# Mapping the mind under pressure: Can brain imaging research tell us anything new about stress and physical health?

Pete Gianaros
University of Pittsburgh

CNBC
Center for the Neural Basis of Cognition

PMBC

Context for questions

Research approach

Example findings

Next steps

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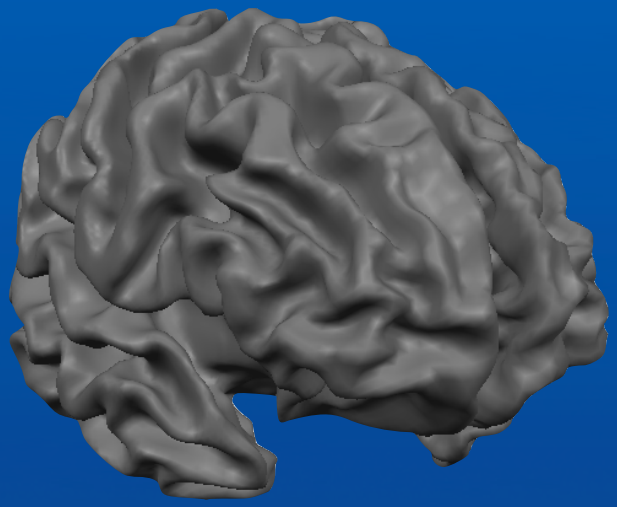
Example findings

Next steps



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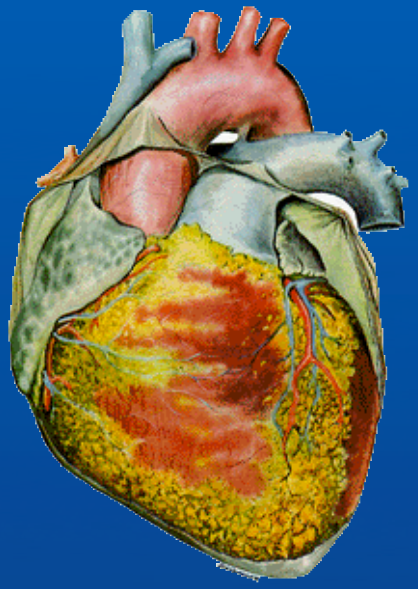
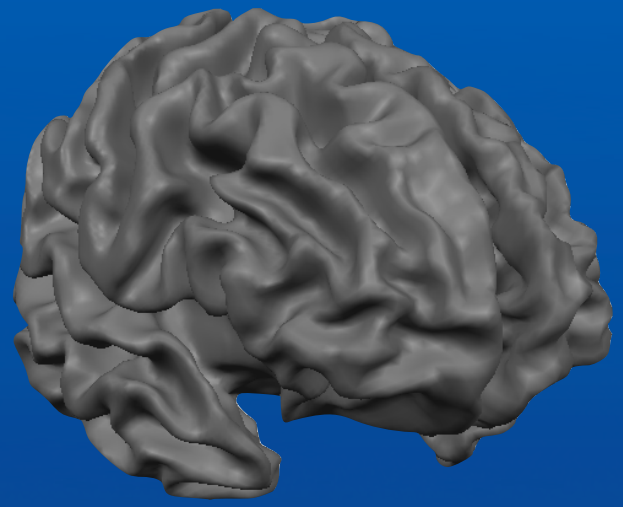


fMRI to study brain systems involved in generating acute cardiovascular stress reactions implicated in CHD risk

sMRI to study brain morphology patterns associated with chronic psychosocial stress and other CHD risk factors



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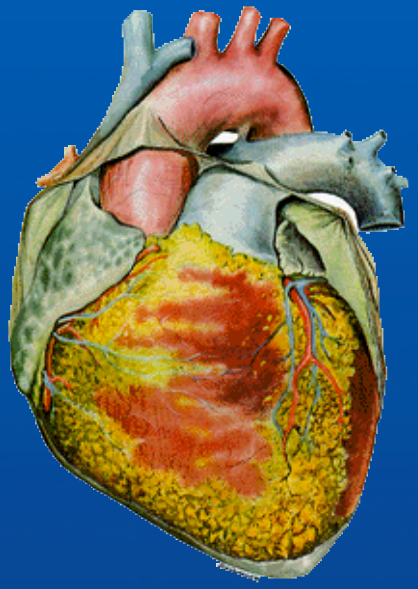


fMRI to study brain systems involved in generating acute cardiovascular stress reactions implicated in CHD risk

Heinz Field in Pittsburgh
Home of the Steelers
(the team that just lost the Super Bowl)

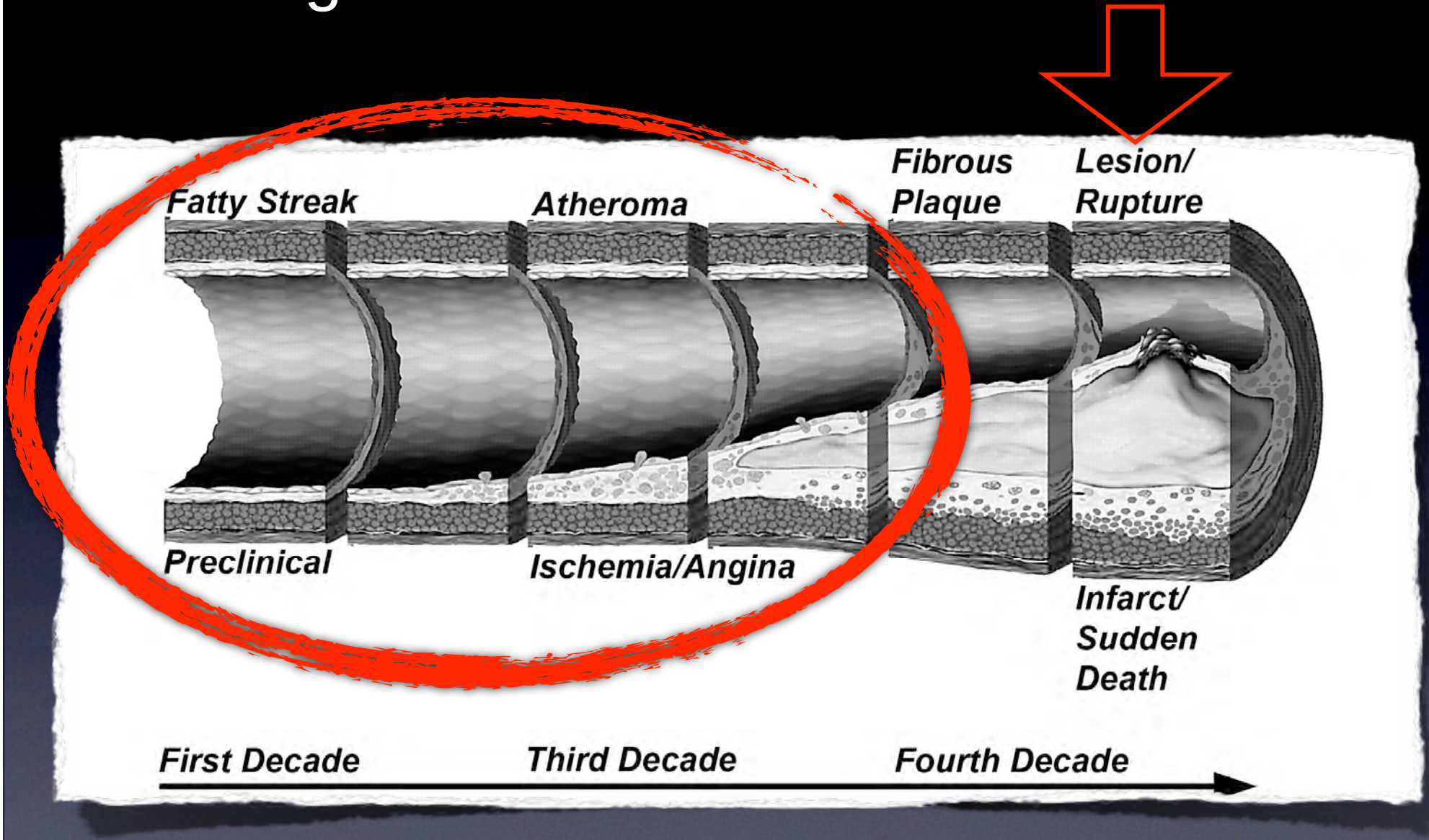
# Steelers vs. Colts 2005 AFC Playoff

Jerome Bettis

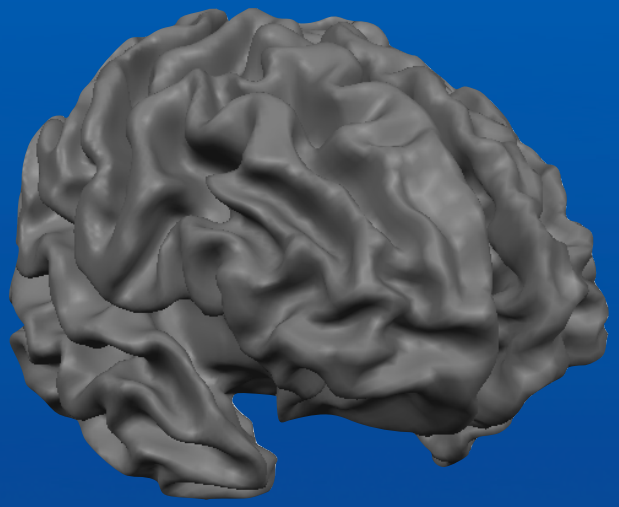
Big Ben & Nick Harper


Terry O'Neil

# CHD begins LONG before events!




Modified from Pepine (1998). Am J Cardiol: 82 (supp); 23-7.



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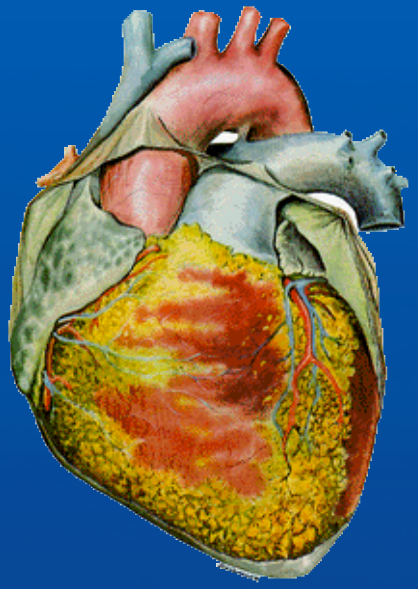


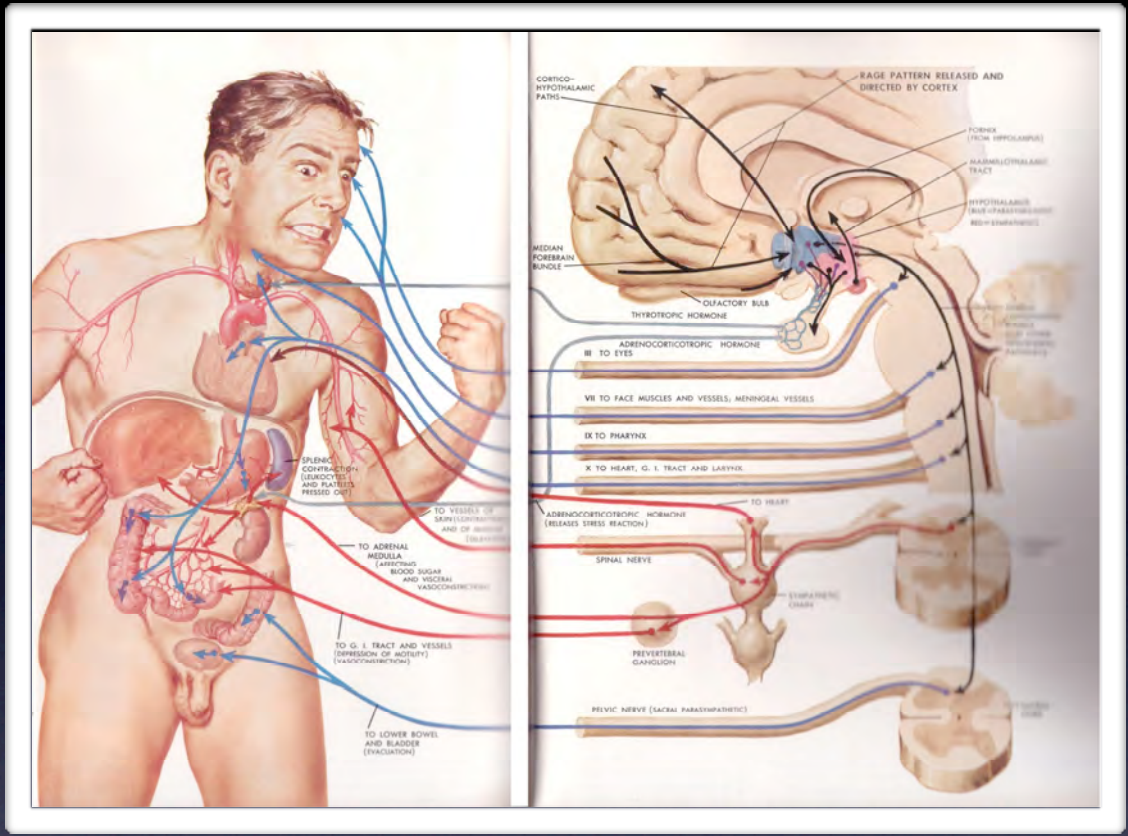
Stress — Pathways — Risk

(***Cardiovascular Reactivity to Acute Stress***)

# What is cardiovascular reactivity?[1-5]

Hallmark of prototypical response to an acute stressor[1]

- BP
- HR
- contractile force
- vessel constriction



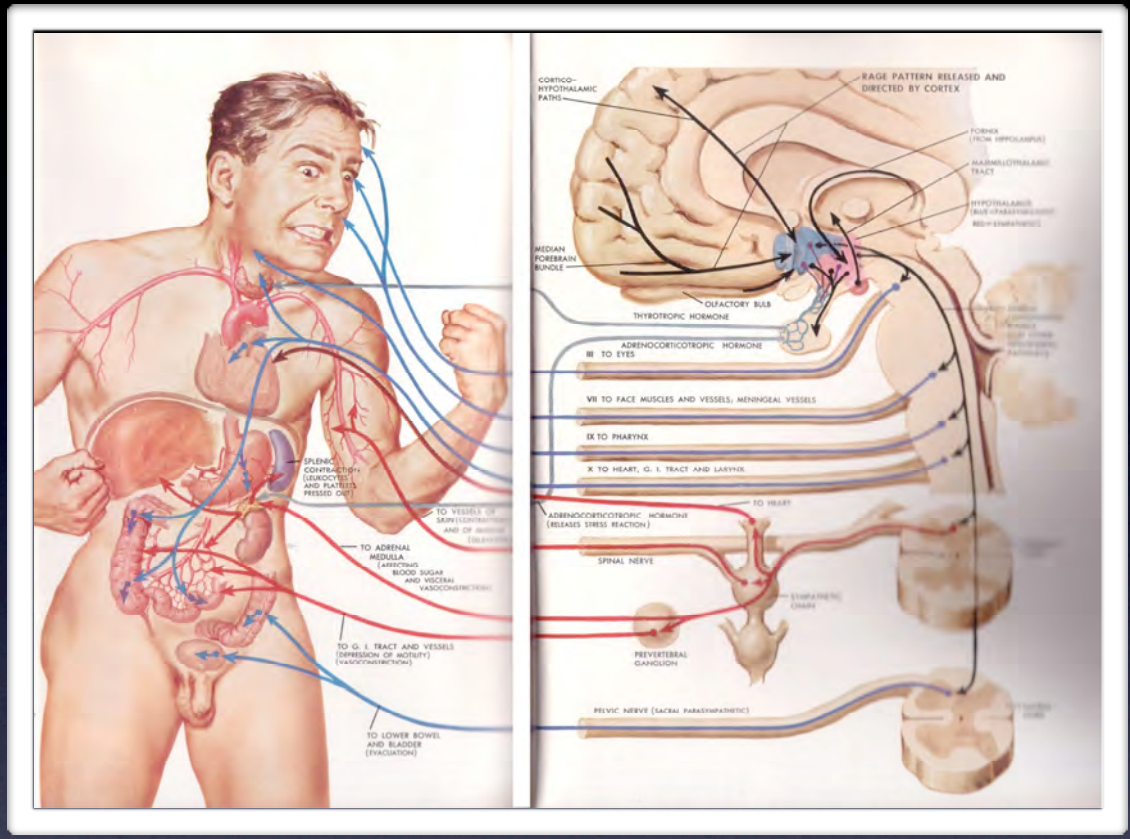


[1]Sapolsky et al (2000) Endocr Rev 21: 55-89
[2]Strike & Steptoe (2004) Prog Cardiovasc Dis 46: 337-47
[3]Manuck et al (1983) Psychosom Med 45: 95-108
[4]Obrist (1981) Cardiovascular psychophysiology
[5]Treiber et al (2003) Psychosom Med 65: 46-62

# What is cardiovascular reactivity?[1-5]

Hallmark of prototypical response to an acute stressor[1]

Wide individual differences associated with psychosocial risk factors for CHD[2]





[1]Sapolsky et al (2000) Endocr Rev 21: 55-89
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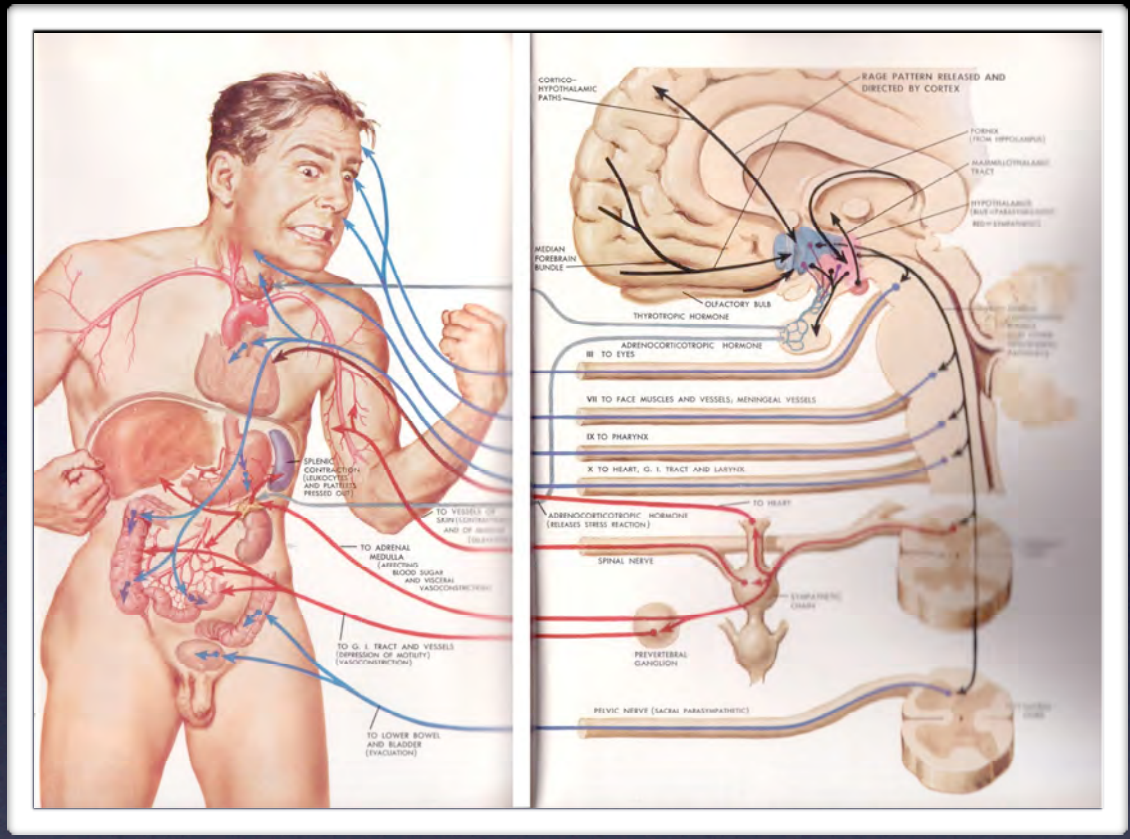
# What is cardiovascular reactivity?[1-5]

Hallmark of prototypical response to an acute stressor[1]

Wide individual differences associated with psychosocial risk factors for CHD[2]

Suspected role in CHD etiology[3-5]

- ☠Hypertension
- ☠Ventricular hypertrophy
- ☠Atherosclerosis





[1]Sapolsky et al (2000) Endocr Rev 21: 55-89
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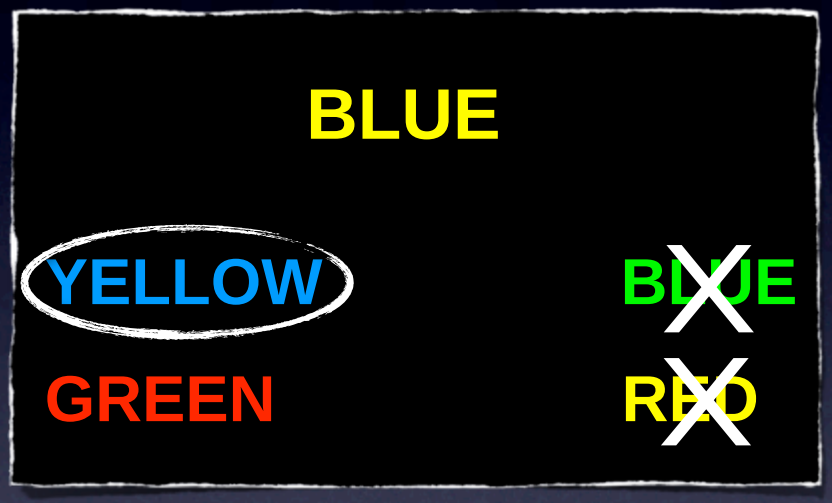
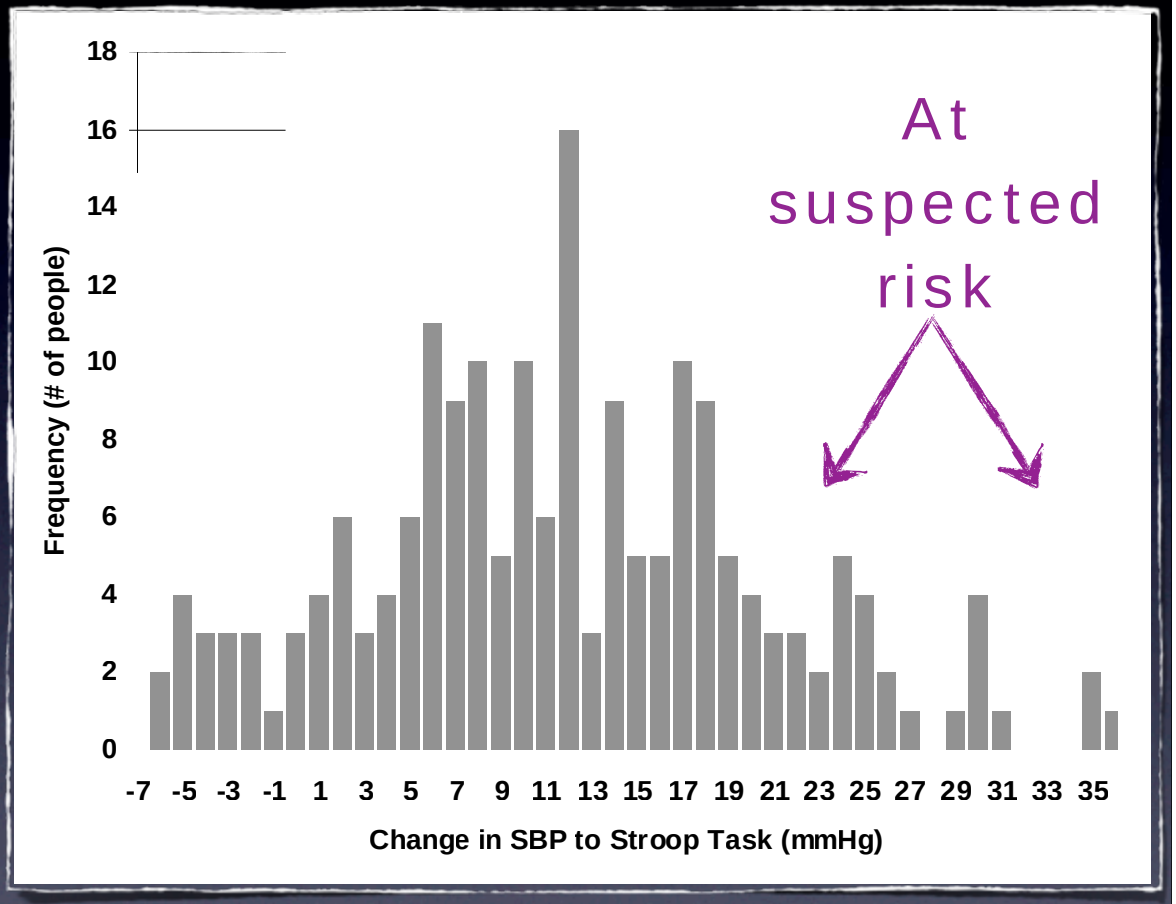
# Cardiovascular reactivity: approach

## Stroop Task[1,2]



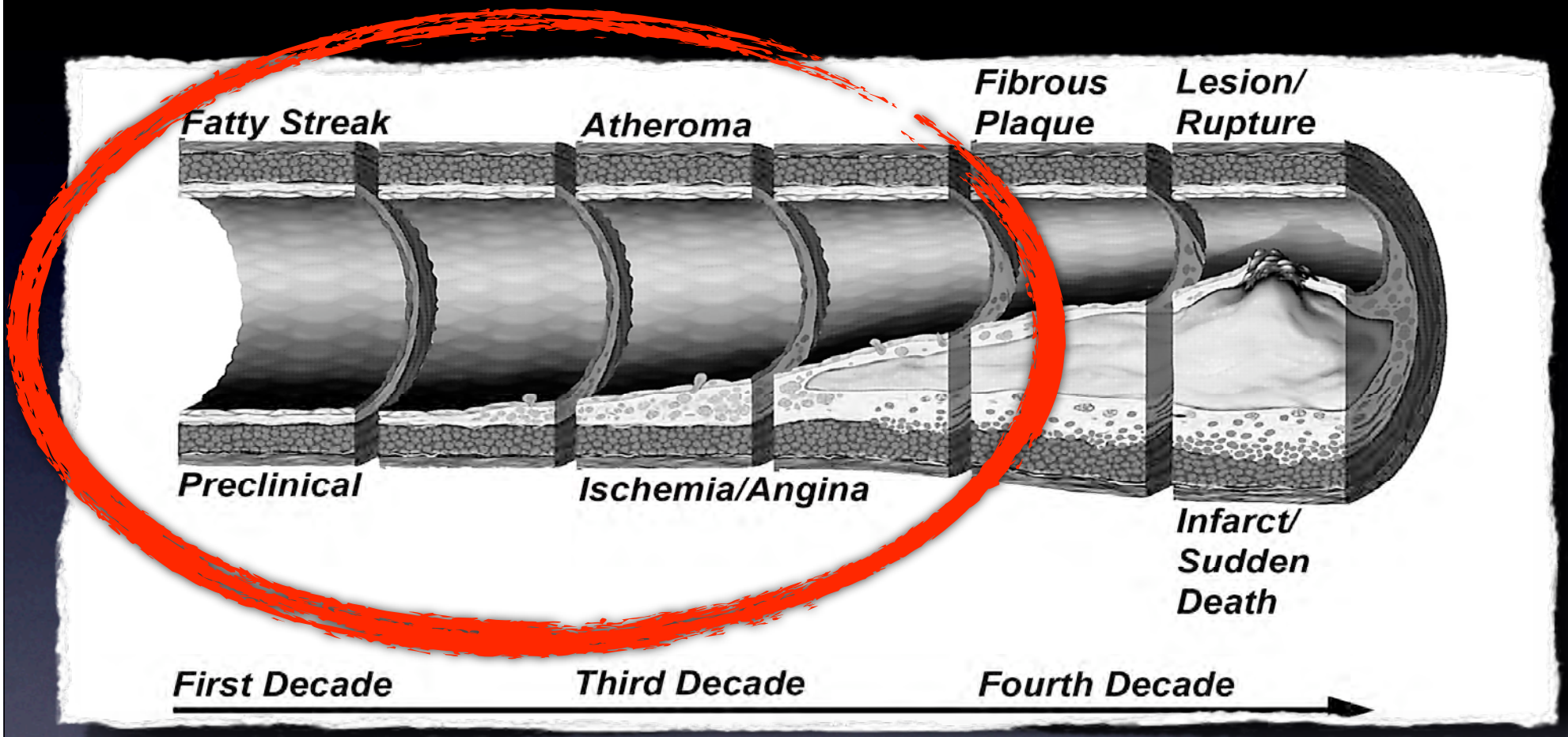

Identify the color of the center word.




[1]Kamarck et al (1992) Psychophysiology 29: 17-28

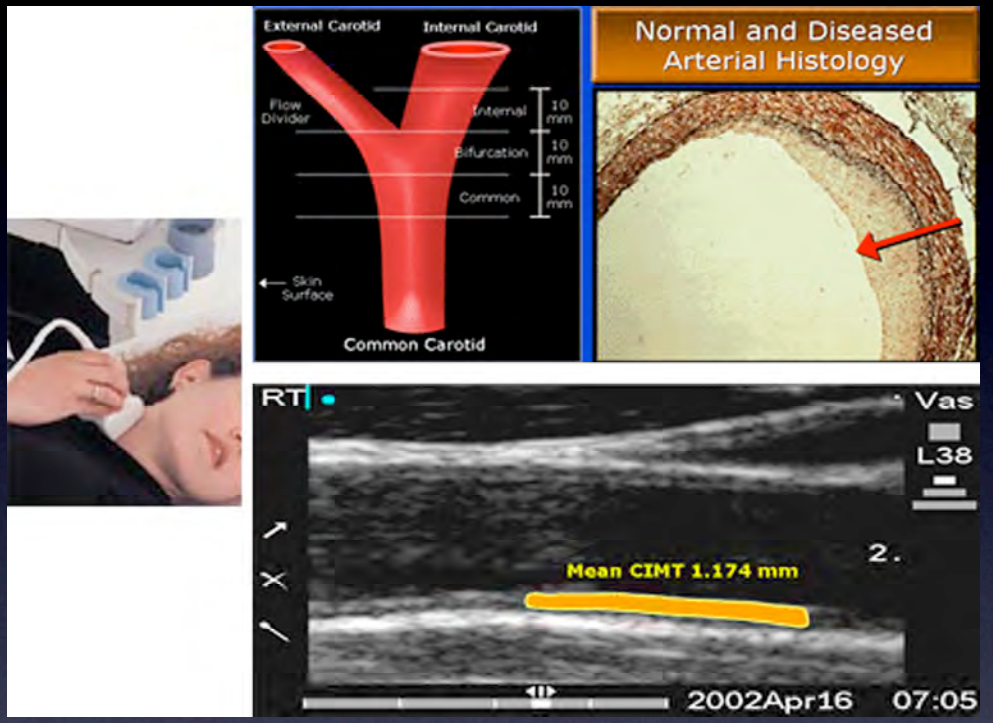
[2]Data from Gianaros et al. (2002) Hypertension 40: 742-747

# Cardiovascular reactivity: approach



# Cardiovascular reactivity: CHD risk[1-6]

- Prospective and cross-sectional associations with preclinical atherosclerosis

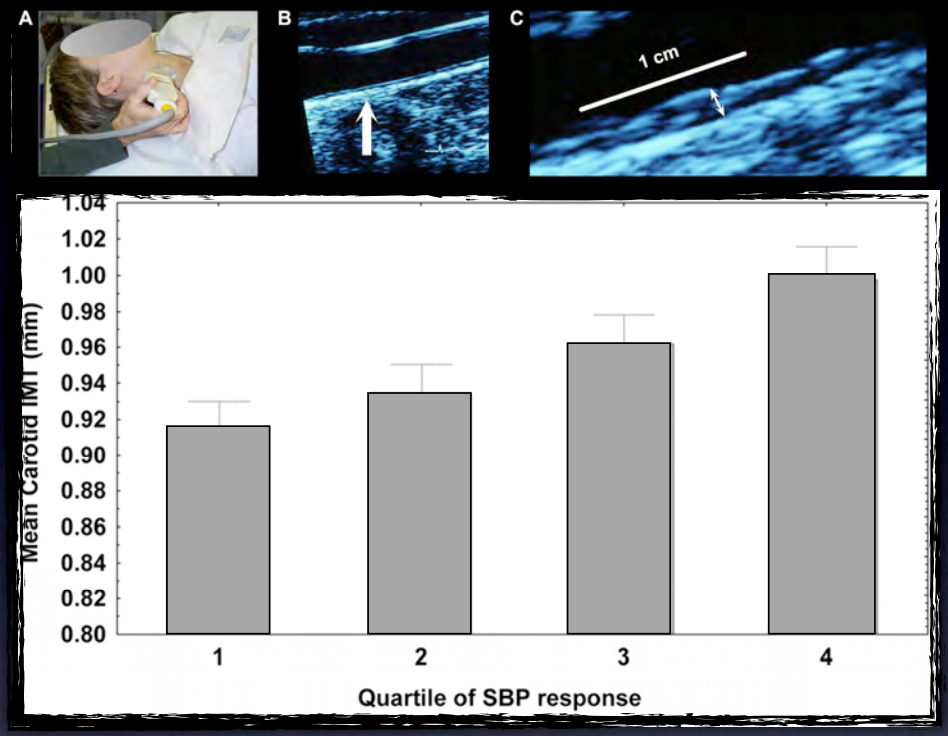




[1]Strike, Steptoe (2004) Prog Cardiovasc Dis 46: 337-47
[2]Manuck et al (1983) Psychosom Med 45: 95-108
[3]Chida, Steptoe (2010) Hypertension 55: 1026-32
[4]Treiber et al (2003) Psychosom Med 65: 46-62
[5]Kamarck et al (1997) Circulation 96: 3842-8
[6]Jennings et al (2004) Circulation 110: 2198-2203

# Cardiovascular reactivity: CHD risk[1-6]

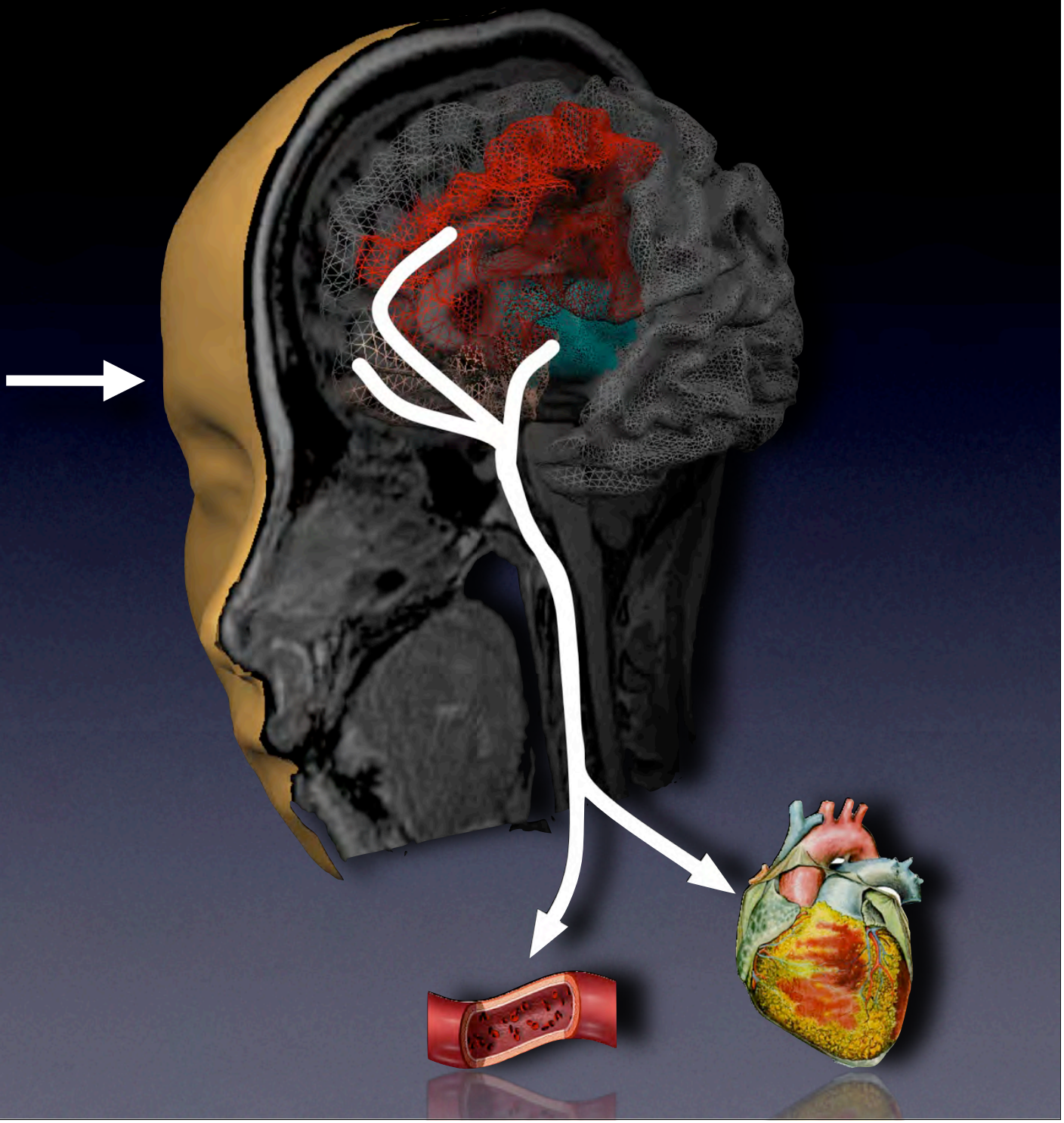
- Prospective and cross-sectional associations with preclinical atherosclerosis




**Mean carotid IMT plotted by quartile of SBP reactivity in Kuopio Ischemic Heart Disease (KIHD) study[6]**

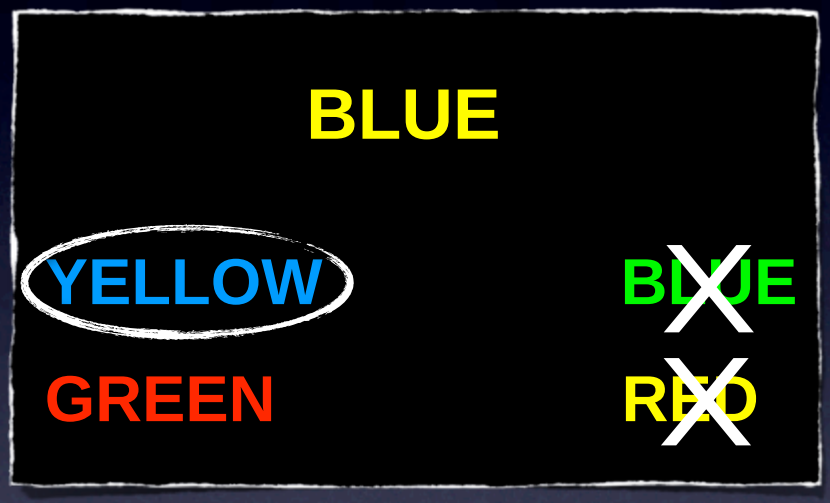

[1]Strike, Steptoe (2004) Prog Cardiovasc Dis 46: 337-47
[2]Manuck et al (1983) Psychosom Med 45: 95-108
[3]Chida, Steptoe (2010) Hypertension 55: 1026-32
[4]Treiber et al (2003) Psychosom Med 65: 46-62
[5]Kamarck et al (1997) Circulation 96: 3842-8
[6]Jennings et al (2004) Circulation 110: 2198-2203

# What brain imaging can do

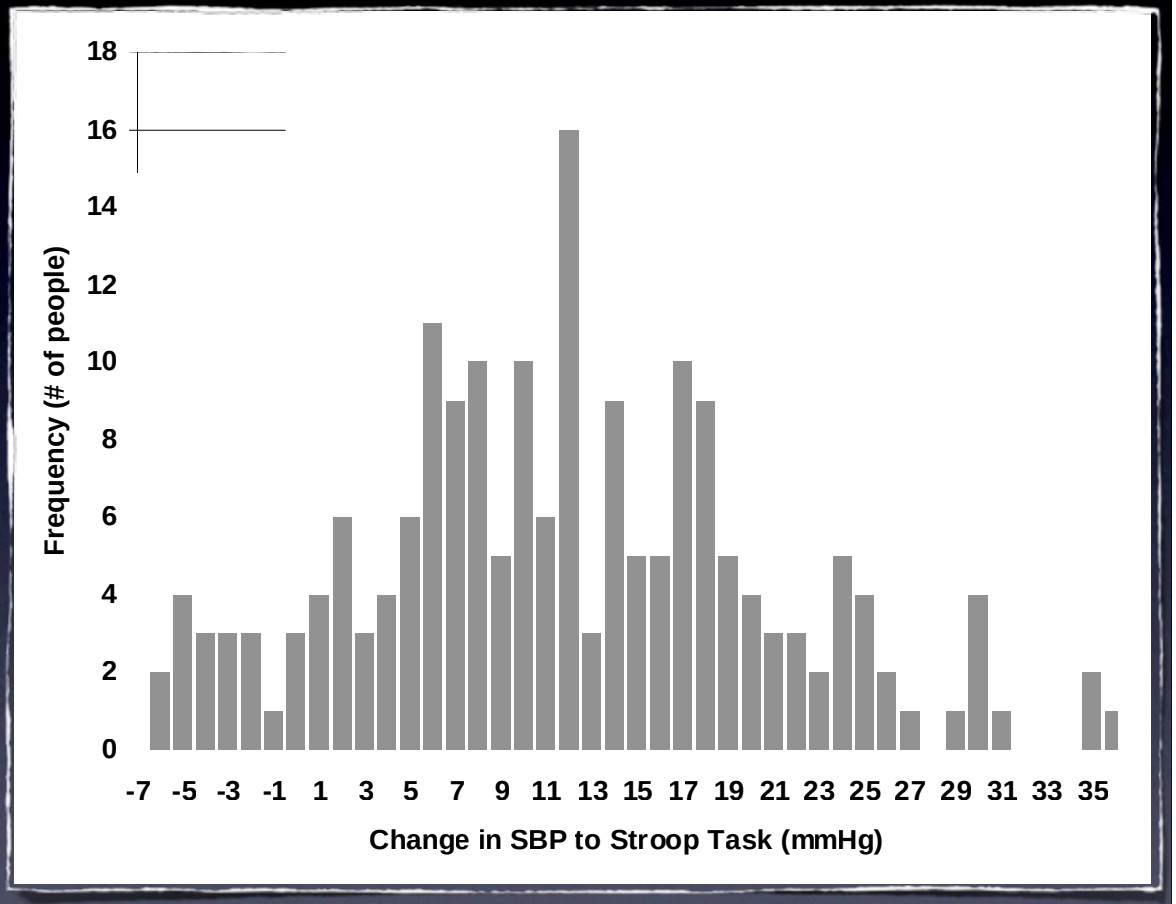


# Cardiovascular reactivity: task translation

## Stroop Task[1,2]




Identify the color of the center word.

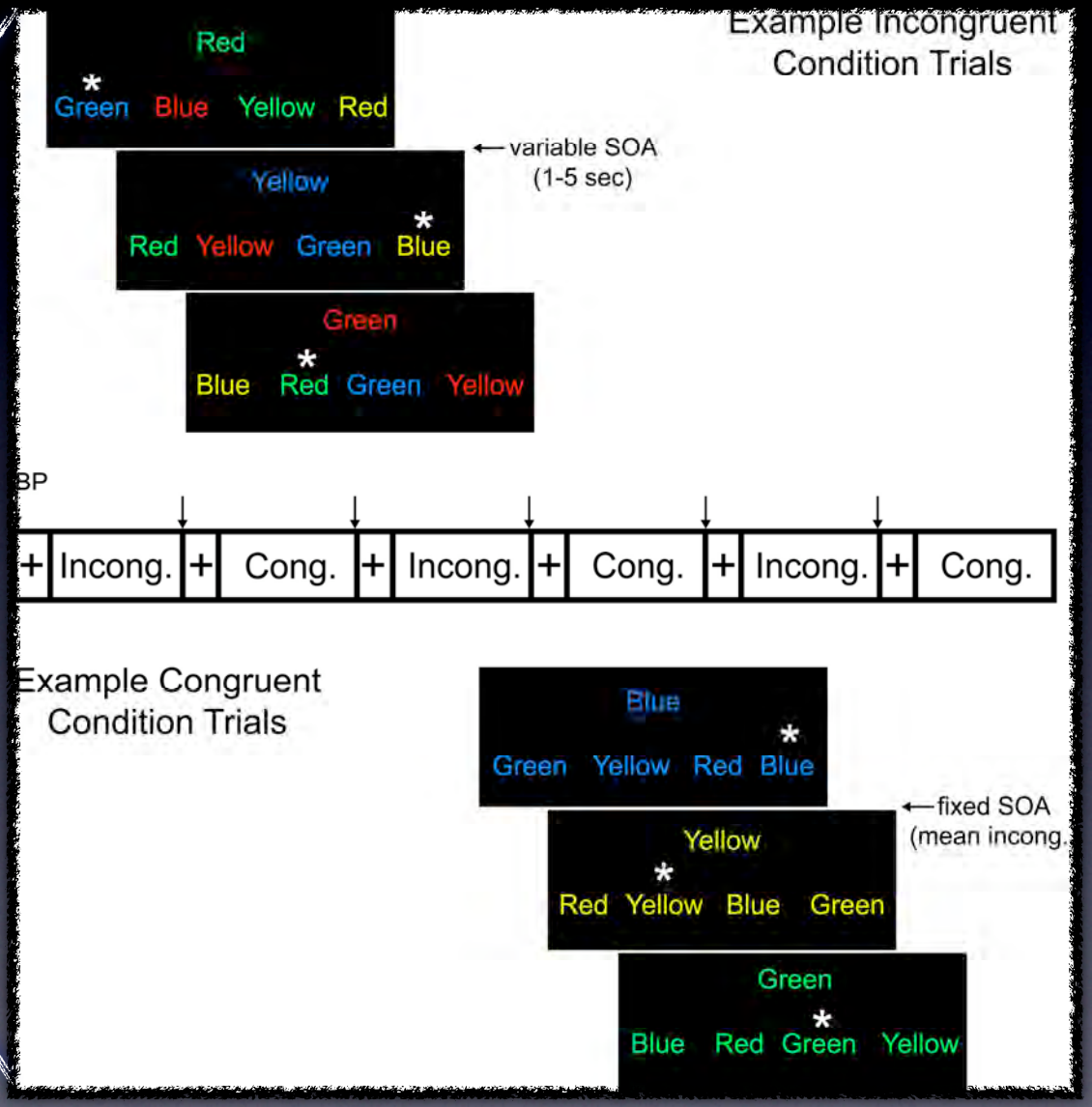



[1]Kamarck et al (1992) Psychophysiology 29: 17-28

[2]Data from Gianaros et al. (2002) Hypertension 40: 742-747

# Cardiovascular reactivity: task translation

Hypertension (2009) 53: 819-25
J Neurosci (2008) 28: 990-9
Hypertension (2007) 49: 134-40
Psychophysiology (2005) 42: 627-35
Psychosom Med (2005) 67: 31-9



conflict resolution

negative feedback

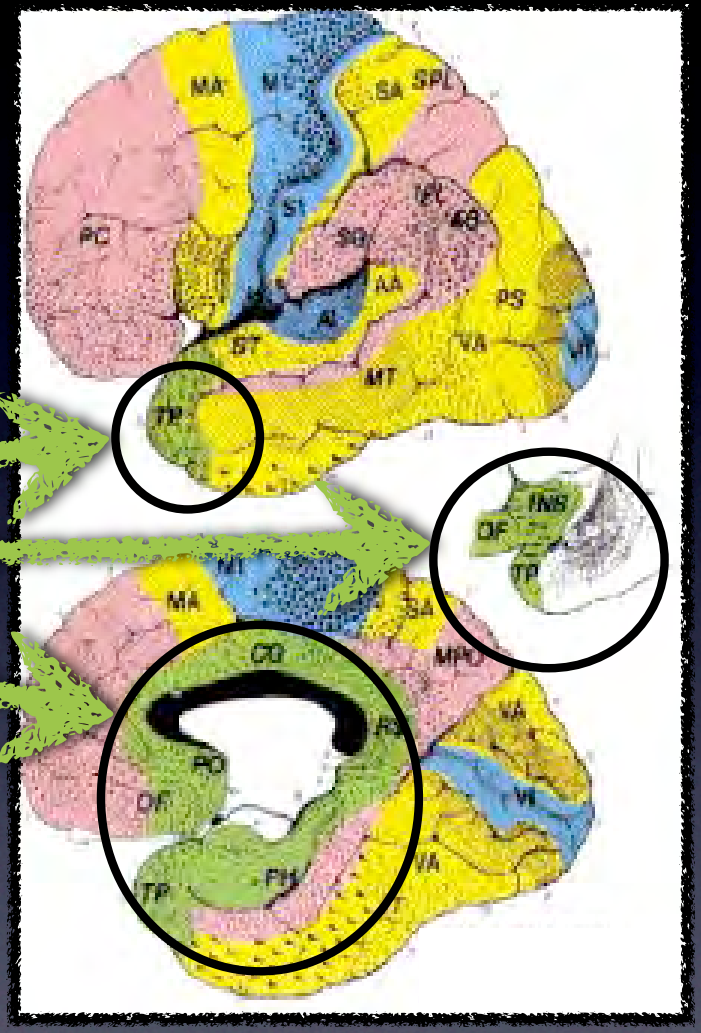
time pressure

lack of control

# A focus on paralimbic brain systems

- Dual role in processing emotional information and regulating peripheral physiology[1-5]

- Key regions
  - Amygdala
  - Cingulate
  - Medial/orbitofrontal cortex
  - Insula




[1]Berntson et al (1998) Beh Brain Res 94: 225-48
[2]Critchley (2005) J Comp Neurol 493: 154-66
[3]Lovallo (2005) Int J Psychophysiol 58: 119-32
[4]Soufer (2004) Circulation 110: 1710-3
[5]Thayer, Lane (2007) Biol Psychol 74: 224-42
*Brodmann (1909) figure from Mesulam (2000)

# Role of amygdala in stress reactivity[1-3]

- Cell complex that plays a broad role in assigning emotional salience to sensory events[1]
- Central nucleus regulates BP via reciprocal cortical and brainstem pathways[2]
- Central nucleus lesions block exaggerated BP reactions in rats genetically prone to hypertension[3]

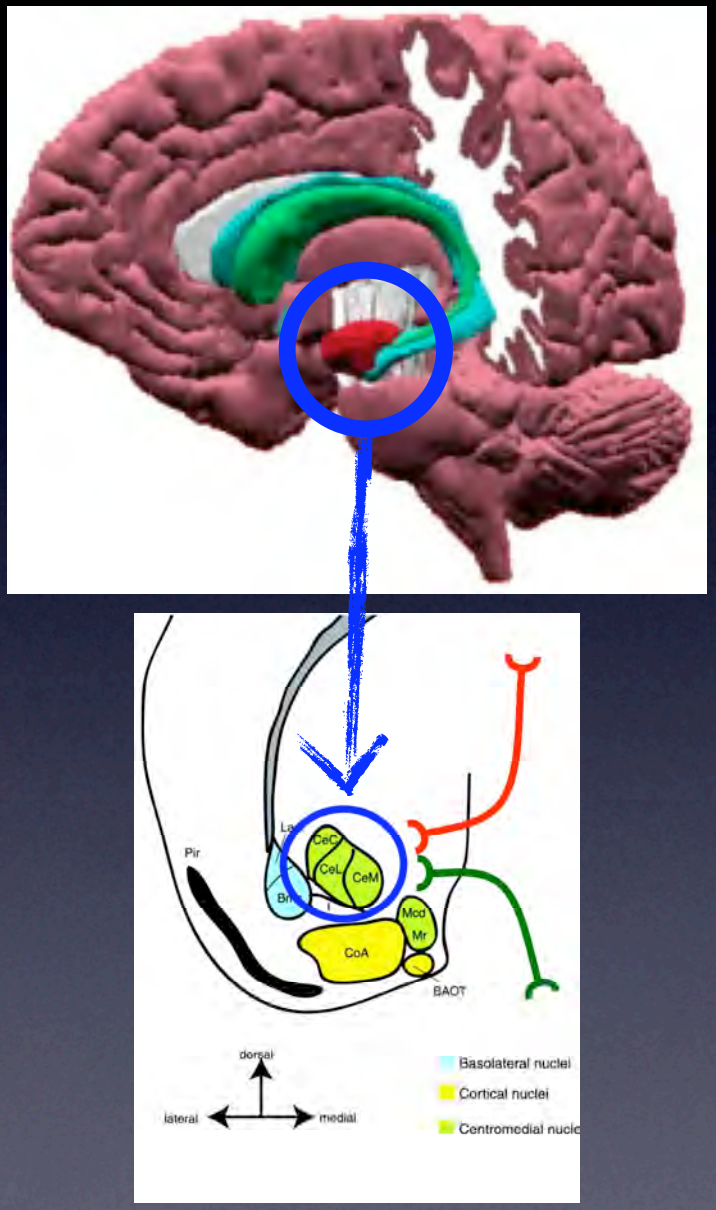



Image from Sah (2003)


[1]Sah (2003) Physiol Rev 83: 803-34
[2]Saha (2005) Clin Exp Pharm Physiol 32: 450-6
[3]Sanders et al (1994) Physiol Behav 56: 709-13

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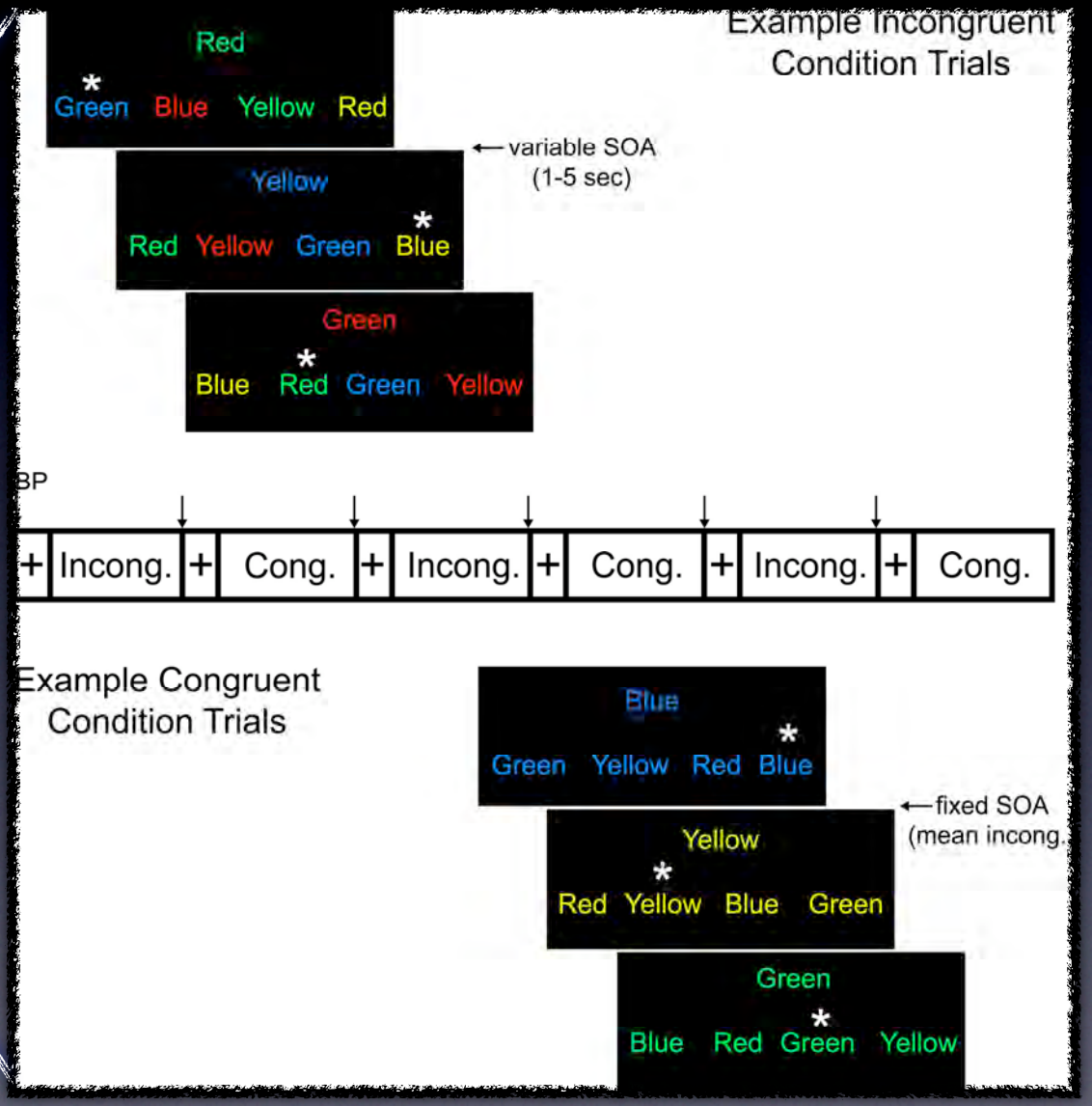
Question:

Does stressor-evoked BP reactivity vary with amygdala activation across individuals?

Gianaros, Sheu, Matthews, Jennings, Manuck, Hariri (2008) J Neurosci 28: 990-99

# Cardiovascular reactivity: task protocol





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Psychophysiology (2005) 42: 627-35
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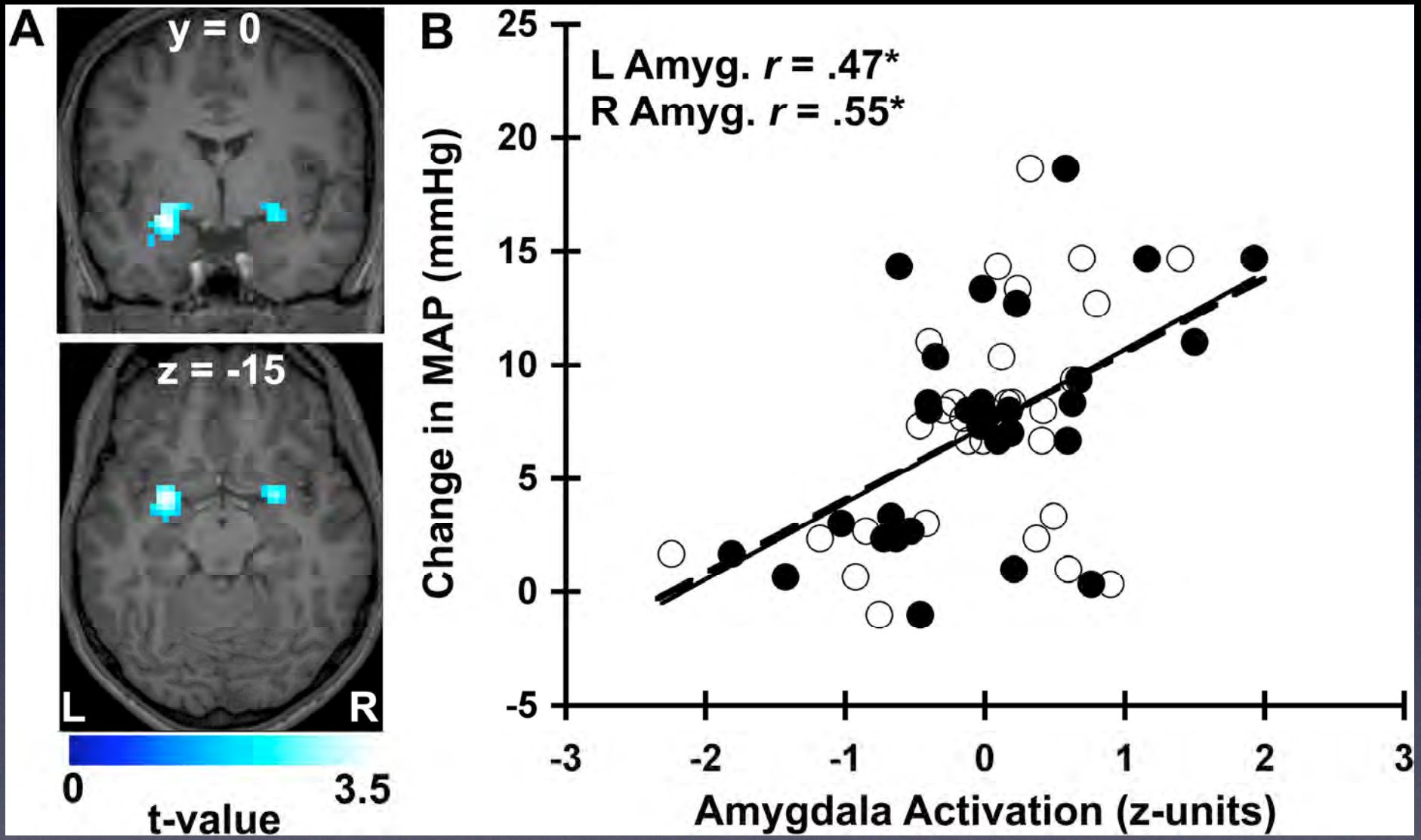
# Amygdala activation to the Stroop stressor and BP reactivity




Gianaros, Sheu, Matthews, Jennings, Manuck, Hariri (2008) J Neurosci 28: 990-99

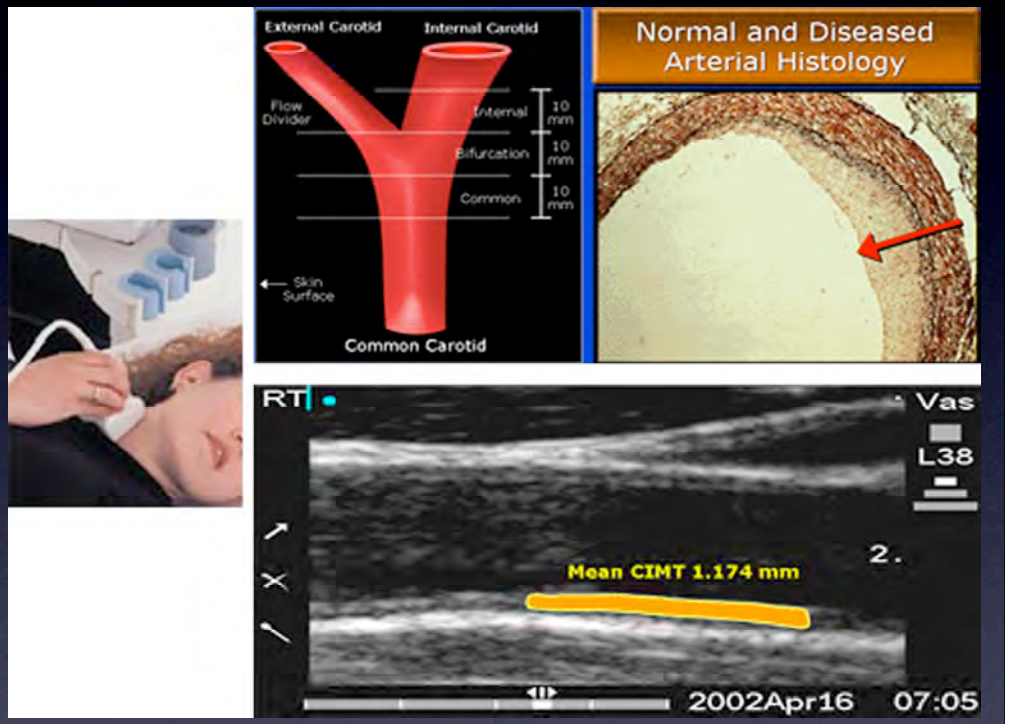
Question:

Is heightened amygdala reactivity associated with preclinical atherosclerosis?

Gianaros, Hariri, Sheu, Sutton-Tyrrell, Muldoon, Manuck (2009) Biol Psychiatry 65: 943-50

# Intima-media thickness (IMT)[1-3]

- Indirect indicator of early, preclinical atherosclerosis
- Validated against postmortem measures of atherosclerotic disease
- IMT predicts clinical events (infarction, stroke) and varies with traditional risk factors



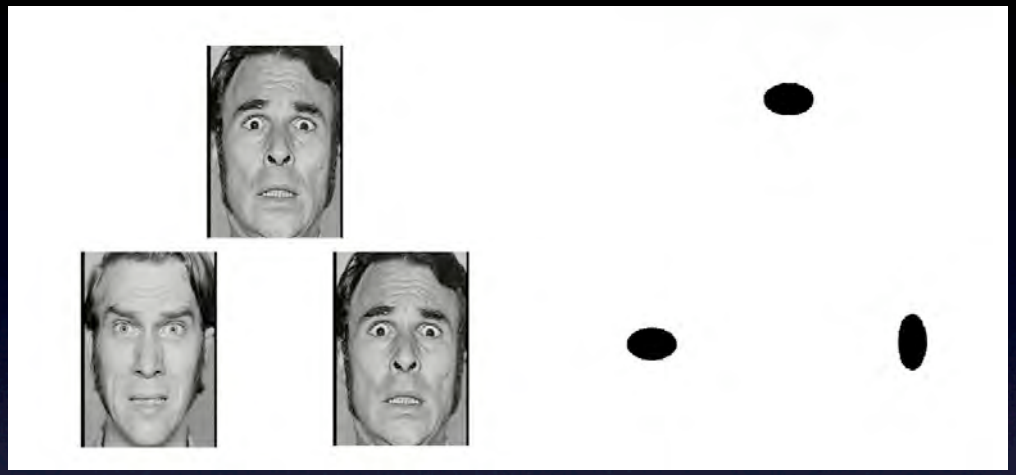


[1]Wong et al (1993) Arterioscler Thromb Vasc Biol 13: 482-86

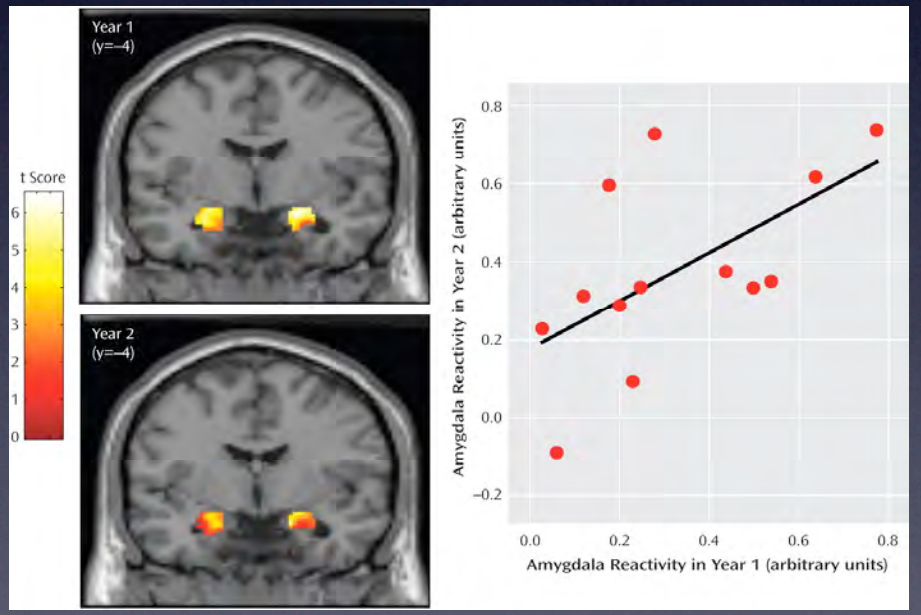
[2]Bots et al (1997) Circulation 96: 1432-37

[3]Hodis et al (1998) Ann Int Med 128: 262-69

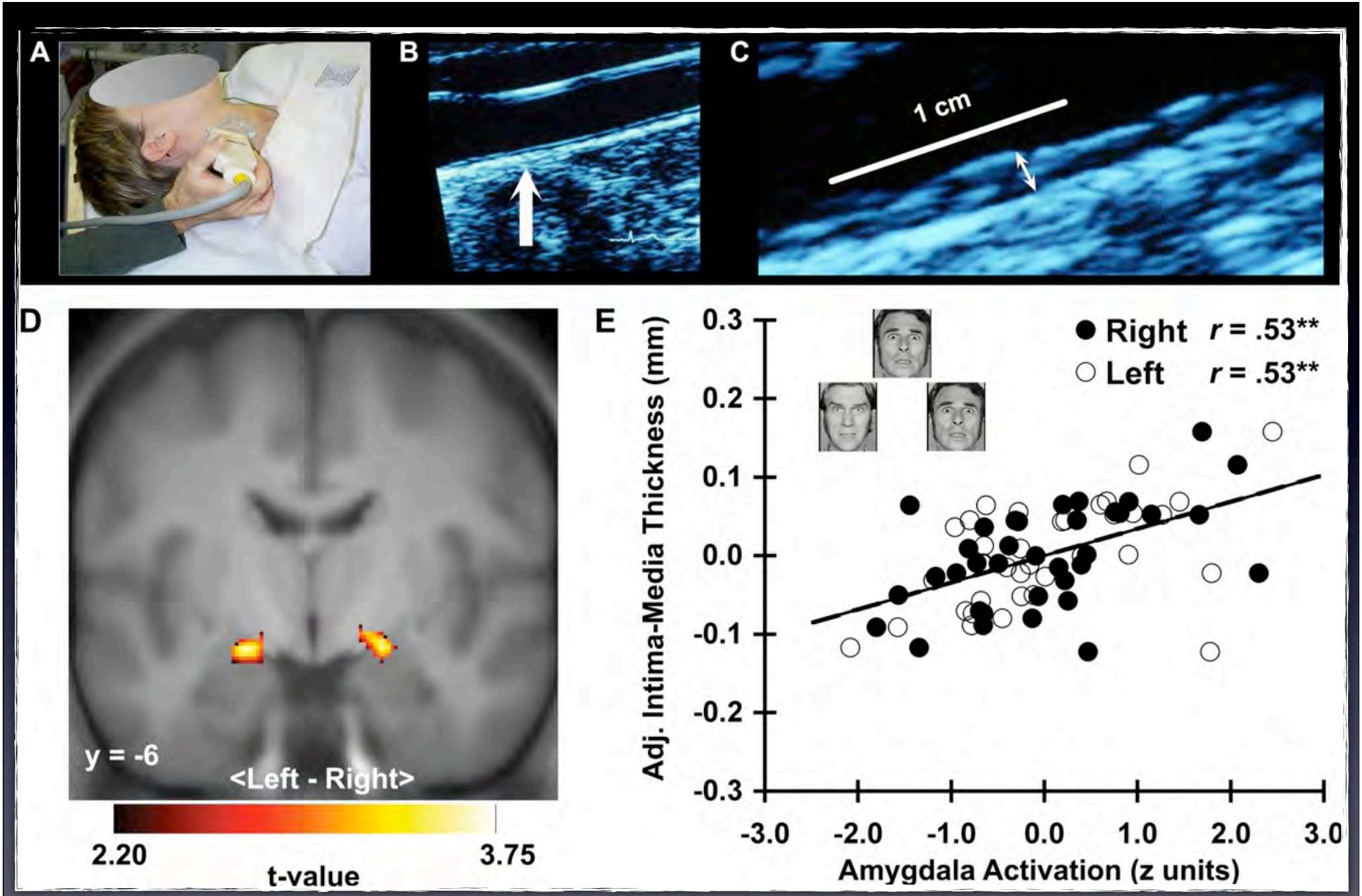
# Amygdala reactivity paradigm[1,2]



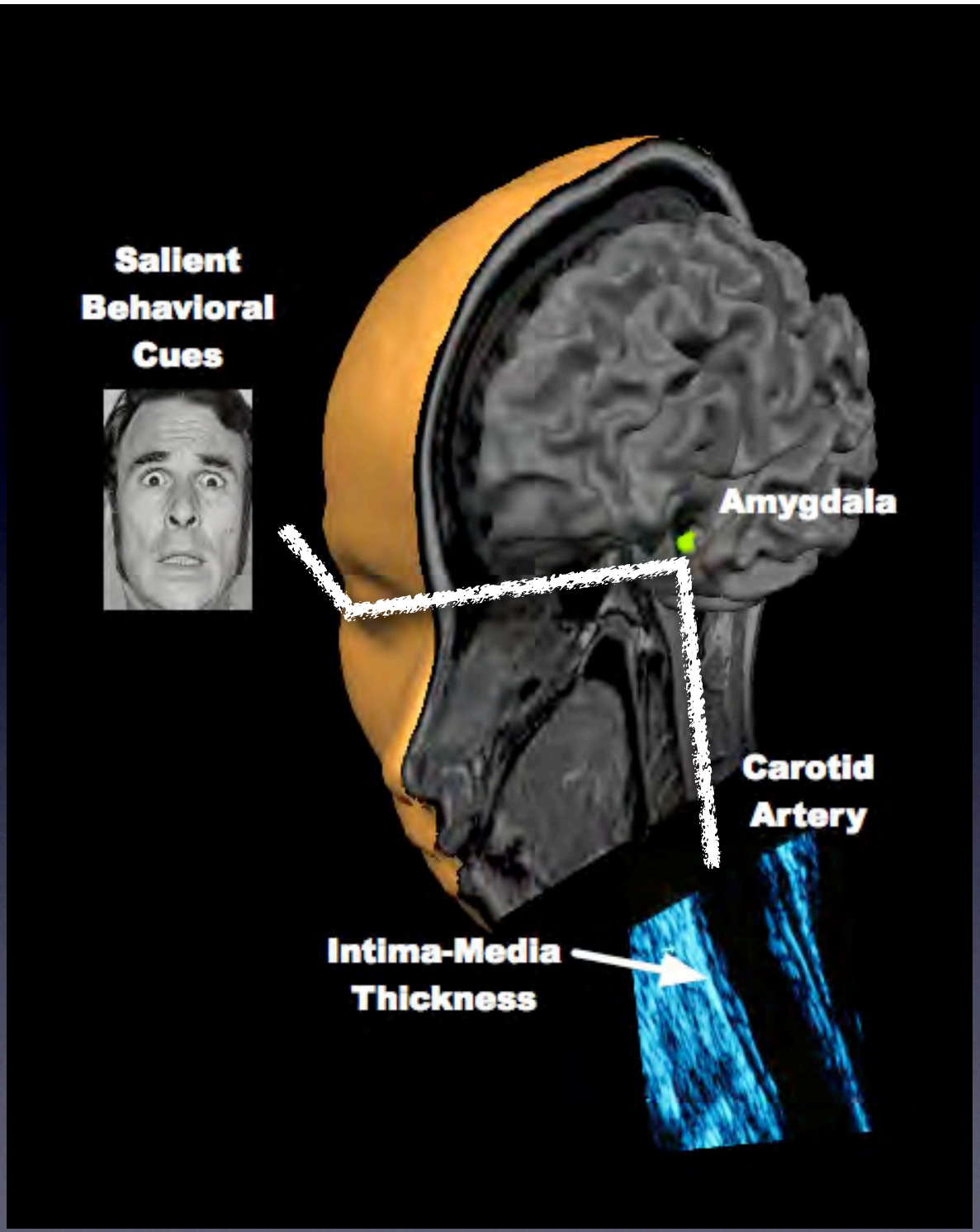
[1]Hariri et al (2002) Science 297: 400-3




[2]Manuck et al (2007) Am J Psychiatry 164: 1613-4




36 adults (18 women, 31–53 yrs) from the Adult Health & Behavior Project, Manuck, PI
Gianaros, Hariri, Sheu, Muldoon, Sutton-Tyrrell, Manuck (2009) Biol Psychiatry 65: 943-50


Salient
Behavioral
Cues
Amygdala
Carotid
Artery
Intima-Media
Thickness

# Interim summary

- Initial evidence for brain systems putatively mediating individual differences in stressor-evoked blood pressure reactivity
- Systems agree with animal work, and have long been speculated to contribute to risk for chronic illnesses (e.g., CHD)
- Preliminary evidence that amygdala functionality is associated with preclinical atherosclerosis

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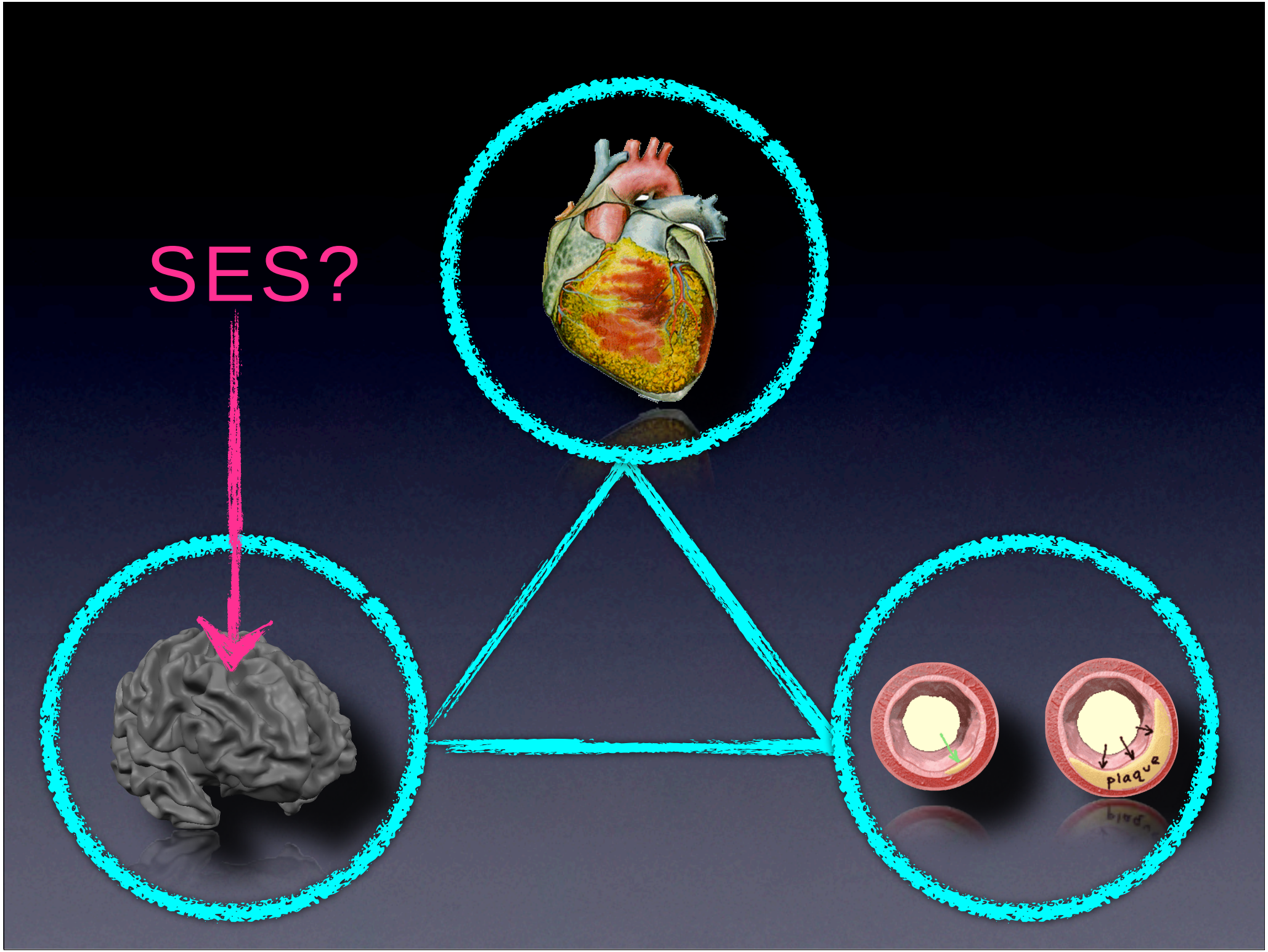
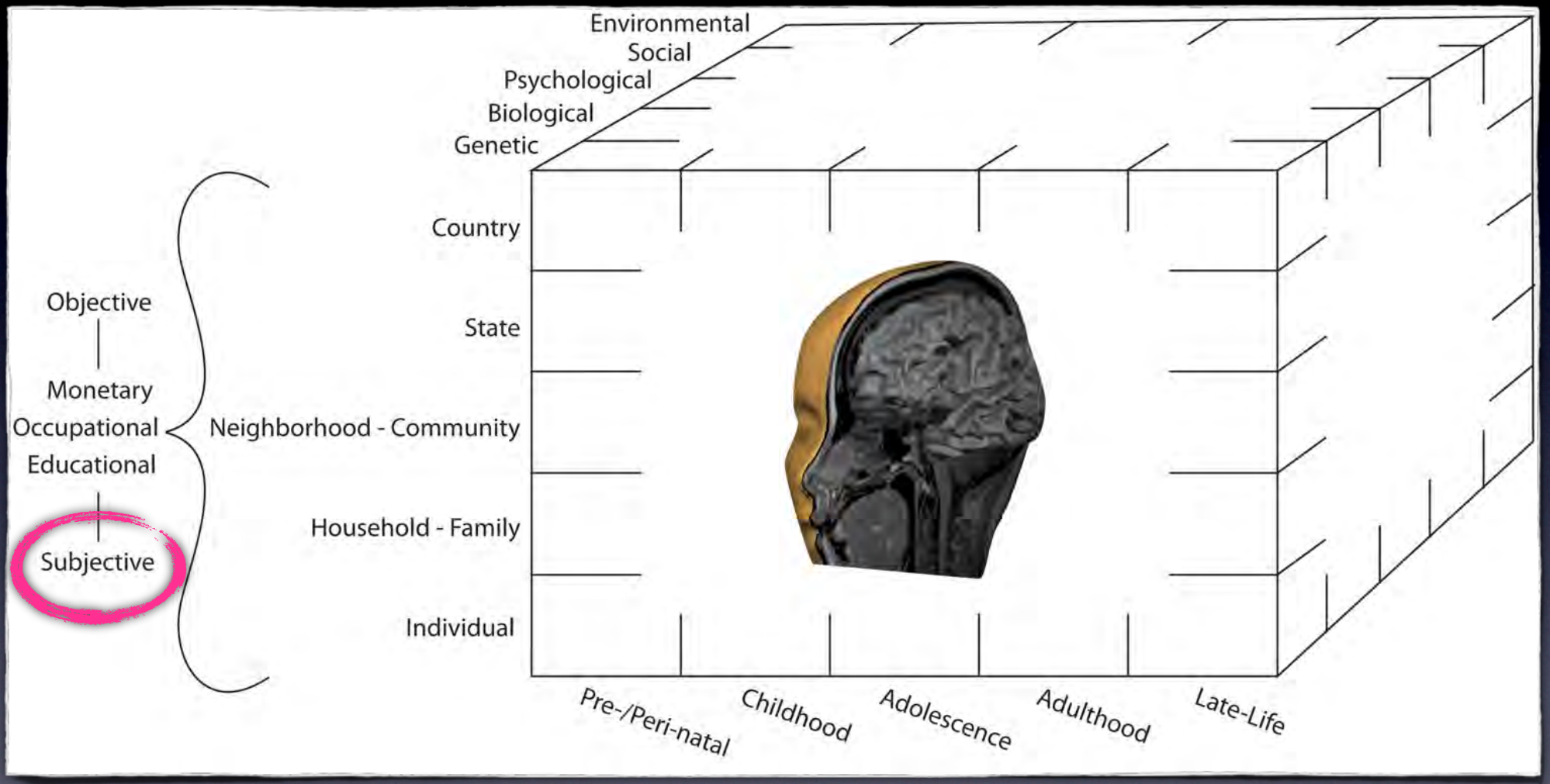

SES?
plaque

# SES is a multilevel & multidimensional construct that relates to CHD risk by multiple neurobiological pathways across life[1-5]




[1]Adler, Rehkopf (2008) Annu Rev Public Health 29:235-52
[2]Braveman (2006) Annu Rev Public Health 27:167-94
[3]Braveman et al (2005) JAMA 294:2879-88
[4]Chen et al (2002) Psychol Bull 128: 295-329
[5]Matthews, Gallo (in press) Annu Rev Psychol

*Figure from Gianaros, Manuck (2010) Psychosom Med 72: 450-61

# Subjective socioeconomic status (sSES)[1-5]

- Refers to perceived standing in a social hierarchy[1]
- Typically anchored to educational, occupational, & monetary indicators at individual or parental level
- Lower sSES associated with:
  - poorer self-reported health[1,2]
  - non-habituating cortisol reaction to stress[1]
  - exaggerated rise in AM cortisol[3]
  - metabolic syndrome[4]
  - common cold susceptibility[5]


[1]Adler et al (2000) Health Psychol 19: 586-92
[2]Singh-Manoux et al (2005) Psychosom Med 67: 855-61
[3]Wright, Steptoe (2005) Psychoneuroendocrinol 30: 582-90
[4]Manuck et al (2010) Psychosom Med 72: 35-45

# sSES assessment: MacArthur Ladder[1]

‘Think of this ladder as representing where people stand in the United States. At the top of the ladder are the people who have the most money, most education, and most respected jobs. At the bottom are the people who have the least money, least education, and least respected jobs or no job. The higher up you are on this ladder, the closer you are to the people at the very top, and the lower you are, the closer you are to the people at the very bottom. Where would you place yourself on this ladder? Please, place an “X” on the rung where you think you stand at this time in your life, relative to other people in the United States.’

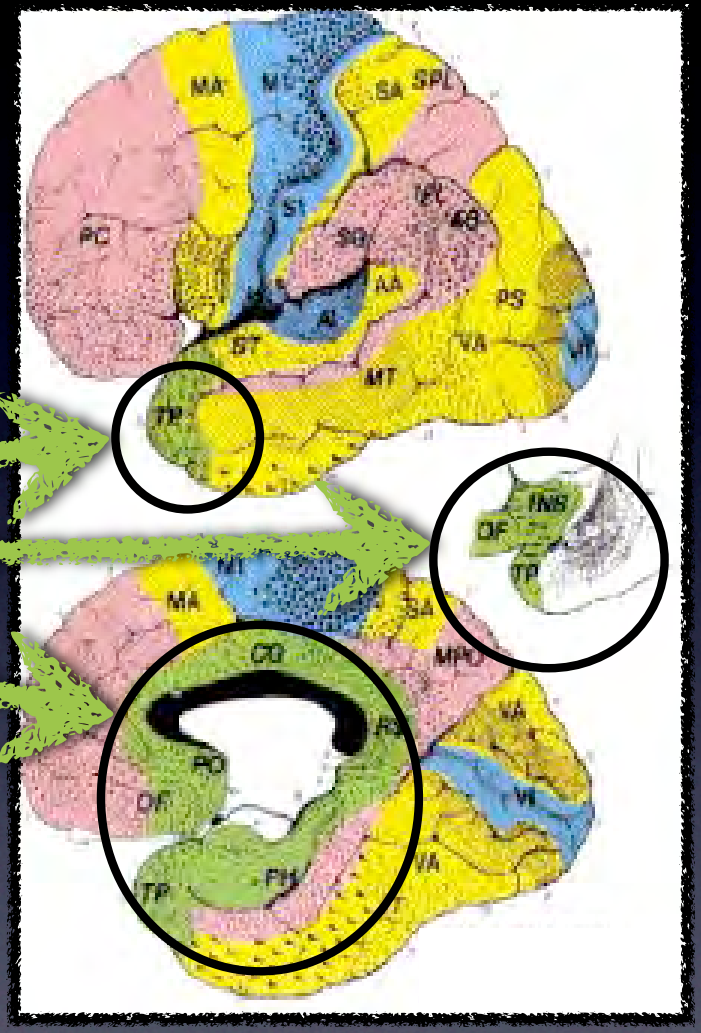
[1]Adler et al (2000) Health Psychol 19: 586-92

http://www.macses.ucsf.edu/

# A focus on paralimbic brain systems

- Dual role in processing emotional information and regulating peripheral physiology[1-5]

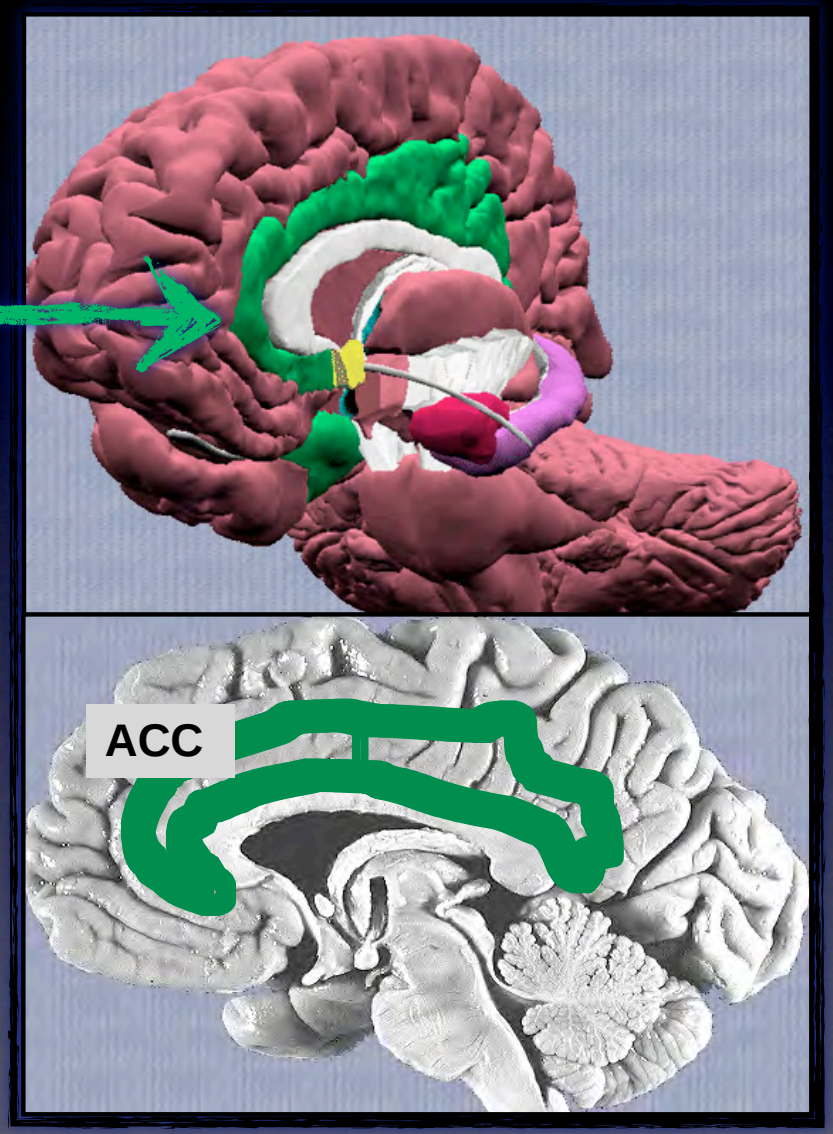
- Key regions
  - Amygdala
  - Cingulate
  - Medial/orbitofrontal cortex
  - Insula




[1]Berntson et al (1998) Beh Brain Res 94: 225-48
[2]Critchley (2005) J Comp Neurol 493: 154-66
[3]Lovallo (2005) Int J Psychophysiol 58: 119-32
[4]Soufer (2004) Circulation 110: 1710-3
[5]Thayer, Lane (2007) Biol Psychol 74: 224-42
*Brodmann (1909) figure from Mesulam (2000)

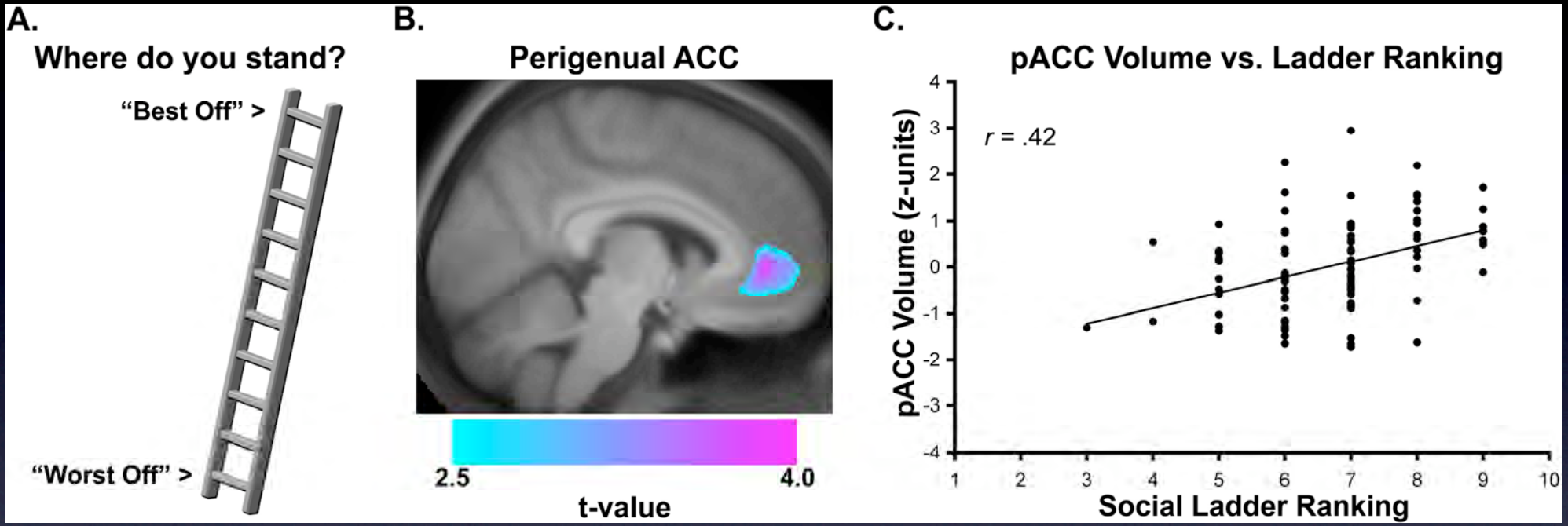
# Role of cingulate in stress reactivity[1-4]

- Part of ‘limbic lobe’ forms a belt around corpus callosum
- ACC implicated in emotion processing & autonomic-neuroendocrine regulation
- Densely networked w/ amygdala
- Morphological changes associated with chronic stress in animal models

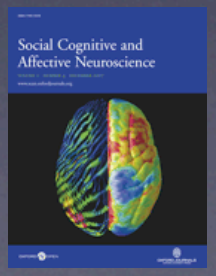



[1]Bush et al (2000) Trends Cogn Sci 4: 215-22
[2]Critchley (2005) J Comp Neurol 493: 154-66
[3]Lane (2008) Psychosomatic Med 70: 214-31
[4]Radley (2005) Ageing Res Rev 4: 271-87
*Images from www9.biostr.washington.edu/da.html

# Covariation between subjective SES and ACC volume



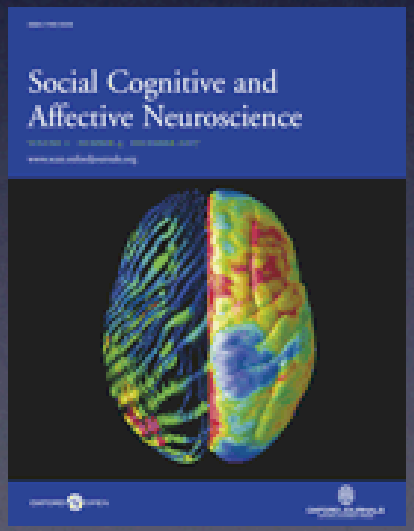

- **Persisted after control for age, sex, total grey matter, depressive symptoms, pessimism, perceived stress, hostile affect, negative affect, hostile attributions, individual SES (income, education), & community SES (census tract), $\Delta R^2$=0.13, F(1, 87)=14.4, p<0.001.**




Gianaros, Horenstein, Cohen, Matthews, Brown, Flory, Critchley, Manuck, Hariri (2007) Perigenual anterior cingulate morphology covaries with perceived social standing. Soc Cogn Affect Neurosci 2: 161-73

# Question:

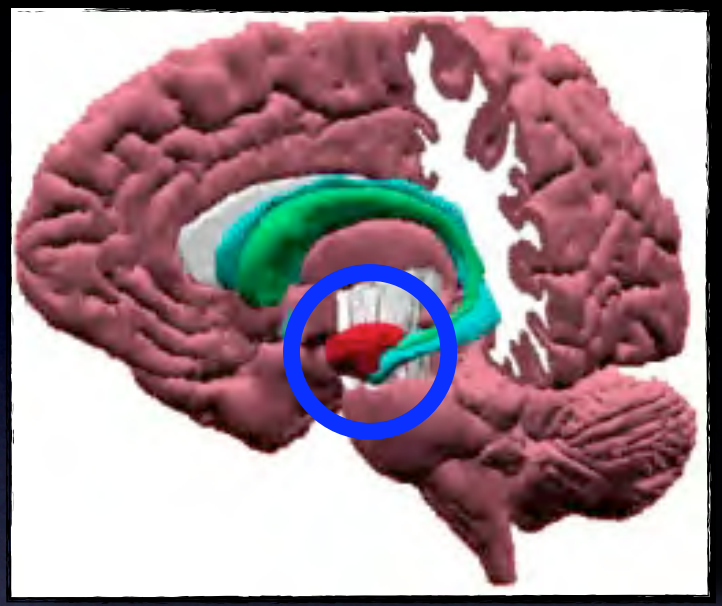
Is subjective childhood SES associated with amygdala reactivity to threatening or ambiguous emotional facial expressions?




Gianaros, Horenstein, Hariri, Manuck, Matthews, Cohen (2008) Potential neural embedding of parental social standing. Soc Cogn Affect Neurosci 3: 91-6.

# Rationale for question

- Lower childhood SES may increase sensitivity to social threats[1-3]
- Increased threat sensitivity may relate to stress responses that raise risk for ill health[4-5]
- If lower childhood SES increases sensitivity to threats, then lower childhood SES may predict increased amygdala reactivity to threatening social stimuli
- Amygdala expresses developmental plasticity, is sensitive to emotionally salient information, & regulates stress reactivity[6-8]



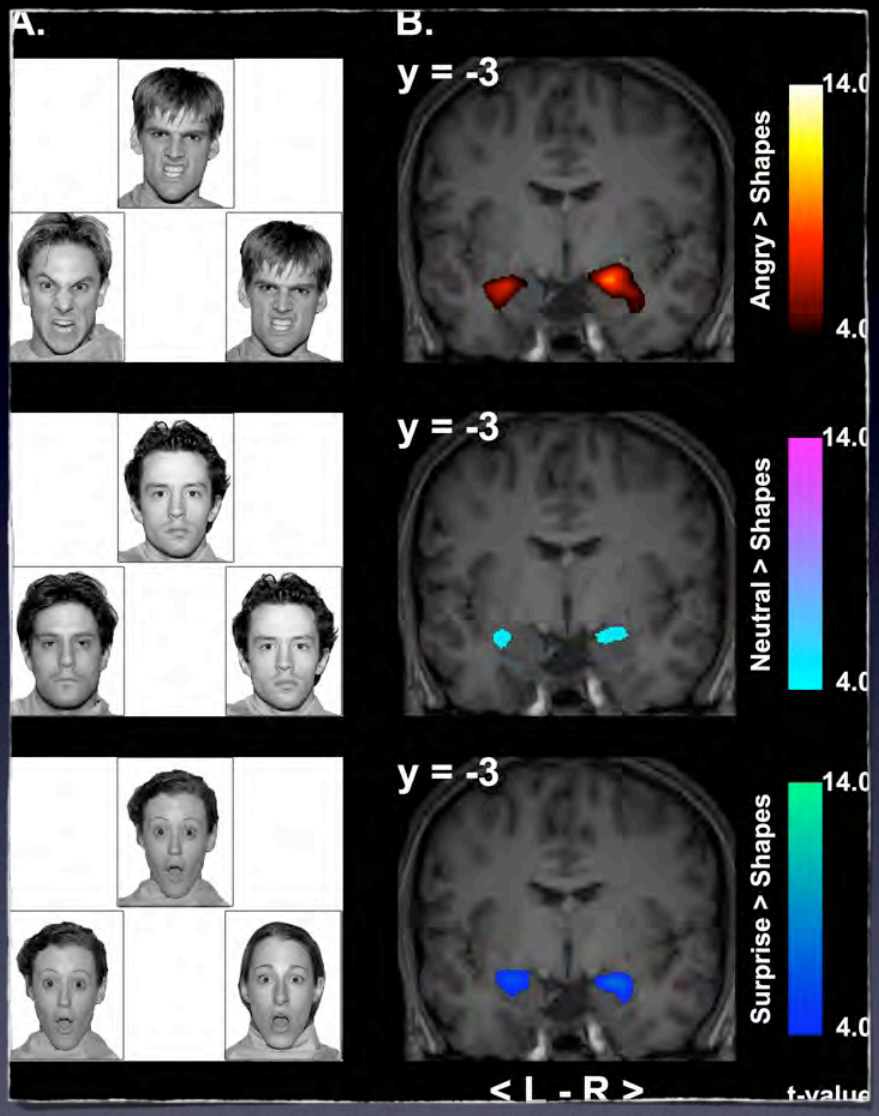

[1]Chen, Matthews (2001) Ann Behav Med 23: 101-11
[2]Chen et al (2002) Psychol Bull 128: 295-329
[3]Taylor et al (2004) J Pers 72: 1376-93
[4]Hertzman (1999) Ann NY Acad Sci 896: 85-95
[5]McEwen, Gianaros (2010) Ann NY Acad Sci
[6]McEwen (2007) Physiol Rev 87: 873-904
[7]Pollak (2005) Dev Psychopathol 17: 735-52
[8]Whalen (1998) Curr Dir Psychol Sci 7: 177-88

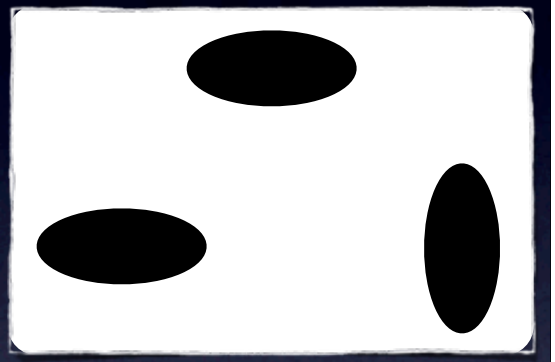
# Protocol (n = 33 healthy undergraduates)

Angry

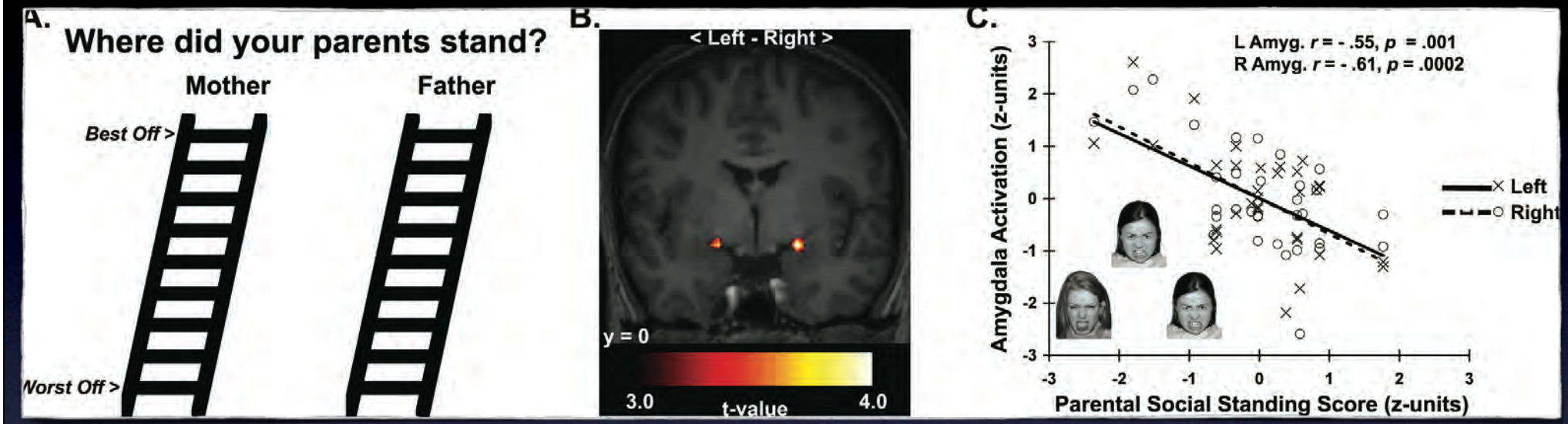
Neutral

Surprised

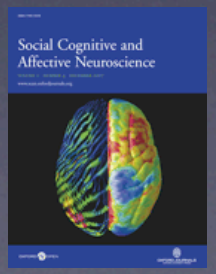


# Lower childhood sSES predicted greater amygdala reactivity to threatening faces*




***Persisted after control for sex, ethnicity, self-mastery, optimism, neuroticism, extraversion, agreeableness, depressive symptoms, parental education, & participants' perceptions of their own sSES (L amyg $\Delta R^2$=0.204, $F$[1,21]=10.9, $p$=0.003; R amyg $\Delta R^2$=0.152, $F$[1,21]=7.4, $p$=0.01.**




Gianaros, Horenstein, Hariri, Manuck, Matthews, Cohen (2008) Potential neural embedding of parental social standing. Soc Cogn Affect Neurosci 3: 91-6.

# New questions

- Are there prospective associations between neural reactivity to behaviorally salient stimuli and preclinical disease markers?
- Do individual differences in stress reactions orchestrated by the brain partly link SES and CHD risk?

# *Thank you!*

Israel Christie
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Steve Manuck
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Ike Onyewuenyi
Lei Sheu
Sara Snyder
Kim Sutton-Tyrrell
Natasha Tokowicz



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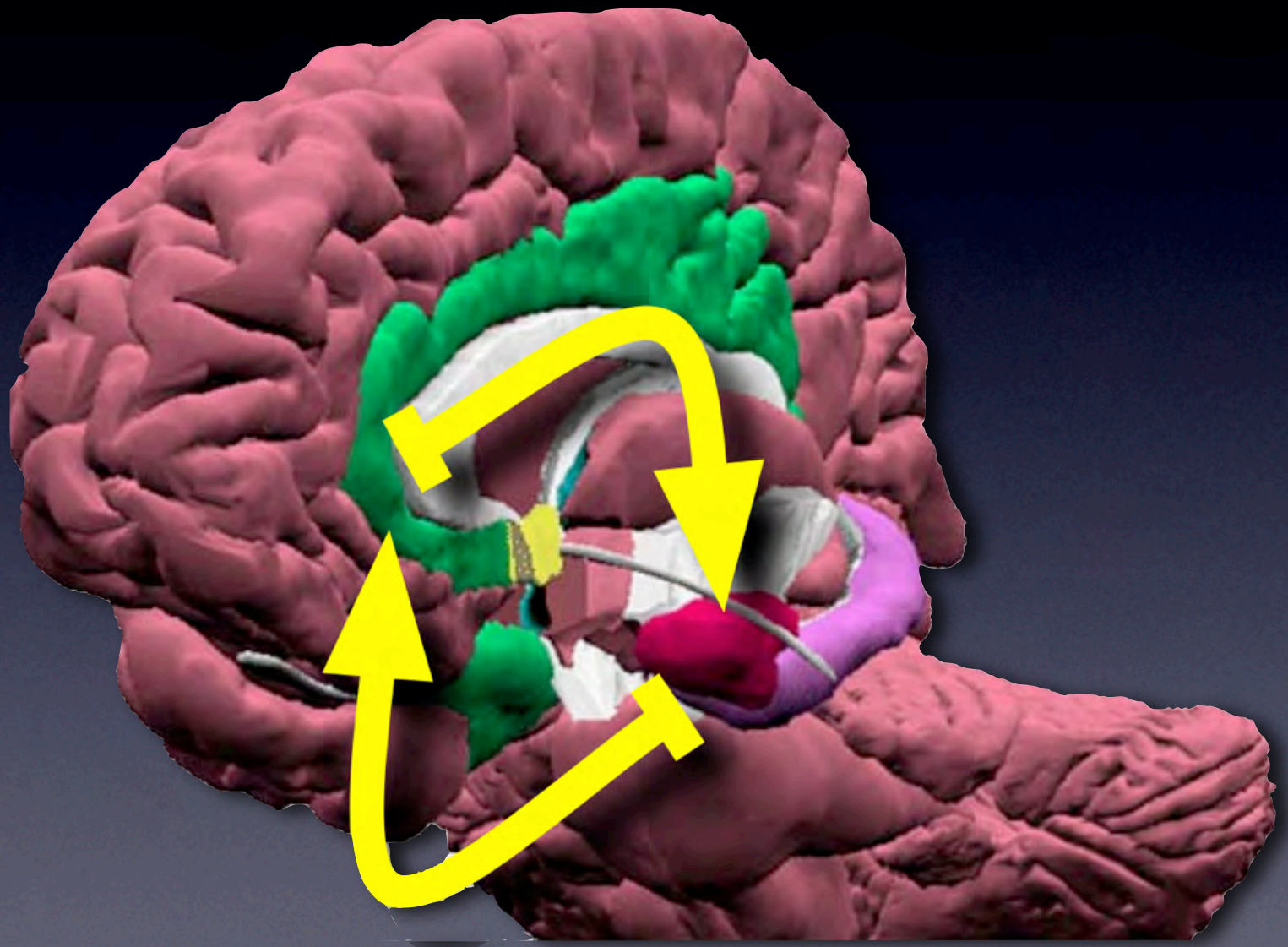
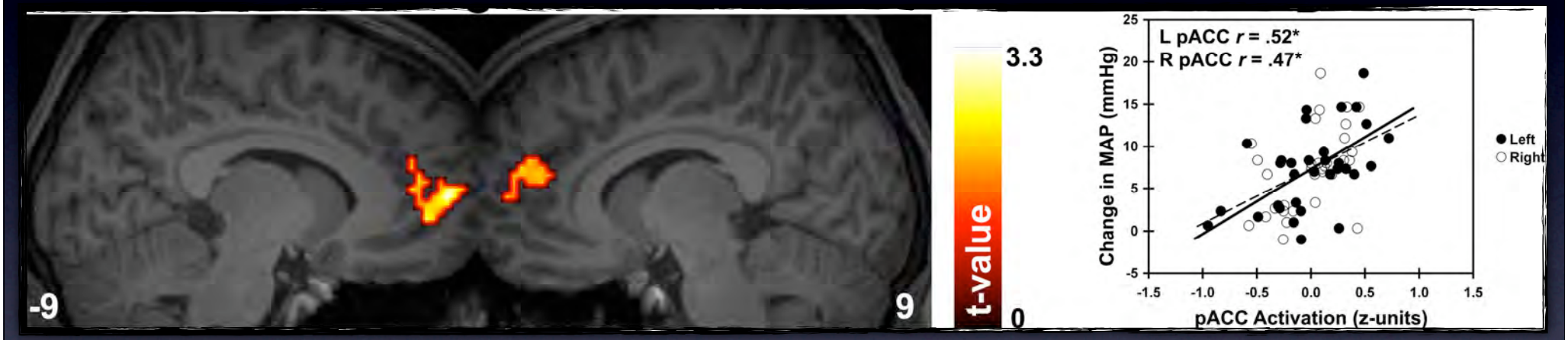
R24-HL076852
R01-HL089850
American Reinvestment and Recovery Act
Pennsylvania Department of Health

Main lesson learned: cingulate - amygdala functionality and interactions relate to stressor-evoked cardiovascular reactivity & CHD risk



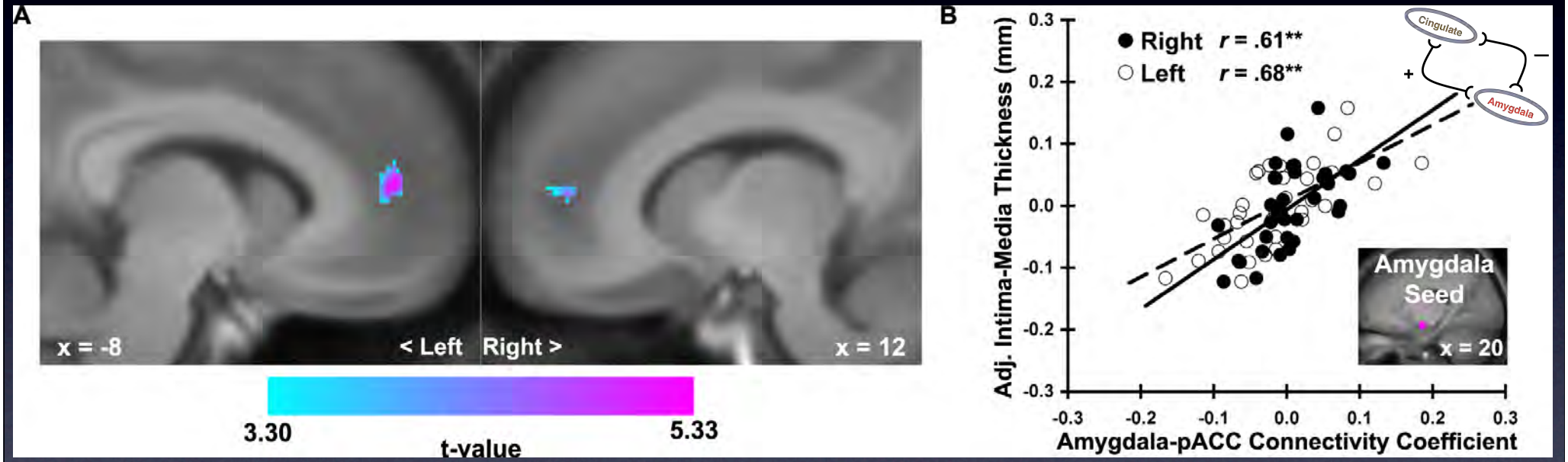
# Cingulate activation and BP reactivity




N = 32 healthy undergraduates (20 women, 18 - 21 yrs)

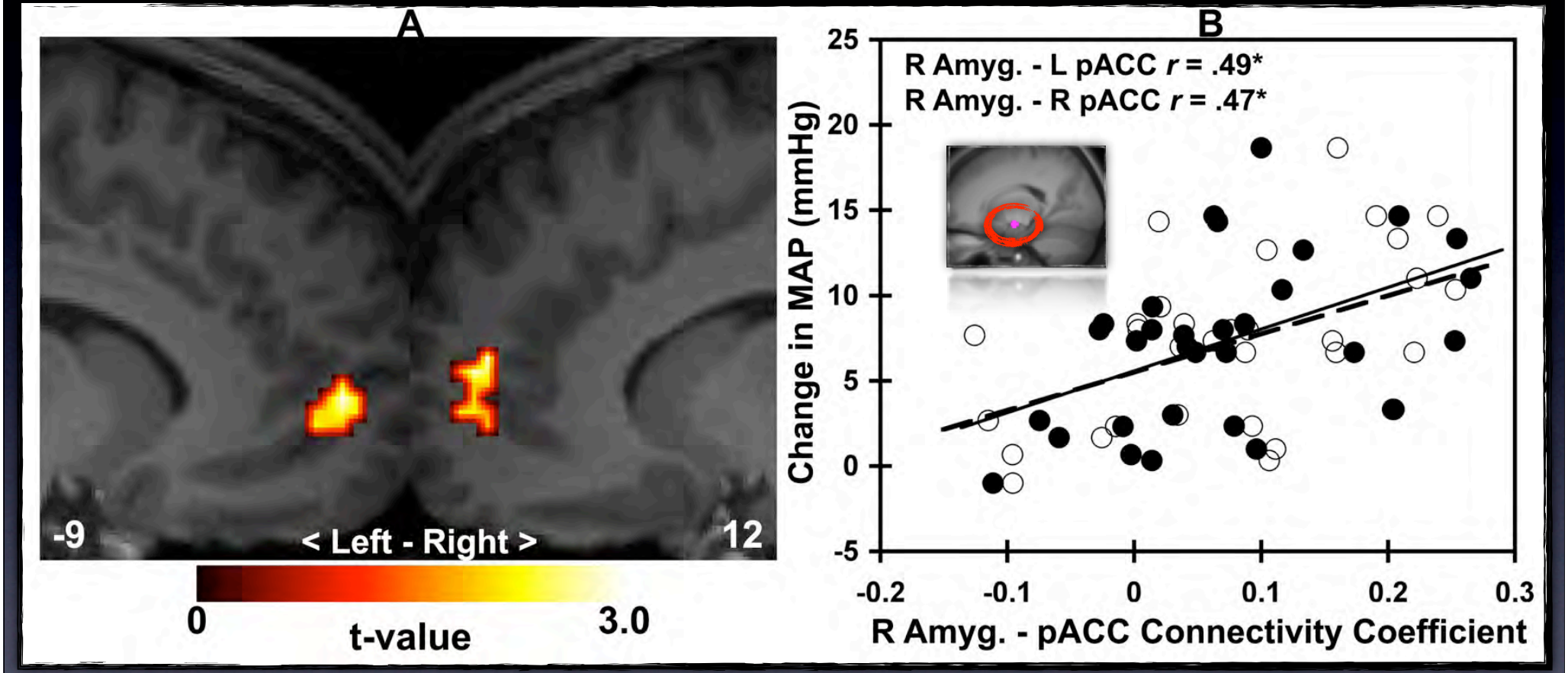
Gianaros, Sheu, Matthews, Jennings, Manuck, Hariri (2008) J Neurosci 28: 990-99

# Covariation between IMT and amygdala-pACC connectivity




IMT adjusted for age, resting SBP, sex, & income. **ps < 0.005.

# Positive covariation: BP reactivity - Amygdala-pACC functional connectivity




N = 32 healthy undergraduates (20 women, 18 -21 yrs)

Gianaros, Sheu, Matthews, Jennings, Manuck, Hariri (2008) J Neurosci 28: 990-99