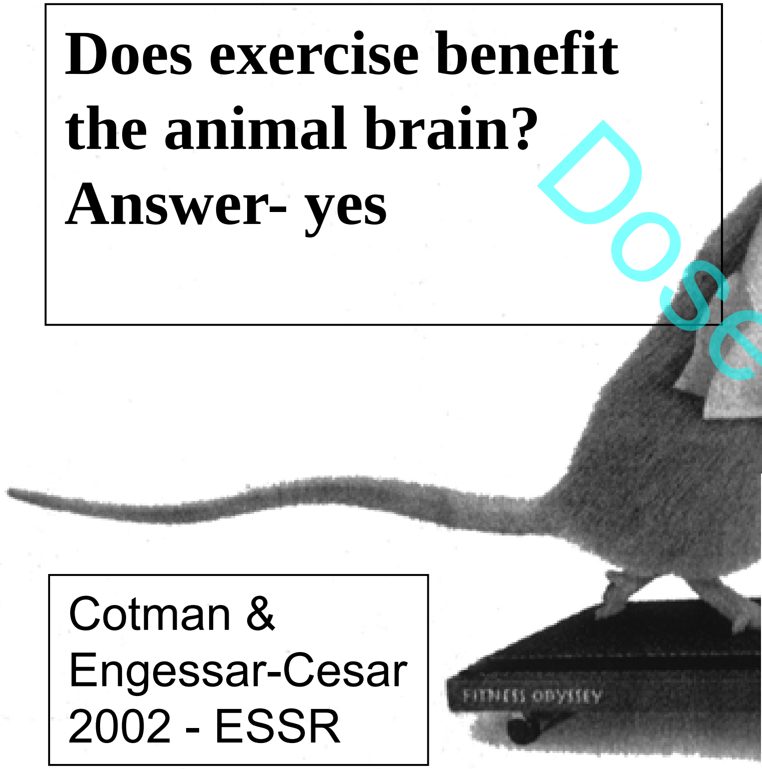
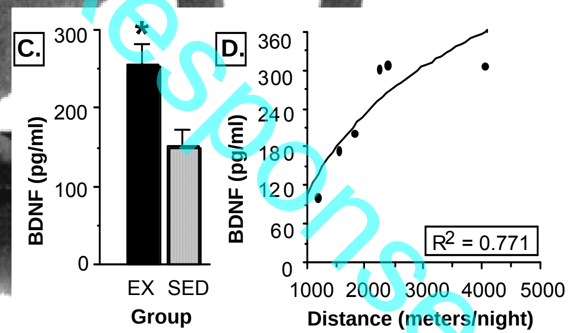


Figure 3.30 The major structures of the limbic system: amygdala, hippocampus, cingulate cortex, fornix, septum, and mammillary body.

Does exercise benefit the animal brain?
Answer- yes





Cotman & Engessar-Cesar 2002 - ESSR

This neurotrophic effect is most pronounced in the areas of the brain devoted to memory (hippo).
Such an effect in the human brain would hold major implications for the delay of dementia and Alzheimer's Disease

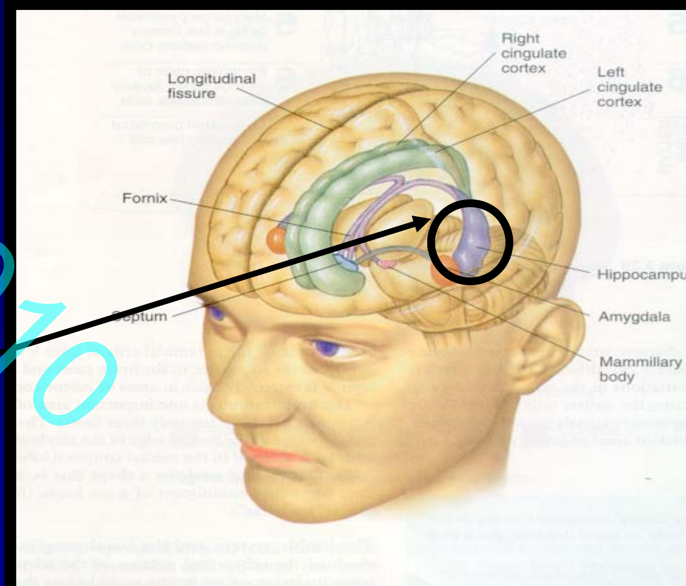
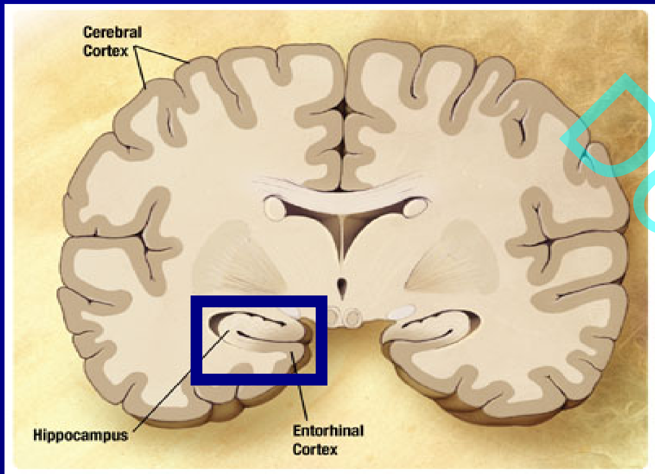
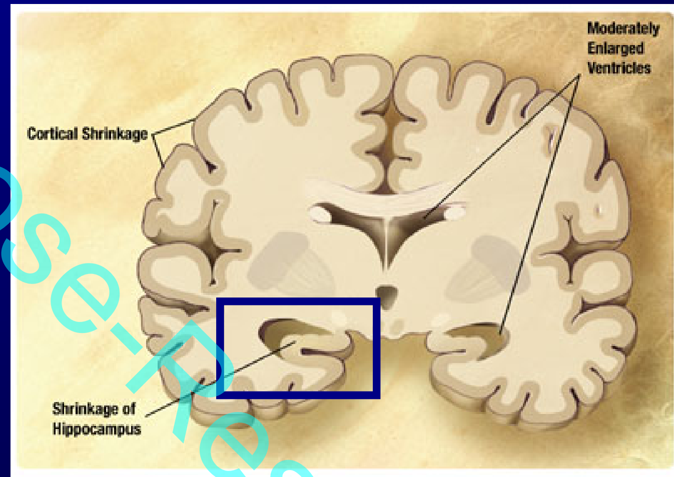
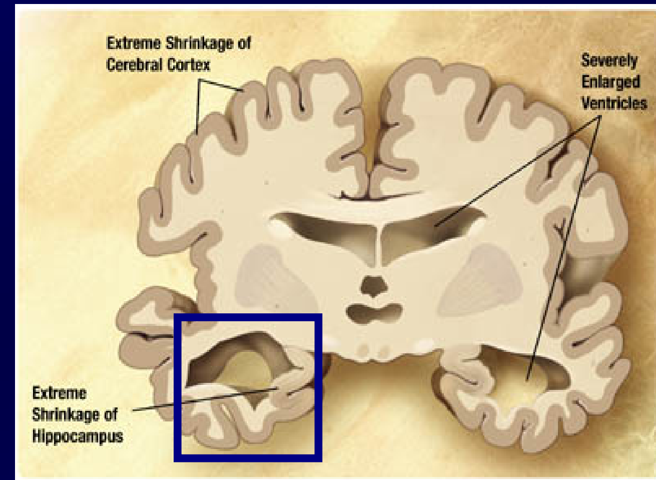


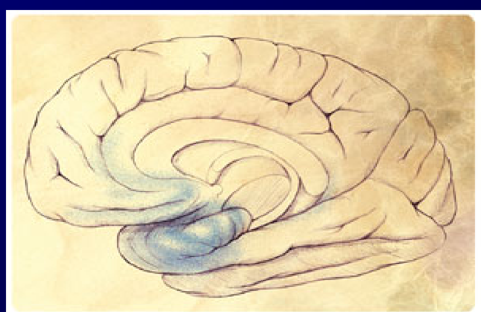
Figure 3.30 The major structures of the limbic system: amygdala, hippocampus, cingulate cortex, fornix, septum, and mammillary body.

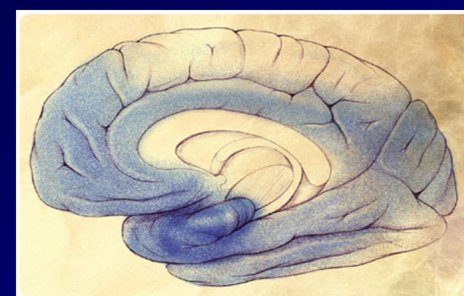
Such a benefit may delay onset of symptoms of Alzheimer's disease







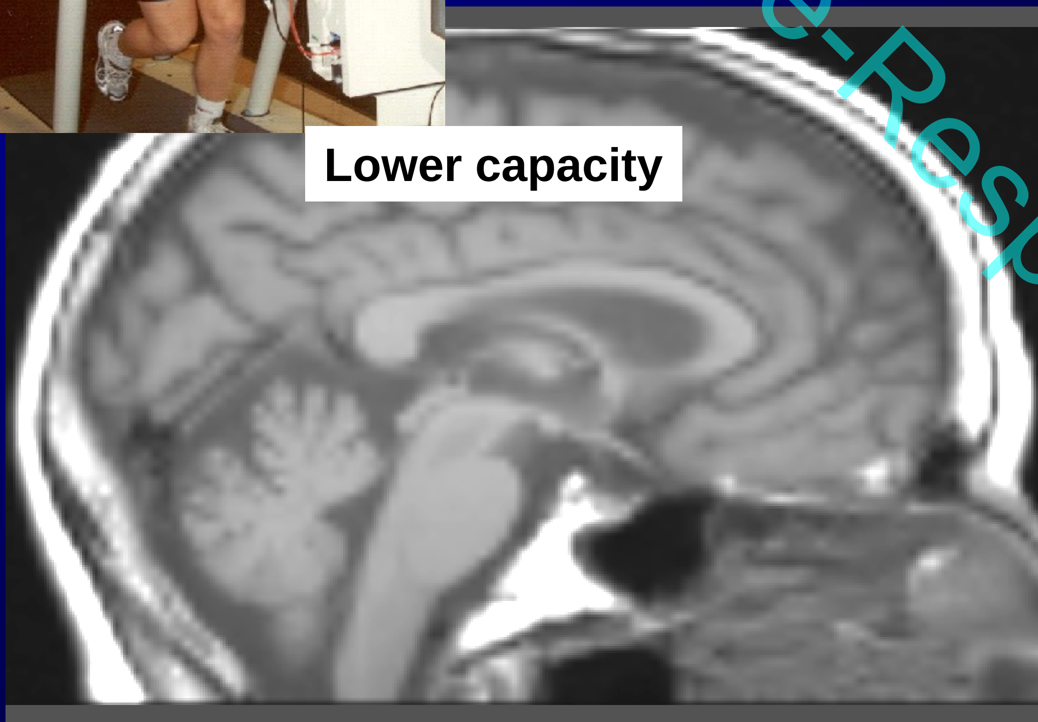


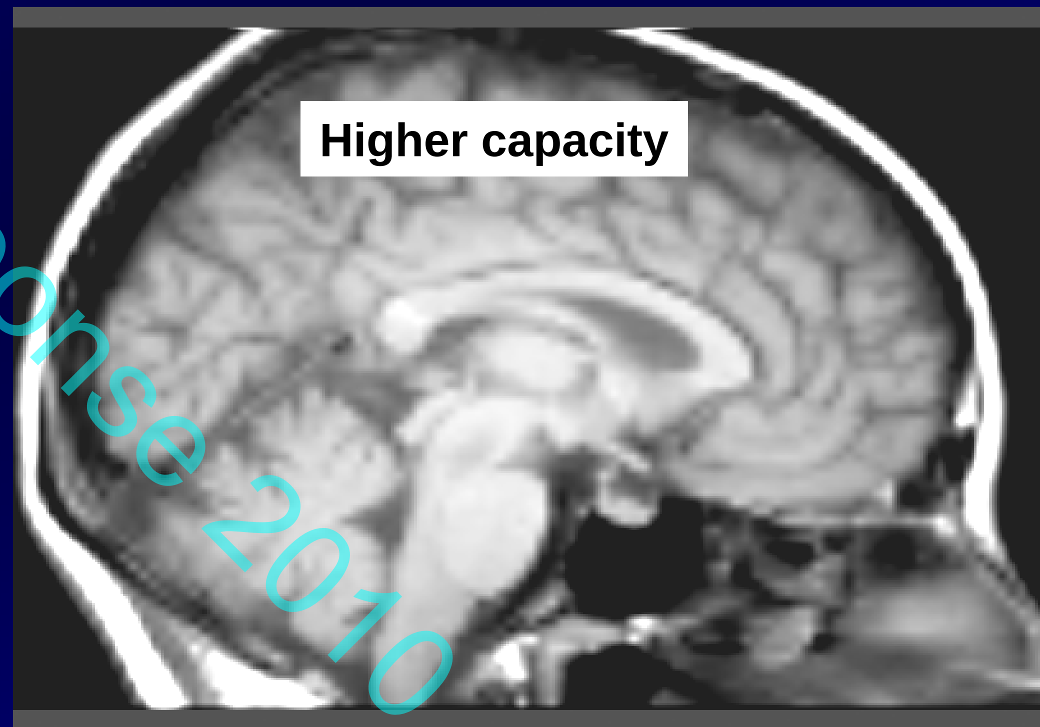


Preclinical AD **Mild to Moderate AD** **Severe AD**

Etiology of Alzheimer's Disease - Memory structures are destroyed
Affects 10% over 65 and 50% of those over 85 years.

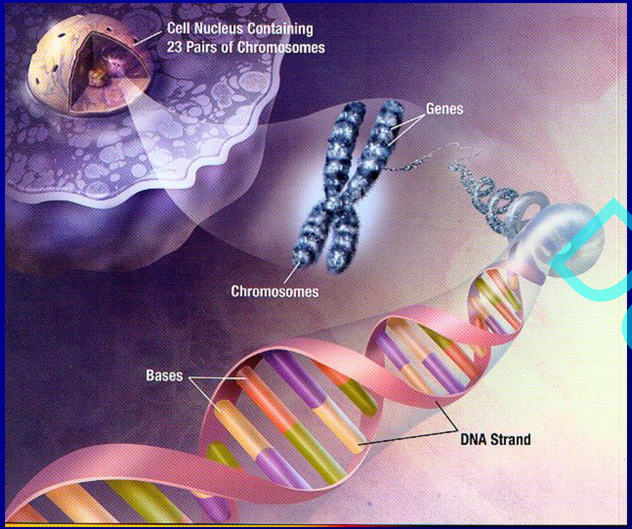
Aerobic capacity is positively related to CNS tissue density in middle age men & women and appears to slow brain aging
Could this be due to neurotrophic effects?





Voxel based morphometry to assess tissue density

Colcombe et al., 2003
J. Gerontology



Some are at greater risk for this terrible disease

A specific polymorphic variation in the APOE gene on chromosome 19, APOE e4 is present in ~ 40% of late-onset AD patients while present in only 17% of the US population. This suggests that the e4 allele interacts with other genes or *lifestyle behaviors* (exercise) in its contribution to decline.

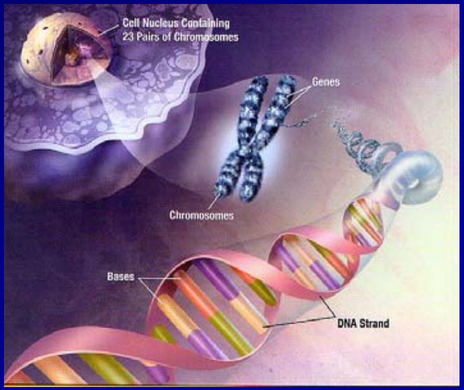
e4: Compromised removal of amyloid burden and cholesterol transport

Exercise, APOE, and working memory:
MEG and behavioral evidence for benefit of exercise in epsilon4 carriers

Deeny et al. (2008) *Biological Psychology*

Purpose

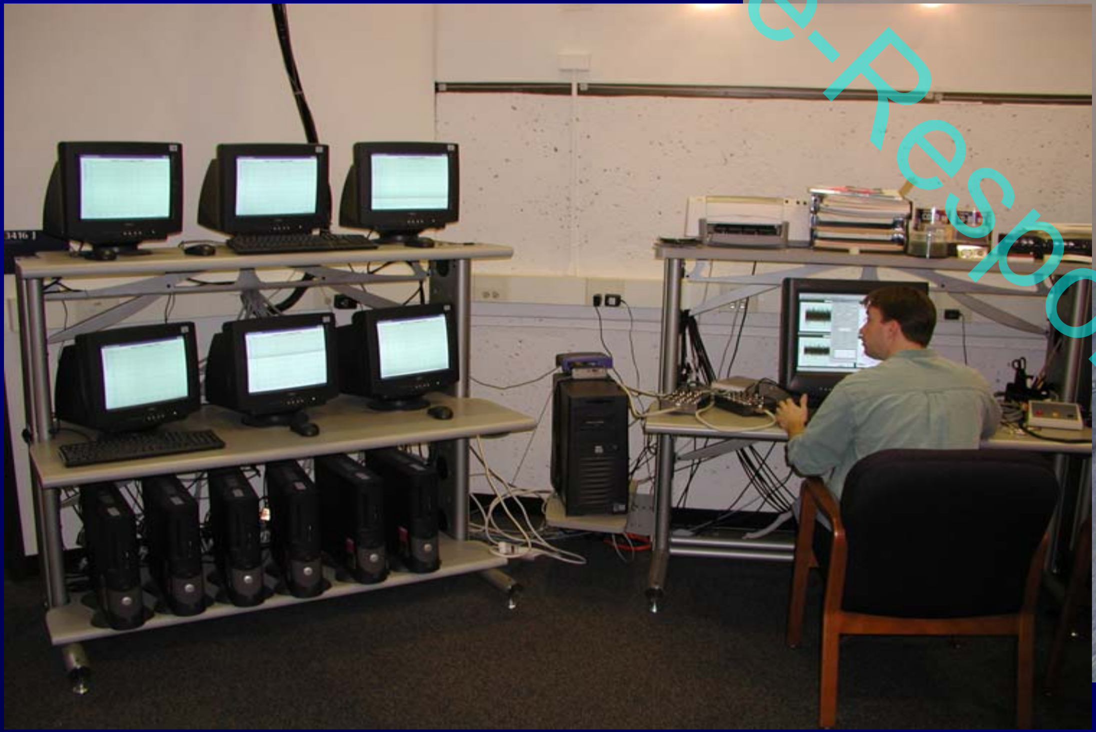
To determine if long-term Physical Activity attenuates APOE e4-related ‘deficits’ in cortical activation in men and women (50 – 70 years) during cognitive challenge



Sternberg Task
(challenging the brain)

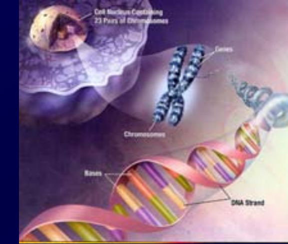
C

Magnetoencephalography (MEG) measures magnetic fields
160 channels of SQUID recording

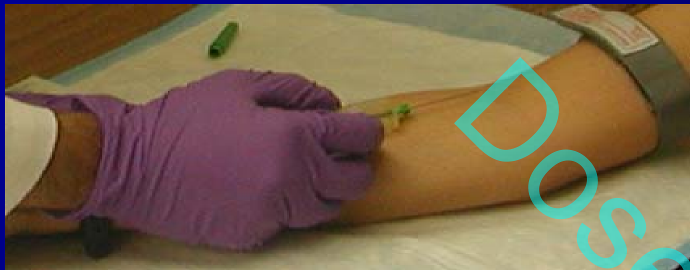


Excellent *temporal resolution*

Plus excellent *spatial resolution* for cerebral cortex



Blood samples were collected
to determine presence or absence of
APOEe4 ((BDNF) (COMT)



Cerebral cortical activity was
assessed in four groups of
intact middle-aged men and women (50 – 70):

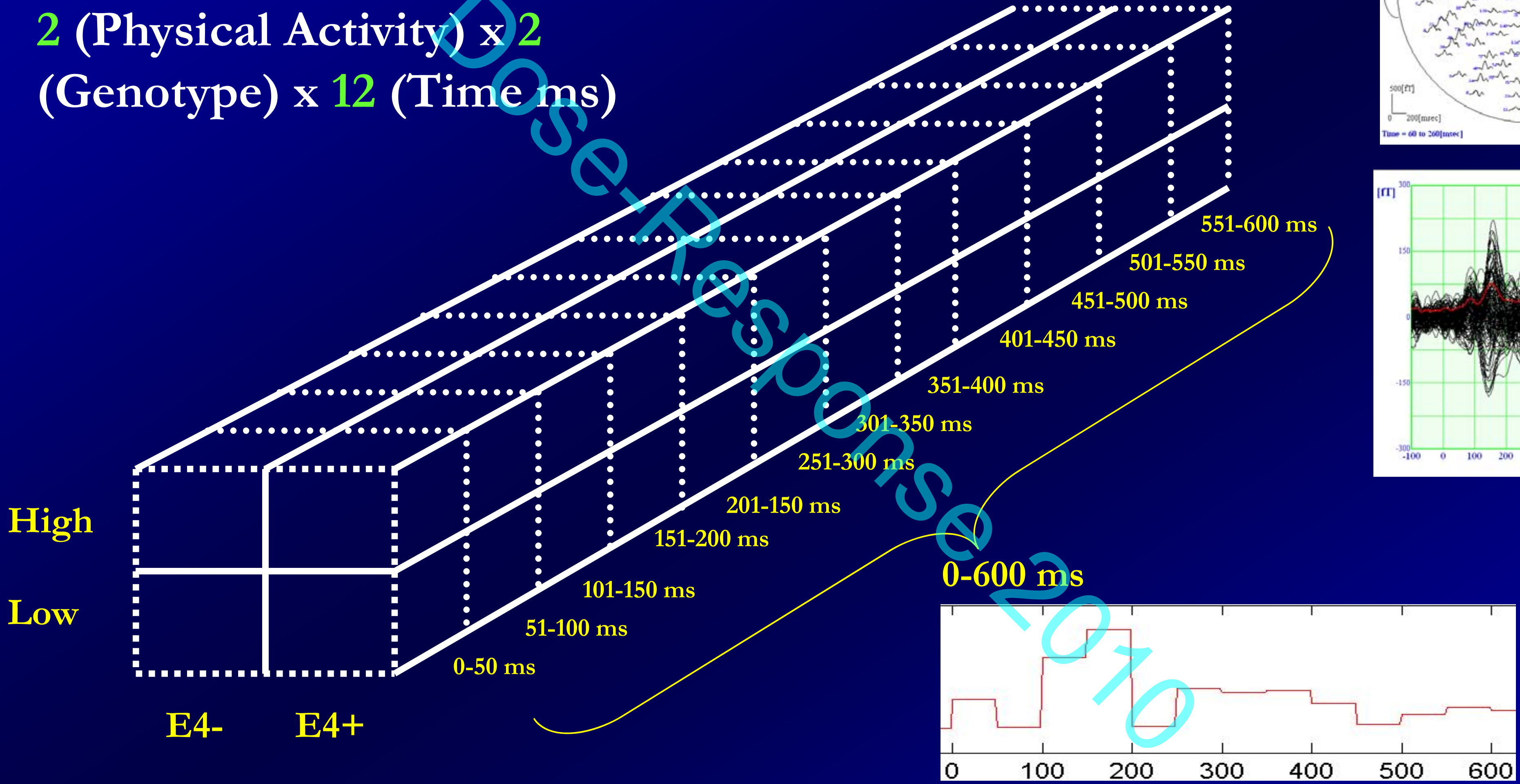
1. Active non-carriers
2. Inactive non-carriers
3. Active e4 carriers
4. Inactive e4 carriers

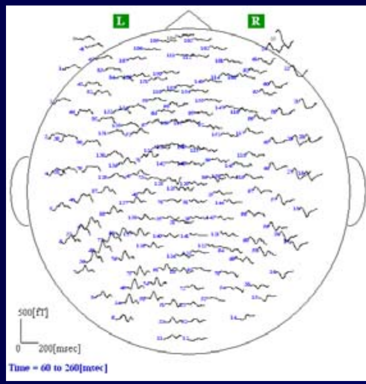
Prediction:
Inactive carriers will show hypoactivation in
critical brain regions
Active carriers will be similar to non-carriers

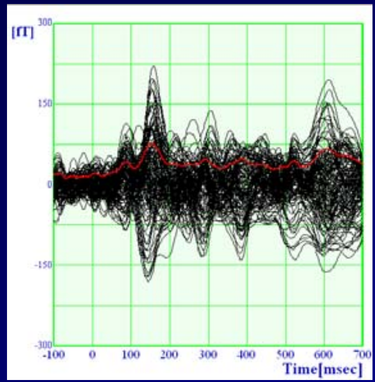
Behavioral measures were also recorded
for Flankers, Stroop, Wisconsin, and Working
Memory and related to physical activity

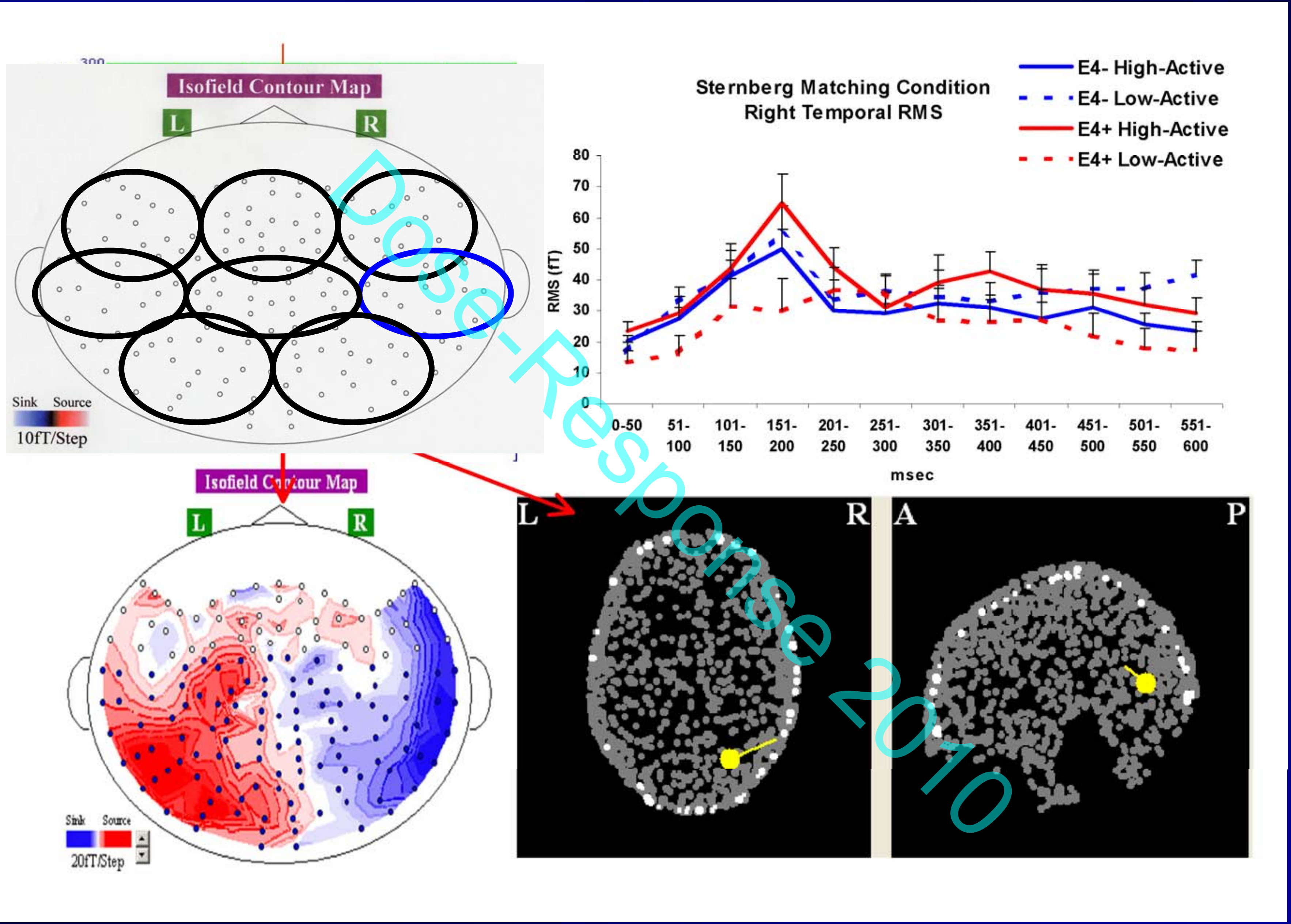
Design

2 (Physical Activity) x 2 (Genotype) x 12 (Time ms)

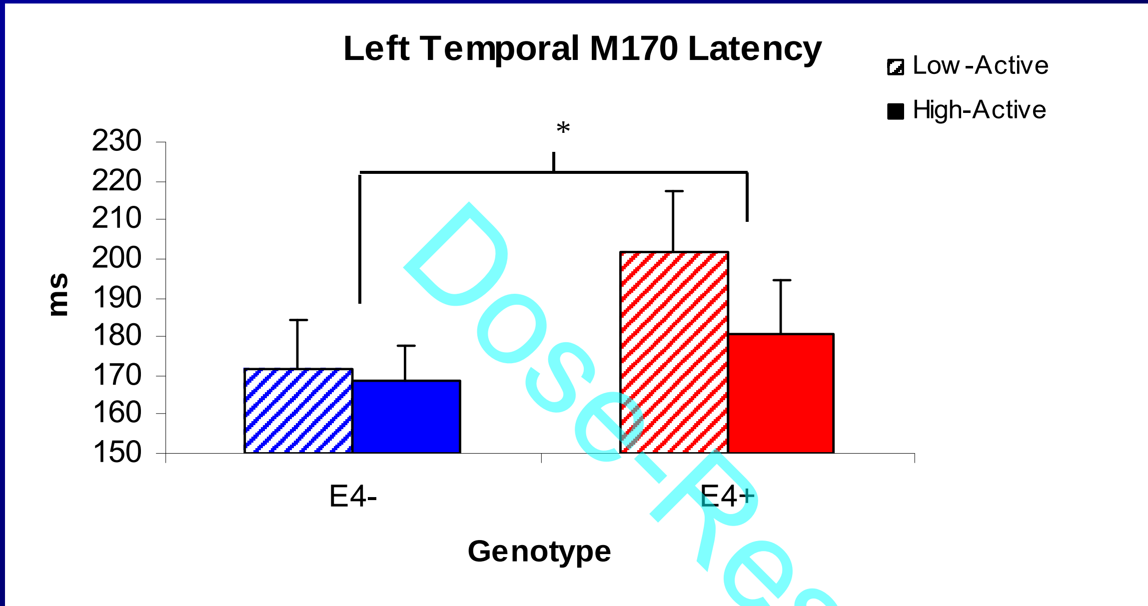


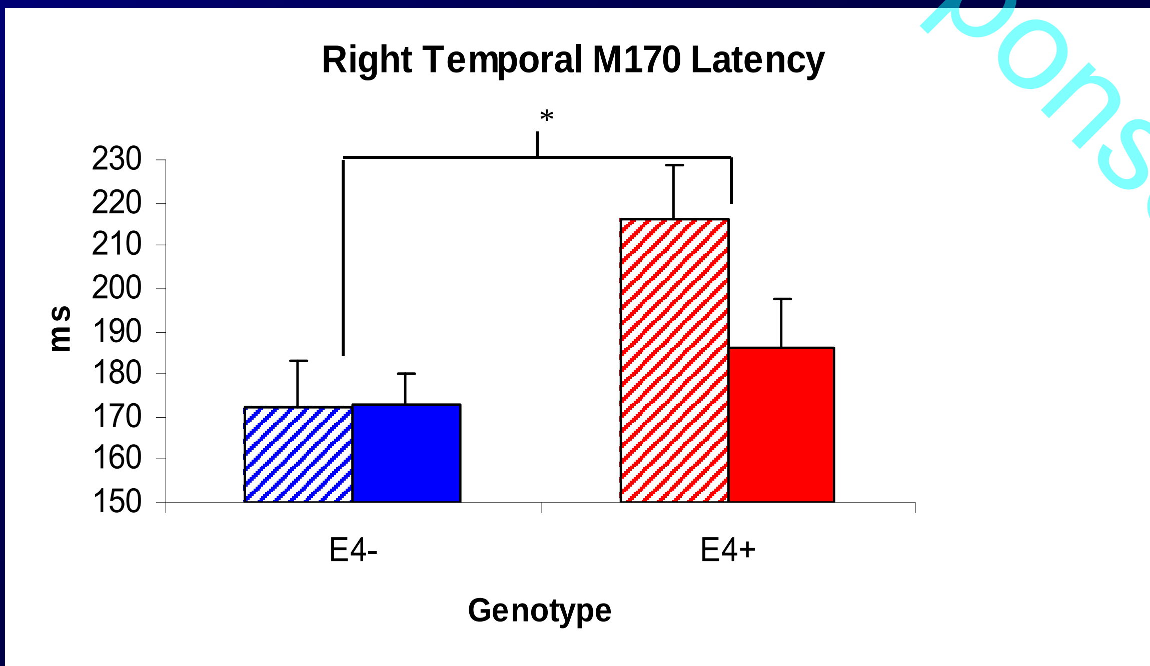


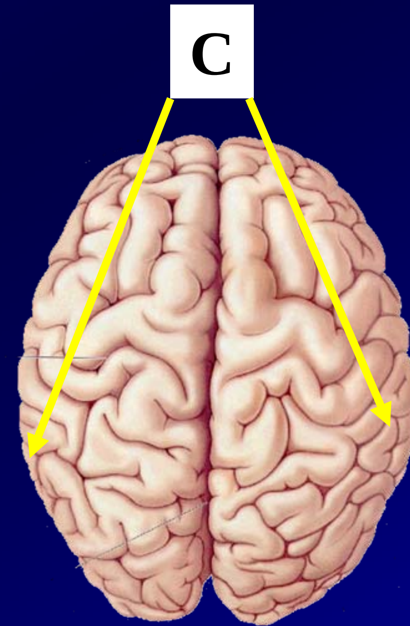




Source reconstruction – fusiform gyrus







The study shows the need to consider genetic factors to detect links between physical activity and brain function

Dose-response dependent on genotype

Sternberg Reaction Time latency

Non-carriers 38

Carriers 16

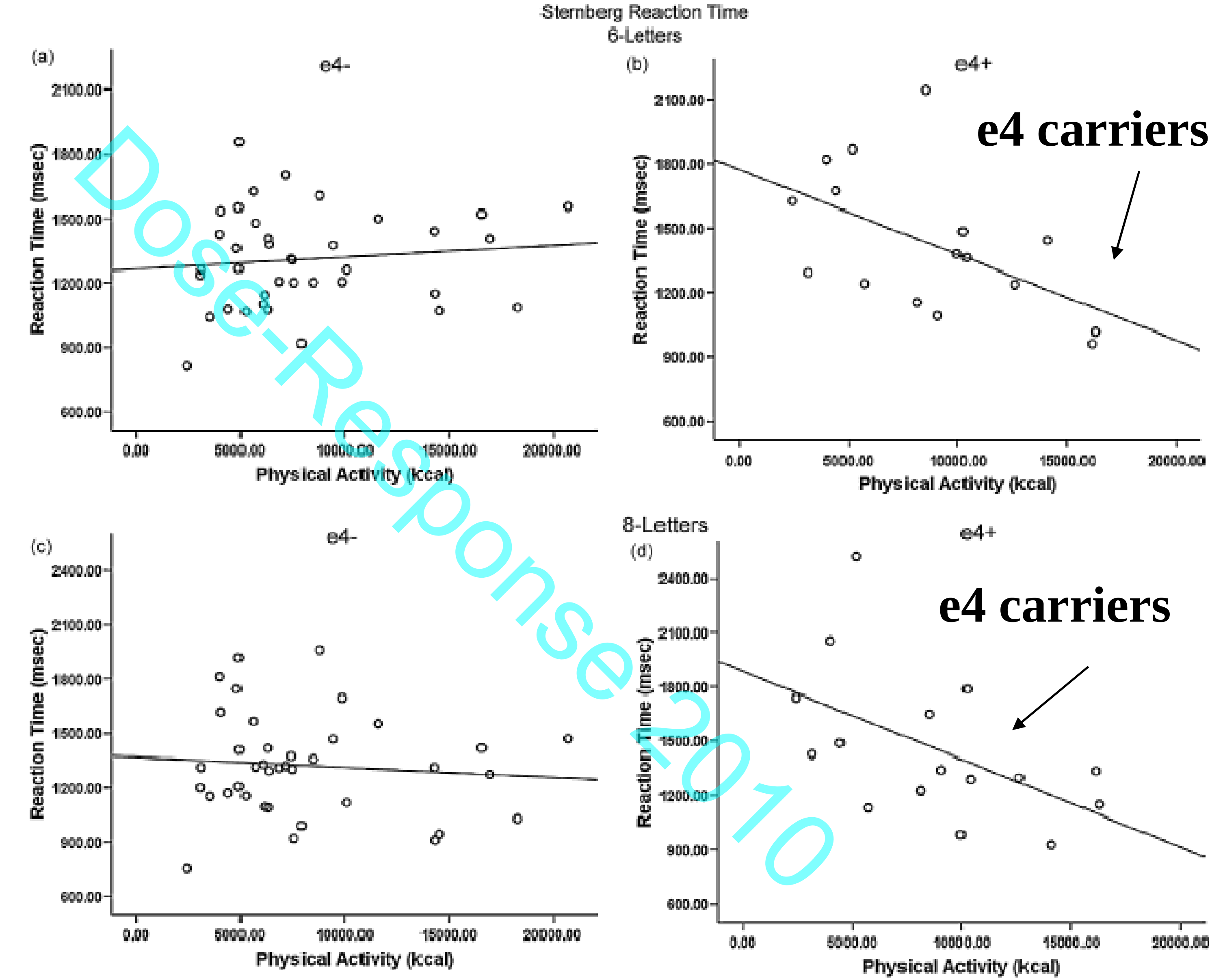
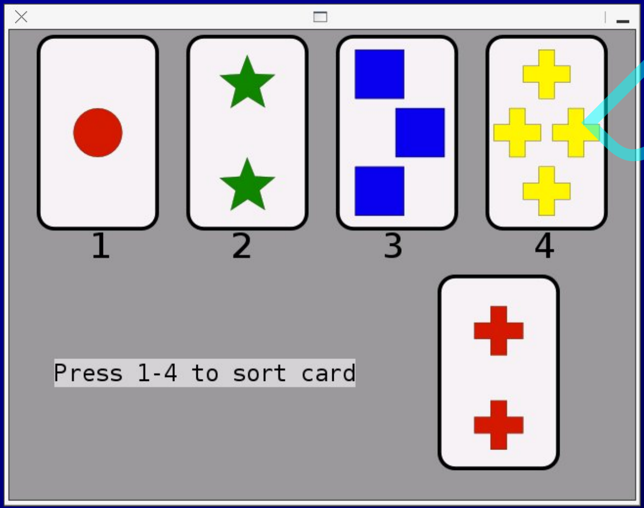
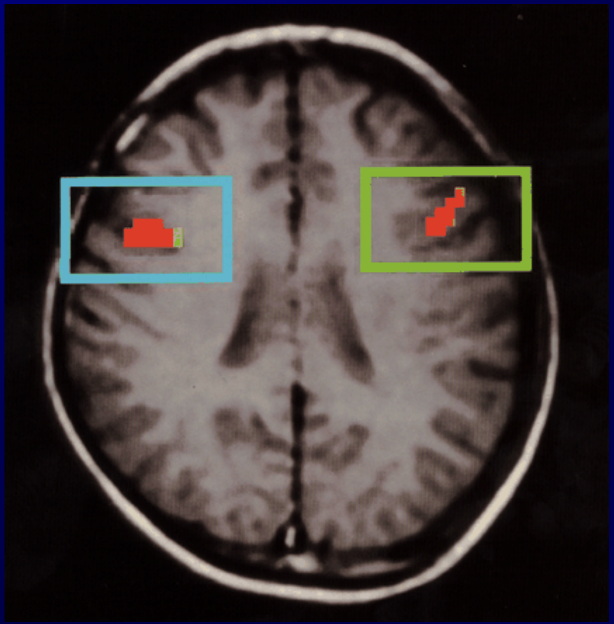
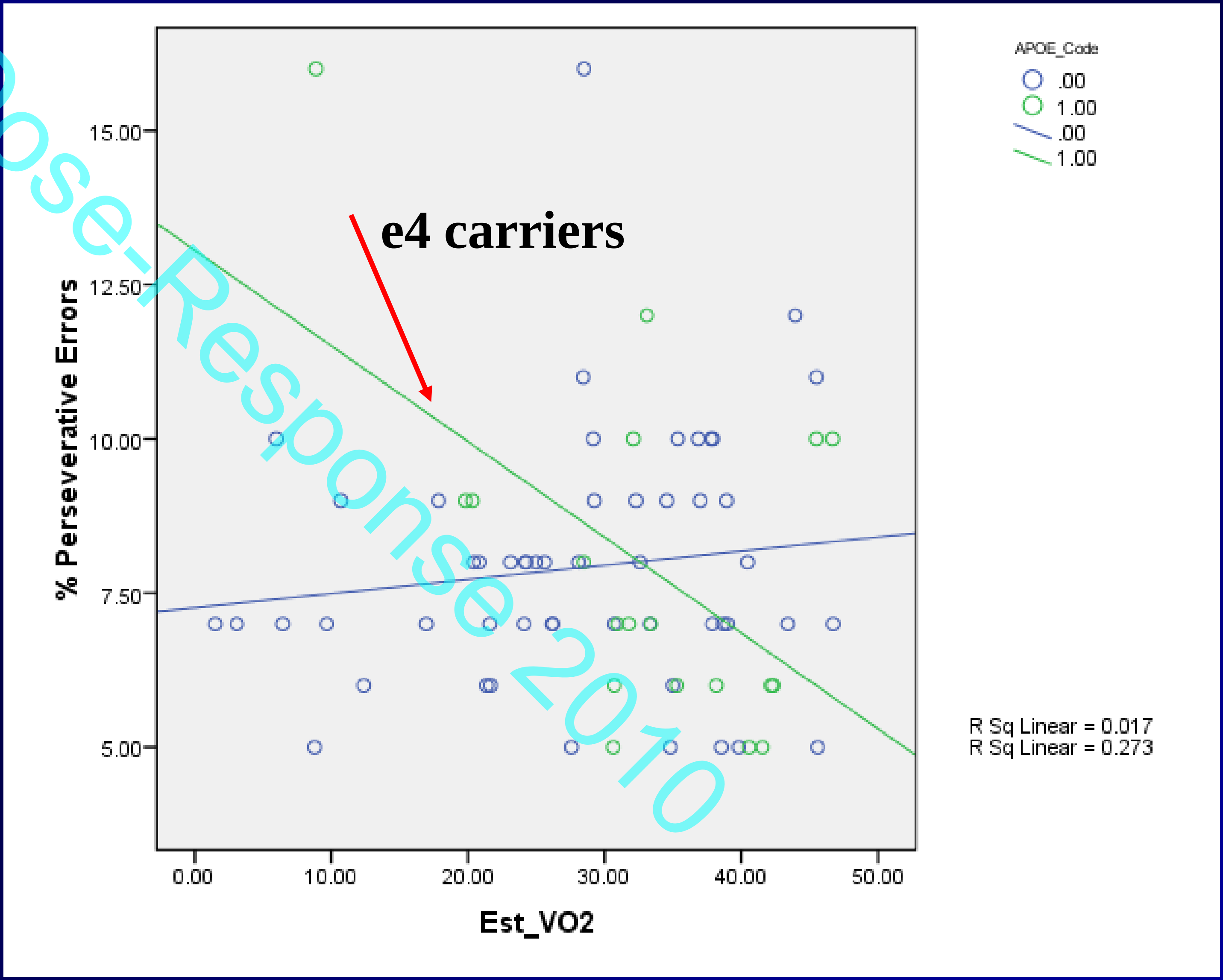


Fig. 2. Genotype × Exercise interaction for the six-letter (a and b) and eight-letter (c and d) behavioral Sternberg testing. ε4 carriers (b and d) show decreased RT with increasing physical activity (kcal).

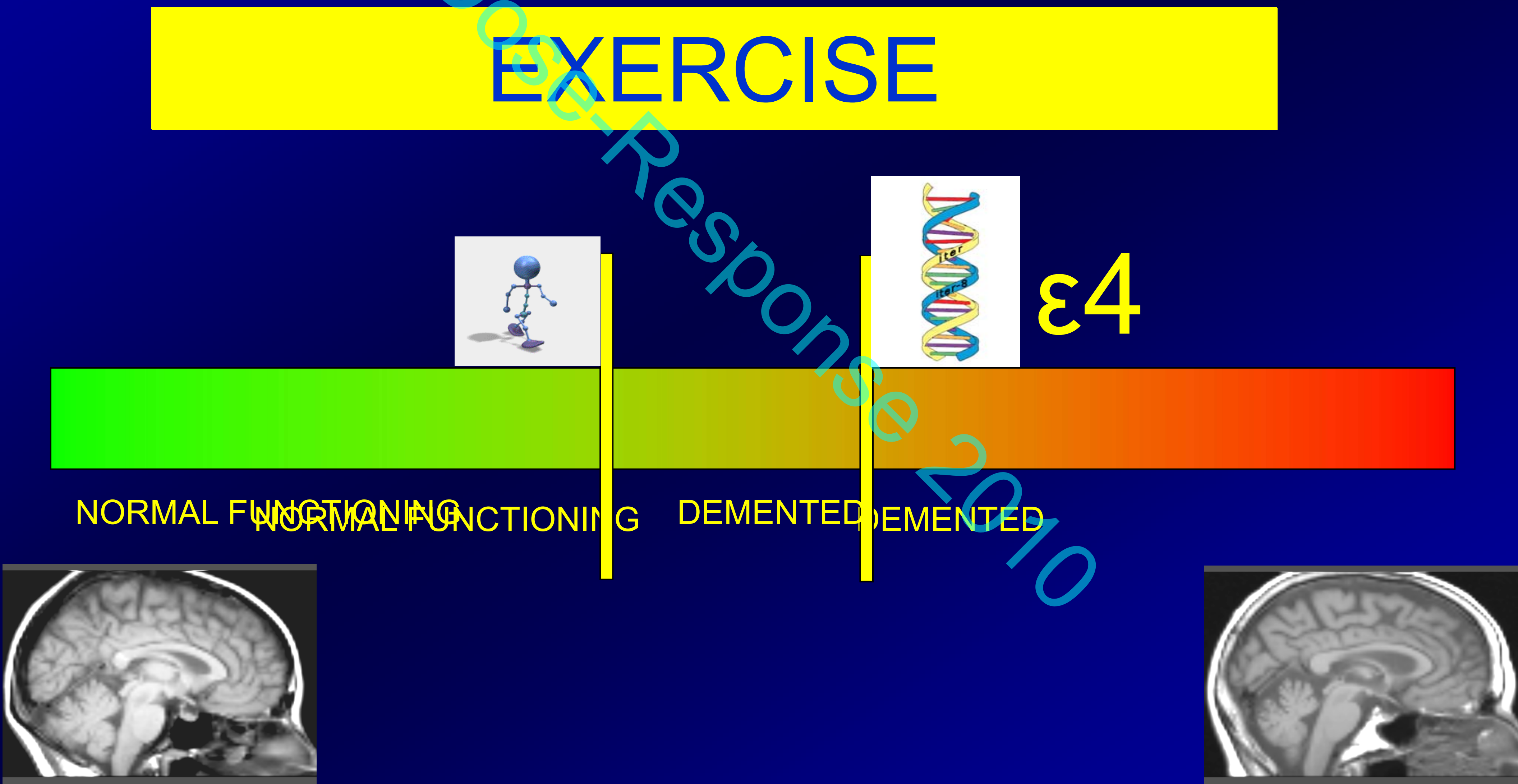
Dose-response dependent on genotype







Threshold of cognitive decline



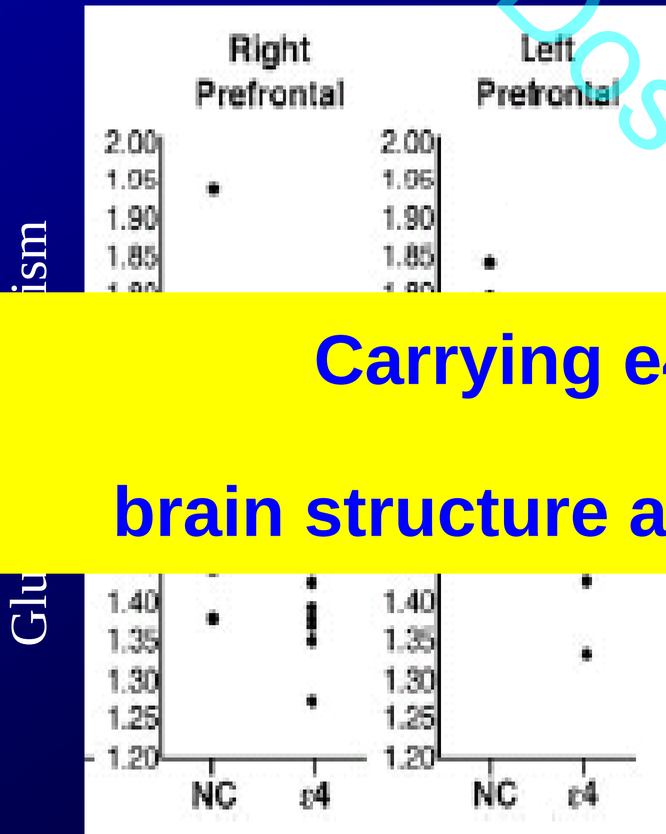
The Future:

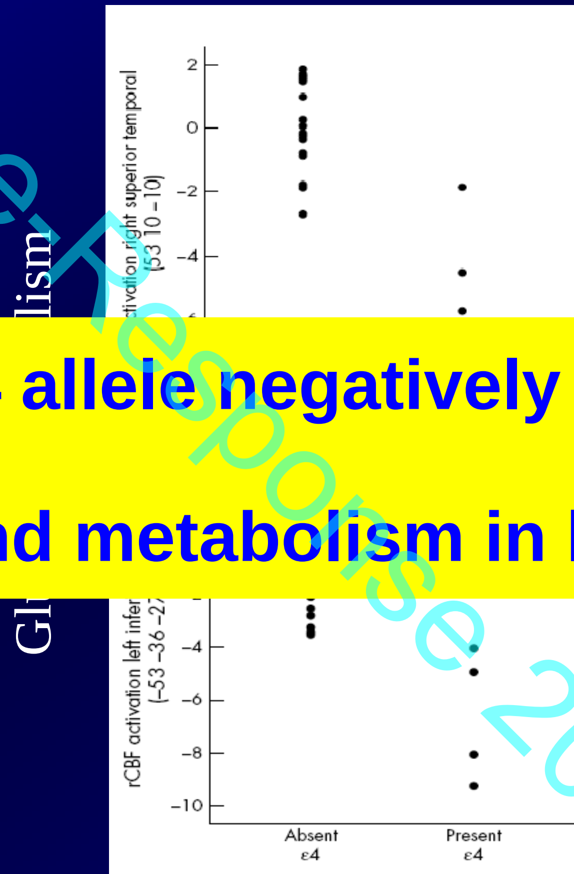
The effect of physical activity on the developing brain and cognitive reserve:

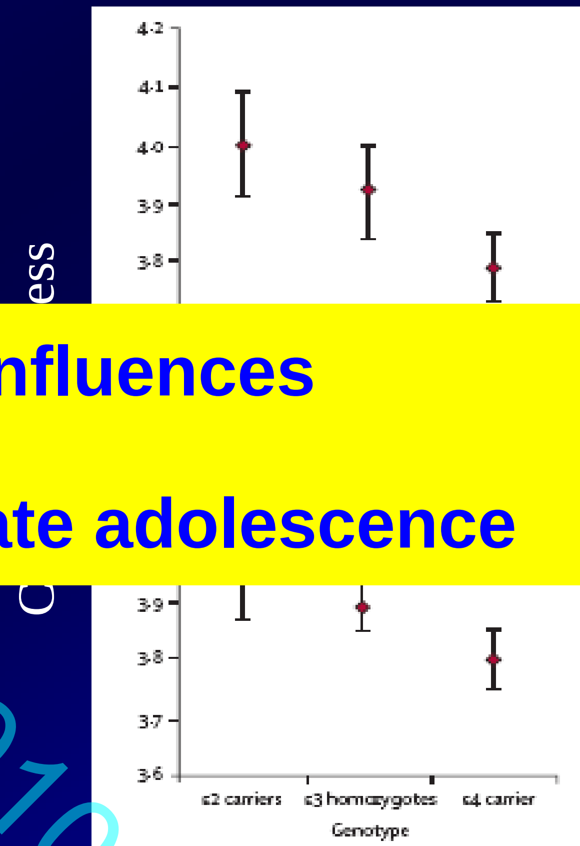
Investment hypothesis

Implications for Physical education

Apolipoprotein E (ApoE) and Brain Structure and Function







Carrying e4 allele negatively influences brain structure and metabolism in late adolescence

Reiman et al. (2004)
Young adult (20-39 years)

Scarmeas et al., (2005)
College age (19-28 years)

Shaw et al., (2007)
Children & adolescents
(< 21 years)

Cardiovascular fitness modifies the relationship between genotype and neurocognitive function during executive challenge in young men

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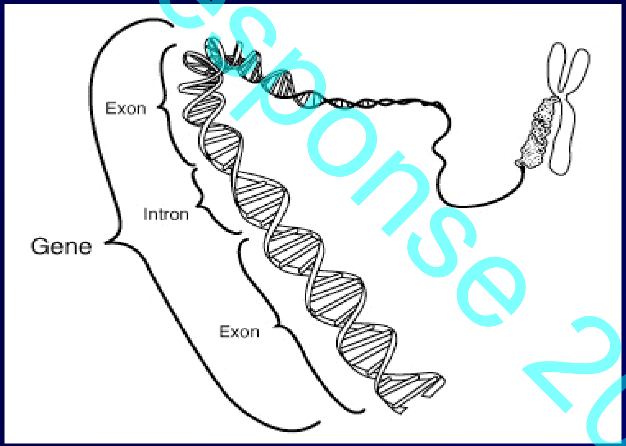

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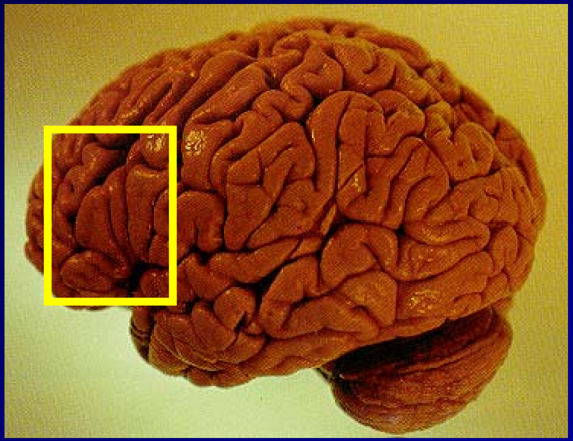

M. Woo, J. Polich, S. Roth & B. Hatfield

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UNIVERSITY OF MARYLAND

KINESIOLOGY UNIVERSITY OF MARYLAND

The purpose of the study

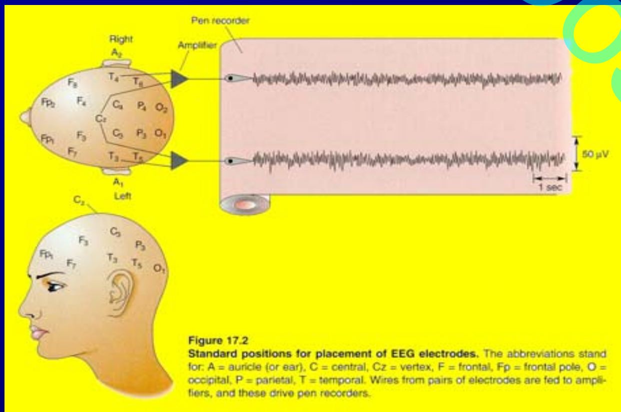
- To examine if cardiovascular fitness modifies the relationship between ApoE genotype and neuro-cognitive response during late adolescence.
- To examine if the relationship between cardiovascular fitness and cortical response in e4 carriers is greater during a frontally-mediated executive challenge relative to a non-executive challenge

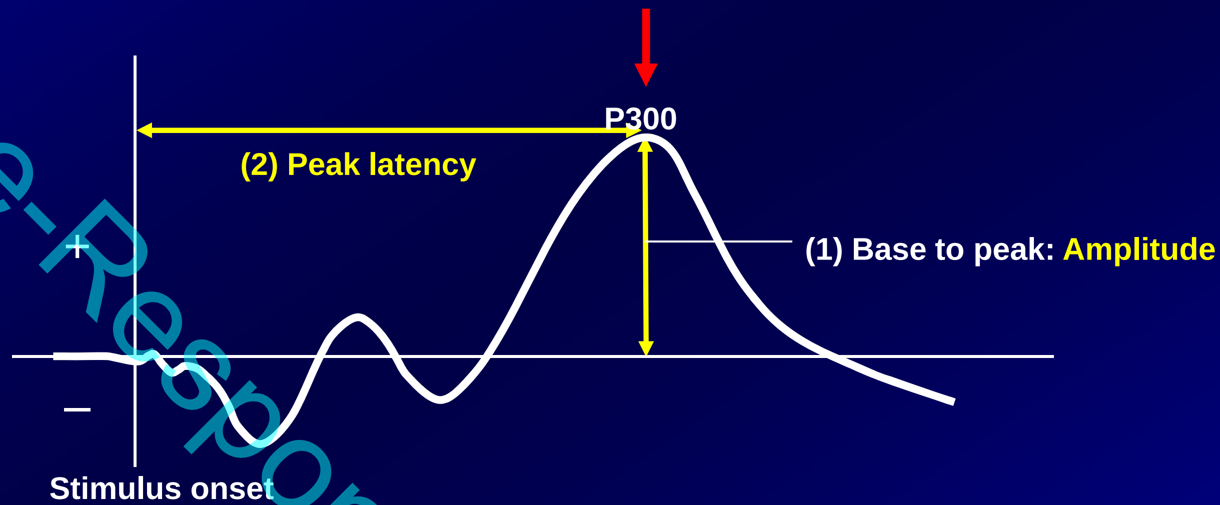
Method

- **Participants**
  - Healthy undergraduate male (18 – 23 years of age)
  - 30 non-carriers (4 of e2/e3 and 26 of e3/e3),
  - 29 e4 carriers (24 of e3/e4, 5 of e4/e4)

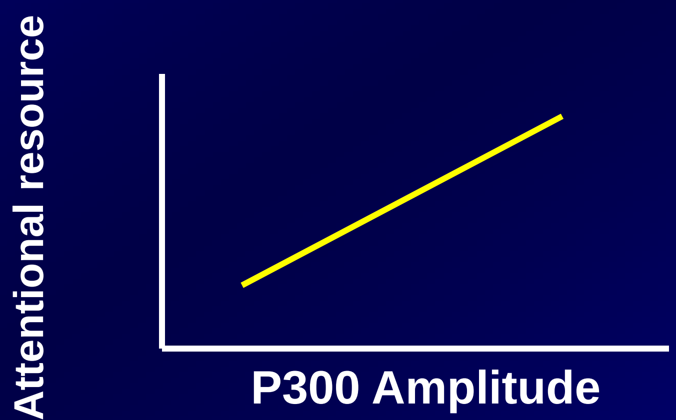
	High fit E4- carrier	Low fit E4-carrier	High fit Non-carrier	Low fit Non-carrier
Number of subjects	15	14	15	15
Age	20.87 (1.30)	20.29 (1.20)	20.67 (1.05)	20.73 (1.71)
Weight	181.87 (35.16)	171.67 (31.03)	175.33 (26.50)	176.73 (26.28)
Estimated VO_2max	52.72 (7.48)	36.622 (5.94)	54.11 (3.91)	40.73 (5.60)
K-BIT Composite	108.93 (9.22)	107.21 (8.63)	104.2 (9.20)	106.53 (9.81)

Physical activity and executive function in the developing brain – a psychophysiological approach

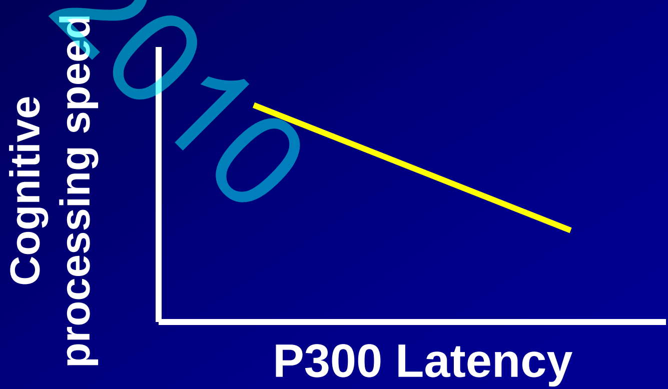




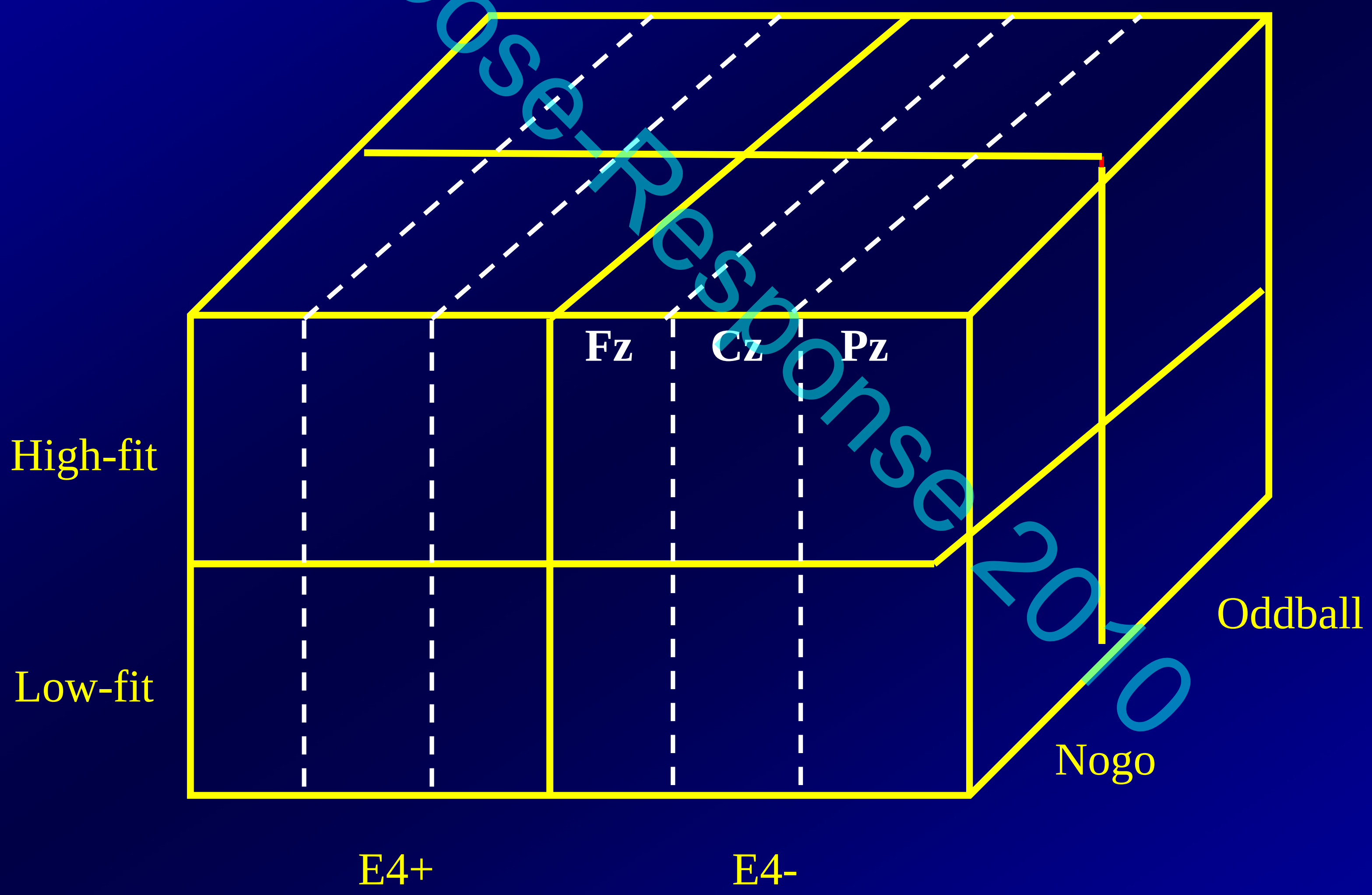
(1) P300 Amplitude



(2) P300 Latency



2 (Genotype) × 2 (Physical fitness) × 2 (Task) × 3 (Region)



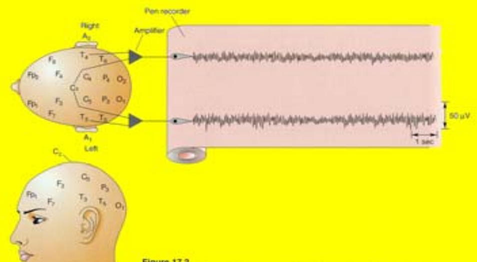
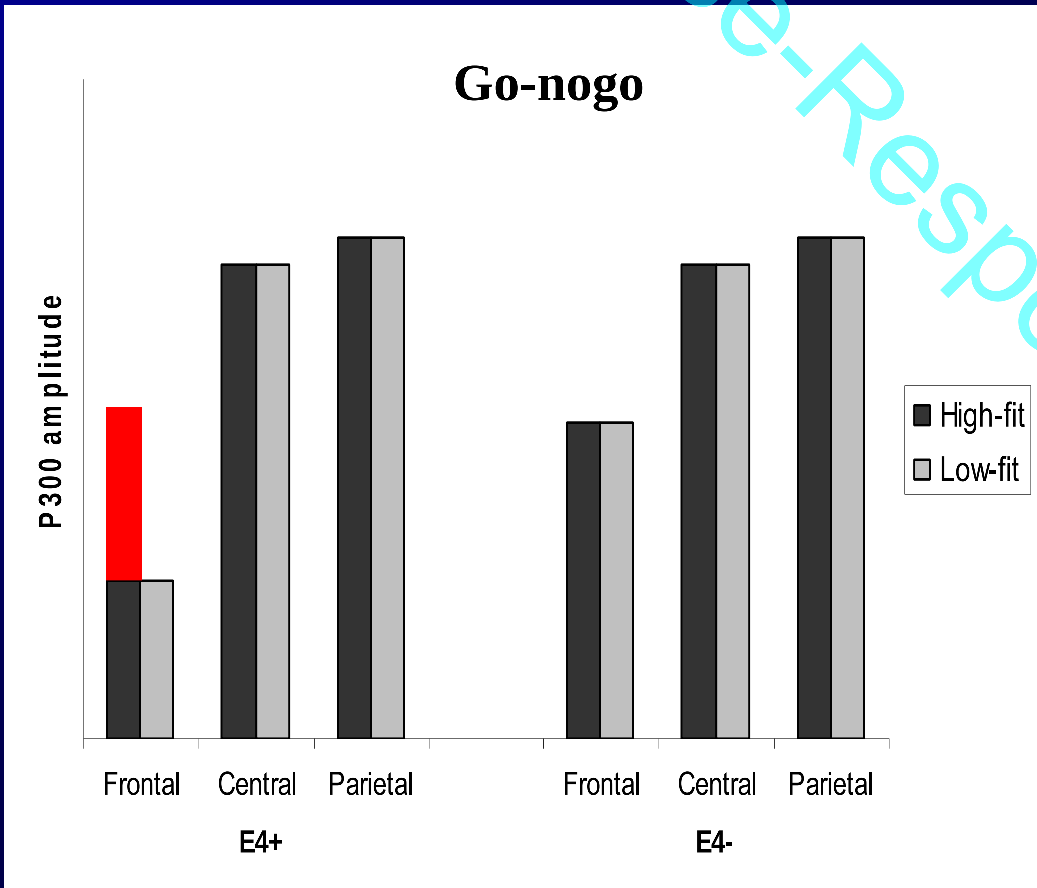
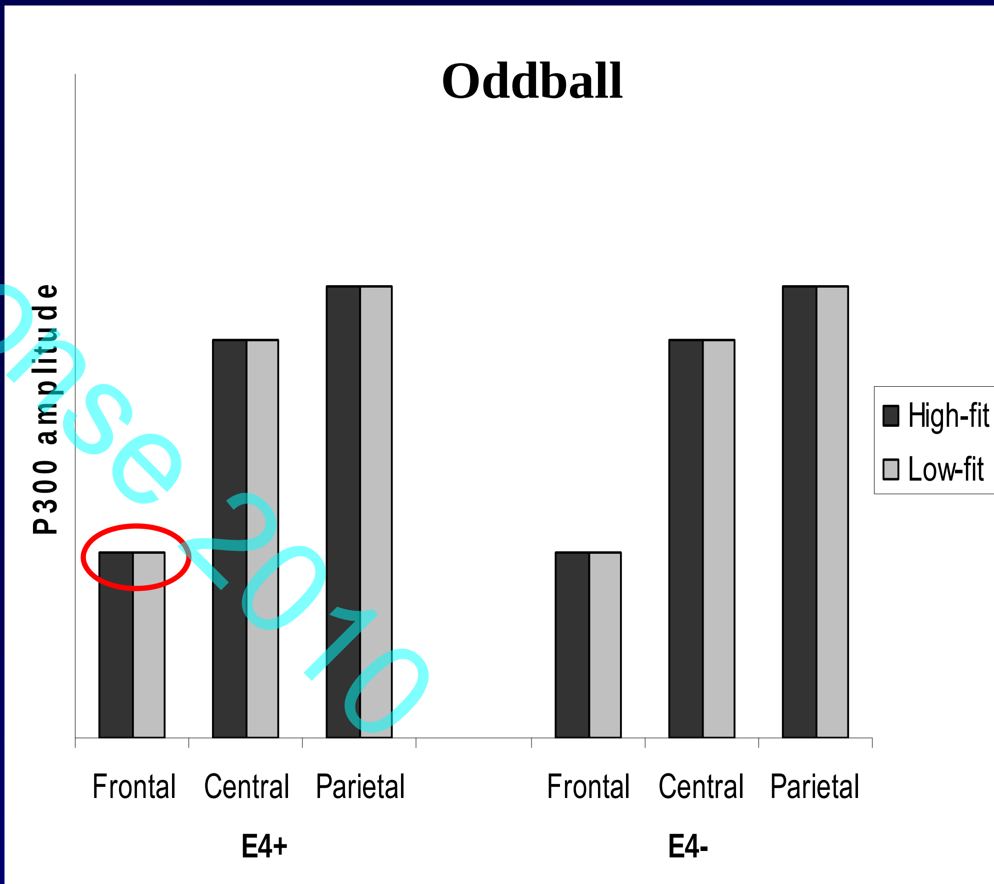
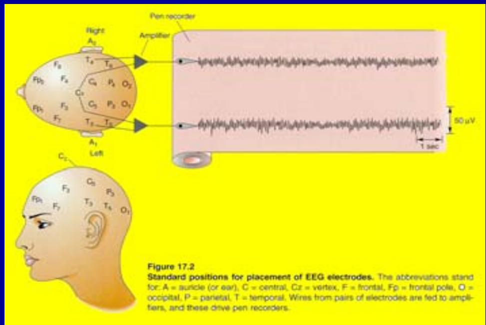


Figure 17.2
Standard positions for placement of EEG electrodes. The abbreviations stand for: A = auricle (or ear), C = central, Cz = vertex, F = frontal, Fp = frontal pole, O = occipital, P = parietal, T = temporal. Wires from pairs of electrodes are fed to amplifiers, and these drive pen recorders.

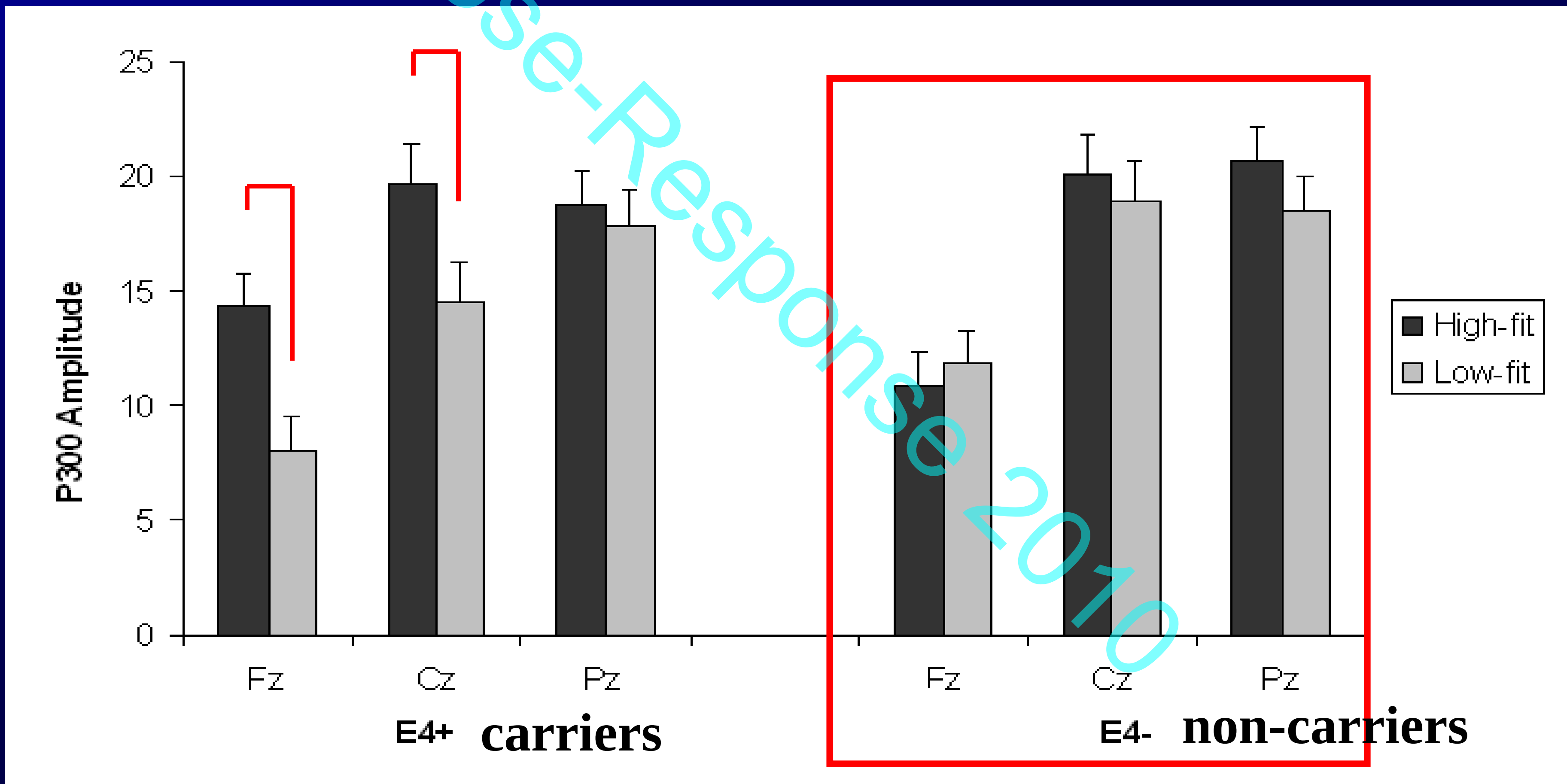
Expected findings: P300 amplitude







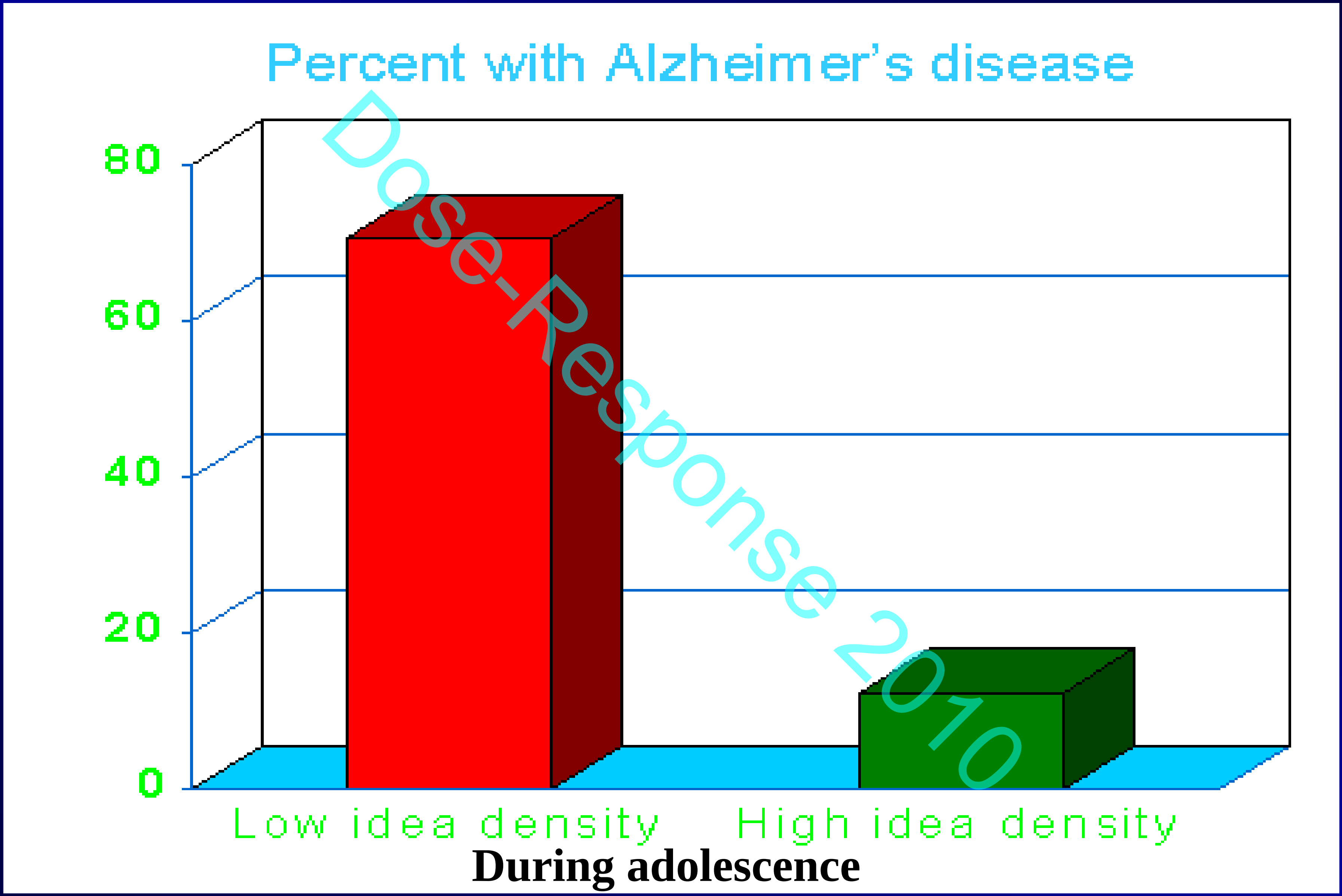
Genotype × Physical fitness × Region interaction on P300 amplitude



- **P300 amplitude**
  - **ApoE e4 carriers may derive particular benefit from fitness**
  - **Cardiovascular fitness in e4 carriers may be protective against the susceptibility to the liabilities (i.e., hypometabolism and cortical thinning) associated with this allele**
- **P300 Latency**
  - **Both genotypes appear to benefit from cardiovascular fitness in regard to the neural processes indexed by P300 latency**

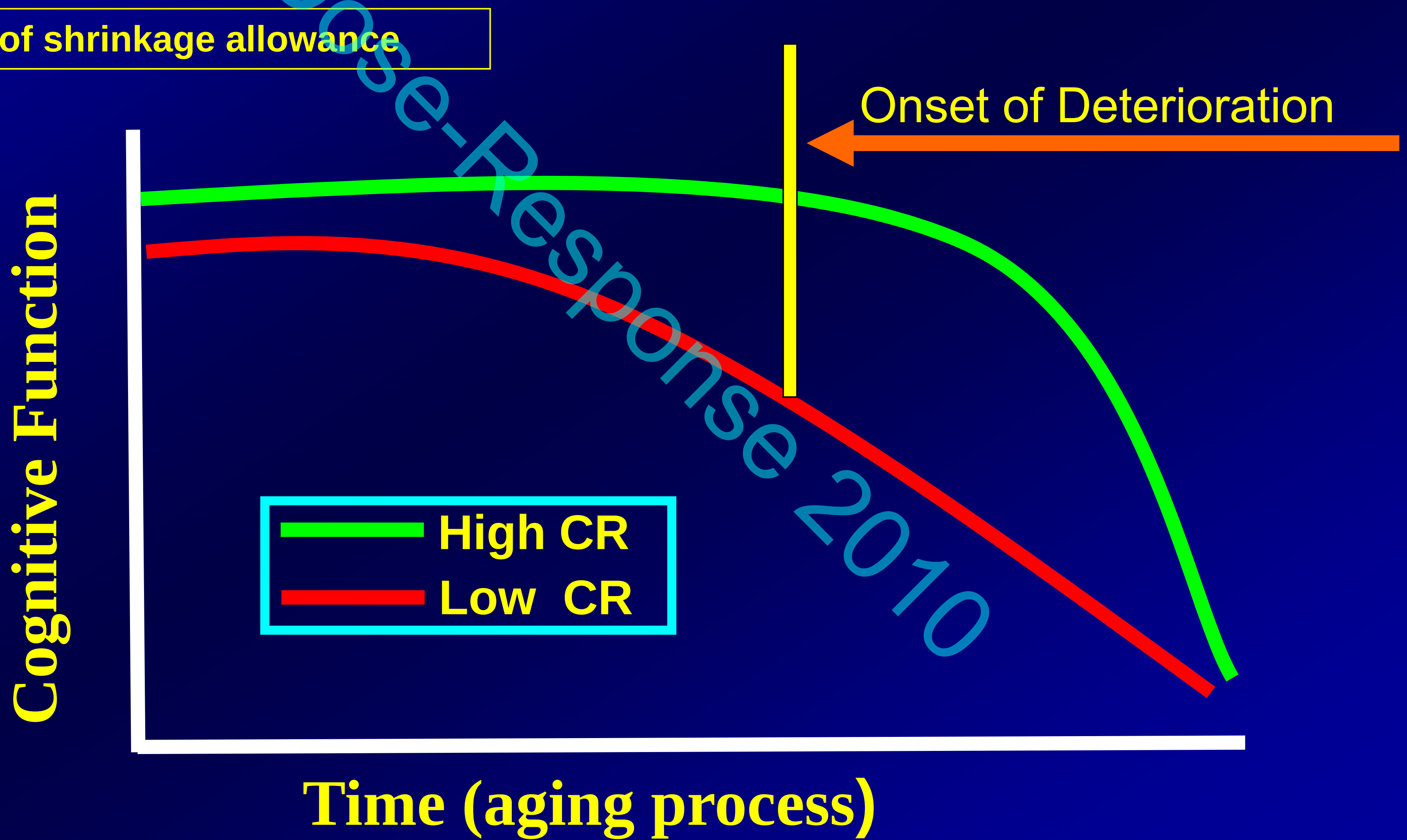
So what?

David Snowdon with participants in the Religious Orders studies

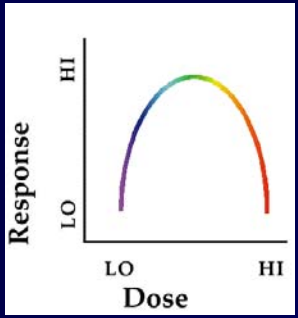


Percent with Alzheimer's disease
80
60
40
20
0
Low idea density
High idea density
During adolescence

Cognitive Functioning Associated with different levels of **Cognitive Reserve**



Conclusions and complexities re dose-response



Acute exercises and affective response – critical to "swallowing the medicine"

Moderate exercise benefits cell aging while higher levels of exercise accelerate aging - a point of diminishing returns (hormesis)

Long-term benefits of moderate exercise on neurocognitive function in older – a case for genetic consideration in the dose-response relationship

Behavioral translation of neurobiological benefits of exercise may be more readily detectable in those who are at a deficit re neural integrity

The 'investment hypothesis' – benefit from PA in youth may not reveal at the behavioral level until a later stage of development (complex temporal dynamic)

Mens Sana in Corpore Sano

A healthy mind in a healthy body

Students
Sean Deeny
Minjung Woo
Jo Zimmerman
Maureen Kayes
Jeremy Rietschel
Ghedem Solomon
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From Philosophy to Science

U Maryland:
Steven Roth
David Poeppel
James Hagberg
Jose Contreras-Vidal
Min Qi Wang
Amy Haufler

Johns Hopkins U:
Jason Brandt
David Youssem
Jay Pillai

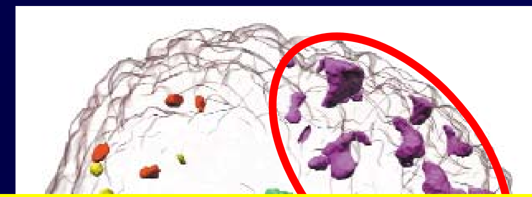
Georgetown U:
John VanMeter
Chandan Vaidya

Scripps Research Inst:
John Polich

George Mason U:
Craig MacDonald

Continued frontal lobe development after puberty

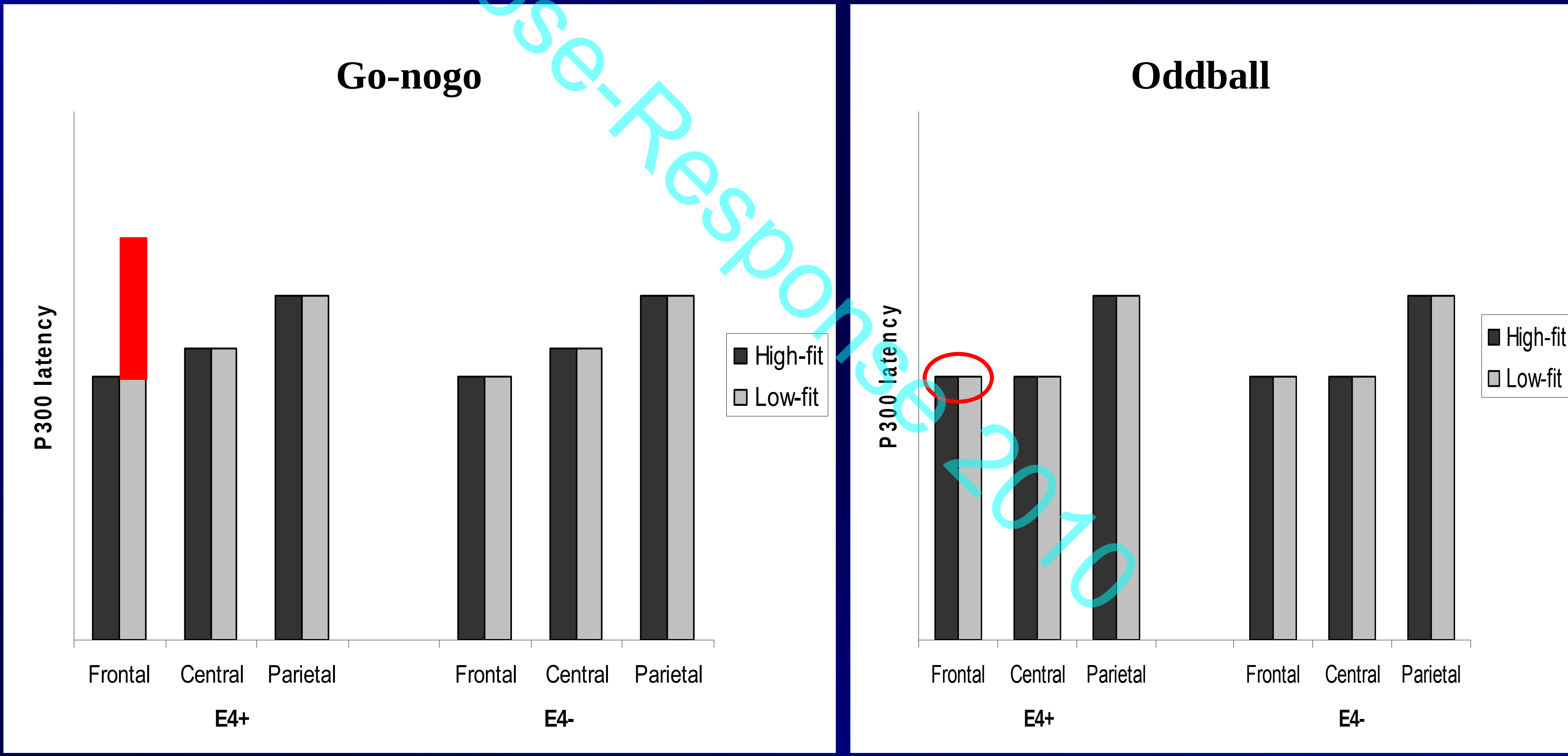
- Myelination
  - Prefrontal cortex continue to myelinate through



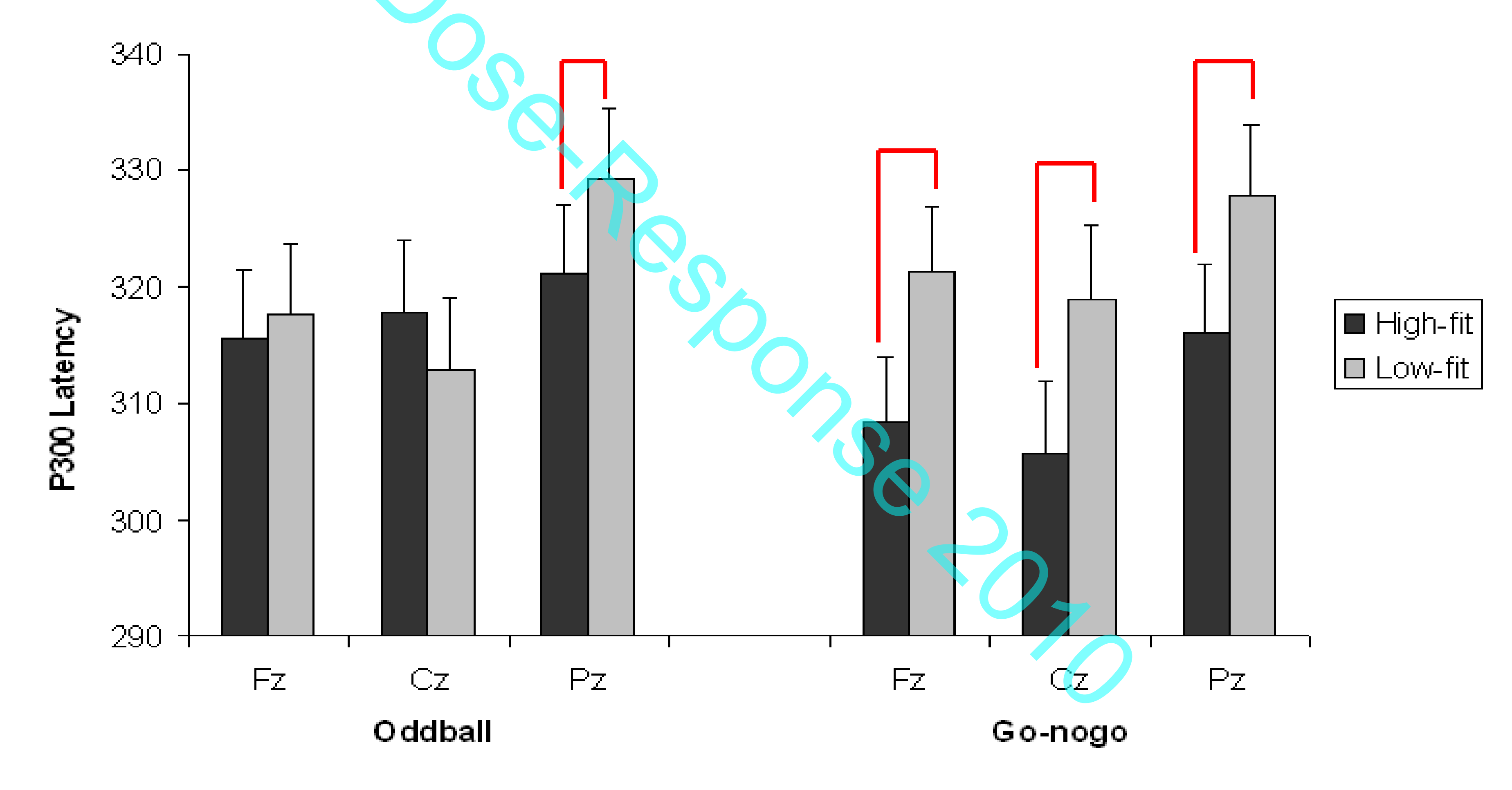
Prefrontal cortex is a brain area
to develop most and last
in the course of individual development

- Synaptic pruning
  - Synapses in prefrontal lobe are overproduced and subsequently pruned up to the age of 30. (Sowell, 2001; 2003)

Expected findings: P300 latency



Physical fitness × Task × Region interaction on the P300 latency




OHIO
C