KING'S College LONDON Institute of Psychiatry at the Maudsley

Advances in neuroimaging of anxiety disorders

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To what extent do the different anxiety disorders fit to the general model of anxiety?

- **PTSD**
- **Social phobia**
- **OCD**
- **Panic disorder**
- **GAD**

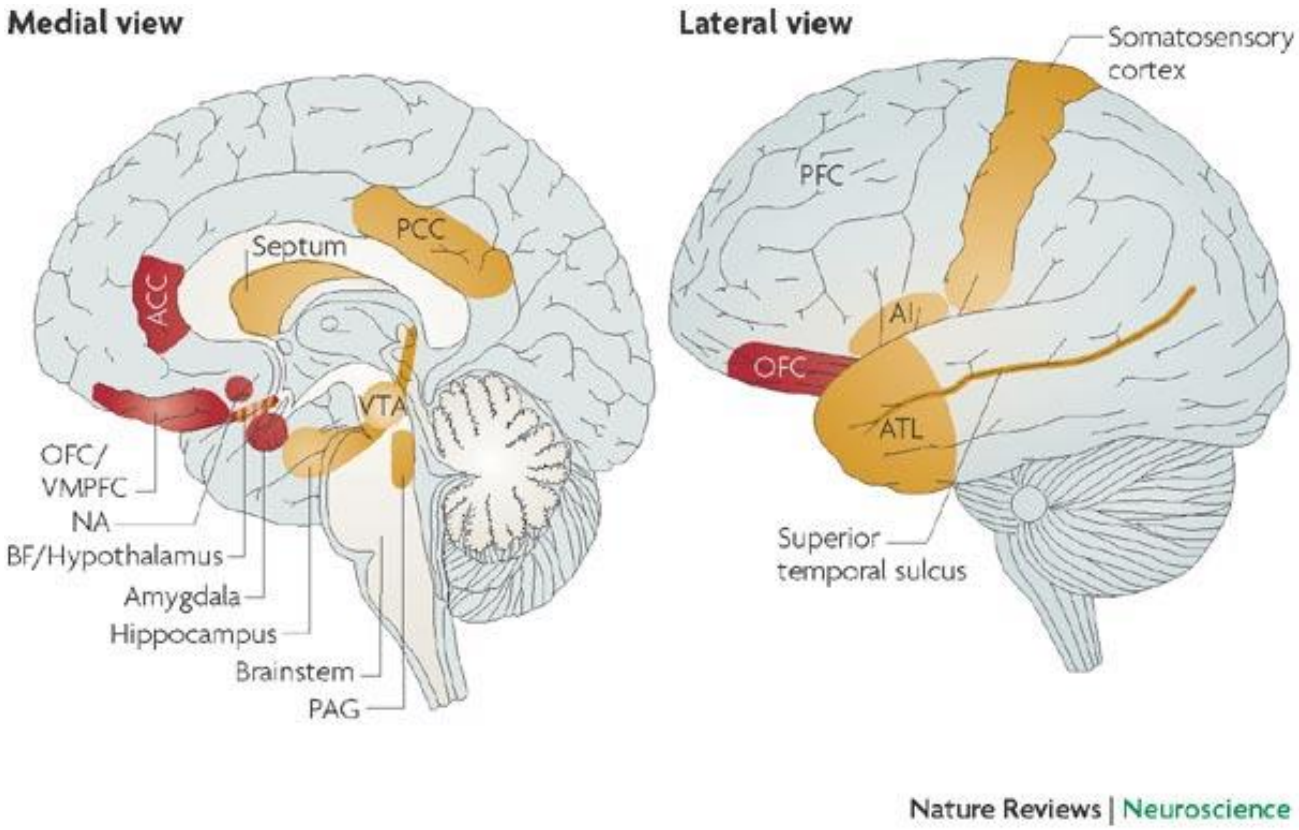
Point of view

- Fear and avoidance are common to many anxiety disorders
- They are also seen in healthy subjects in response to conditioned fear cues
- Anxiety may have evolved to protect us from a broad range of threats (Marks & Nesse, 1994)
  - One would expect common neural substrates to all anxiety disorders and normal anxiety
- It is also possible that specific kinds of anxiety evolved to protect us from specific kinds of threats (Marks & Nesse, 1994)
  - One would expect some specific neural substrates for different types of anxiety

Functional neuroimaging paradigms in the study of anxiety

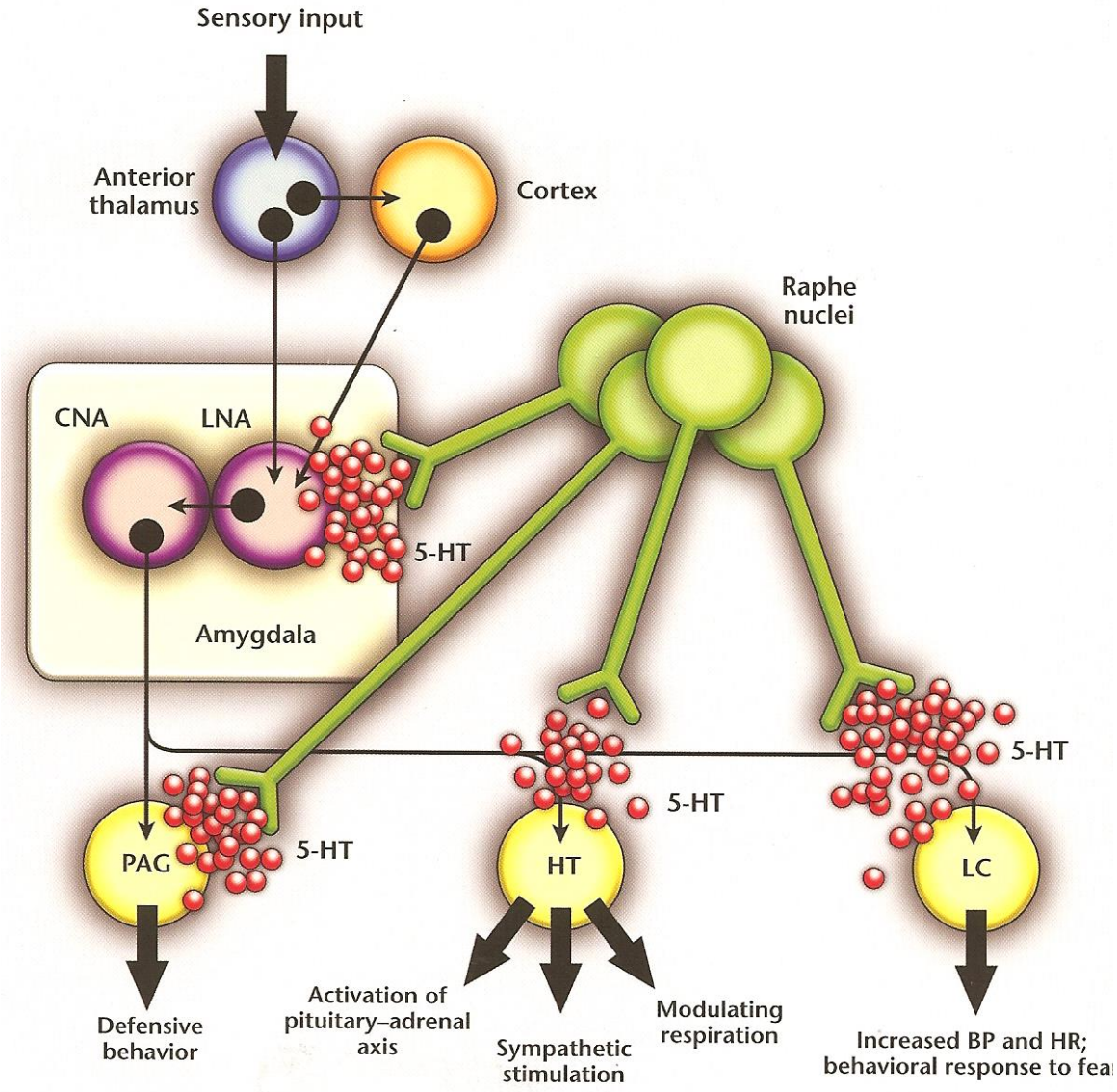
Study design	Technique(s)	Description
Resting state	PET, SPET	Patients are instructed to lie down in the scanner with their eyes closed. No action is required. The results are compared with those of the healthy group
Symptom provocation	PET, SPET, fMRI	Symptom-evoking material is presented either physically or in imagination. Data analysis involves a within-subjects comparison with an emotionally neutral condition
Cognitive challenge	PET, SPET, fMRI	Subjects perform neuropsychological tests (e.g. attention, memory) in the scanner. Patients are compared with controls
Pre-/post-treatment	PET, SPET, fMRI	One of the above paradigms is performed on the same subjects before and after treatment
Outcome predictors	PET, SPET, fMRI	Patterns of neural activity at rest or during symptom provocation are correlated with percentage improvement on clinical scales

Mataix-Cols and Phillips, 2007, Psychiatry



Pessoa, 2008 Nat Rev Neurosci

Fear network and the role of serotonin



From Atlas of Psychiatric Pharmacotherapy. Shilon et al, eds 2006

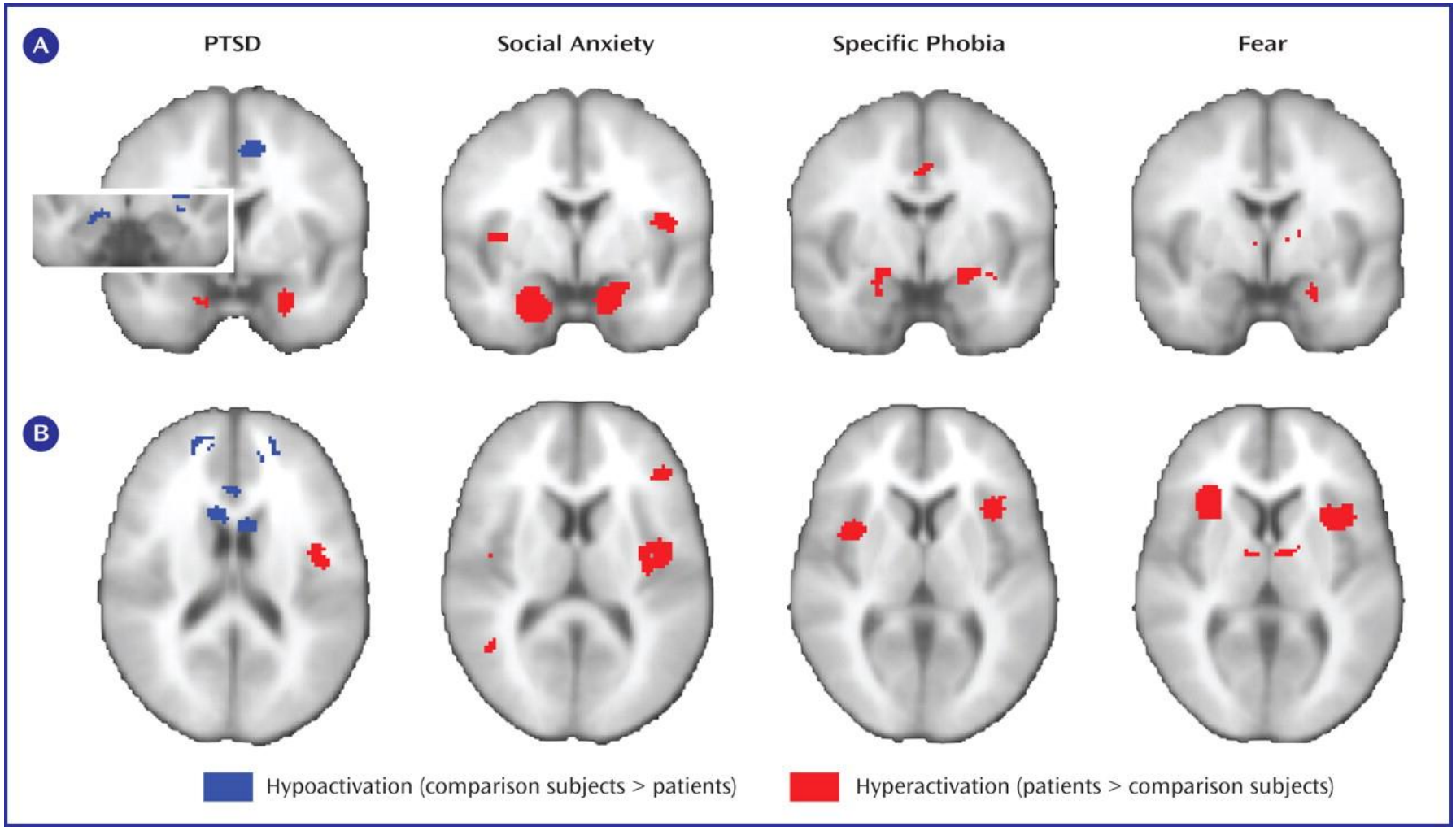
Hardware / neuropathology

- Genetics: polymorphism for oligodendrocyte lineage transcription factor is associated with **OCD** (*Stewart et al., Arch Gen Psychiatry.* 2007;64:209-214.)

- Small lesions in white matter and dilation of lateral ventricules – in 40 % of **panic disorder**; correlate with severity (Ontiveros et al., 1989), structural MRI

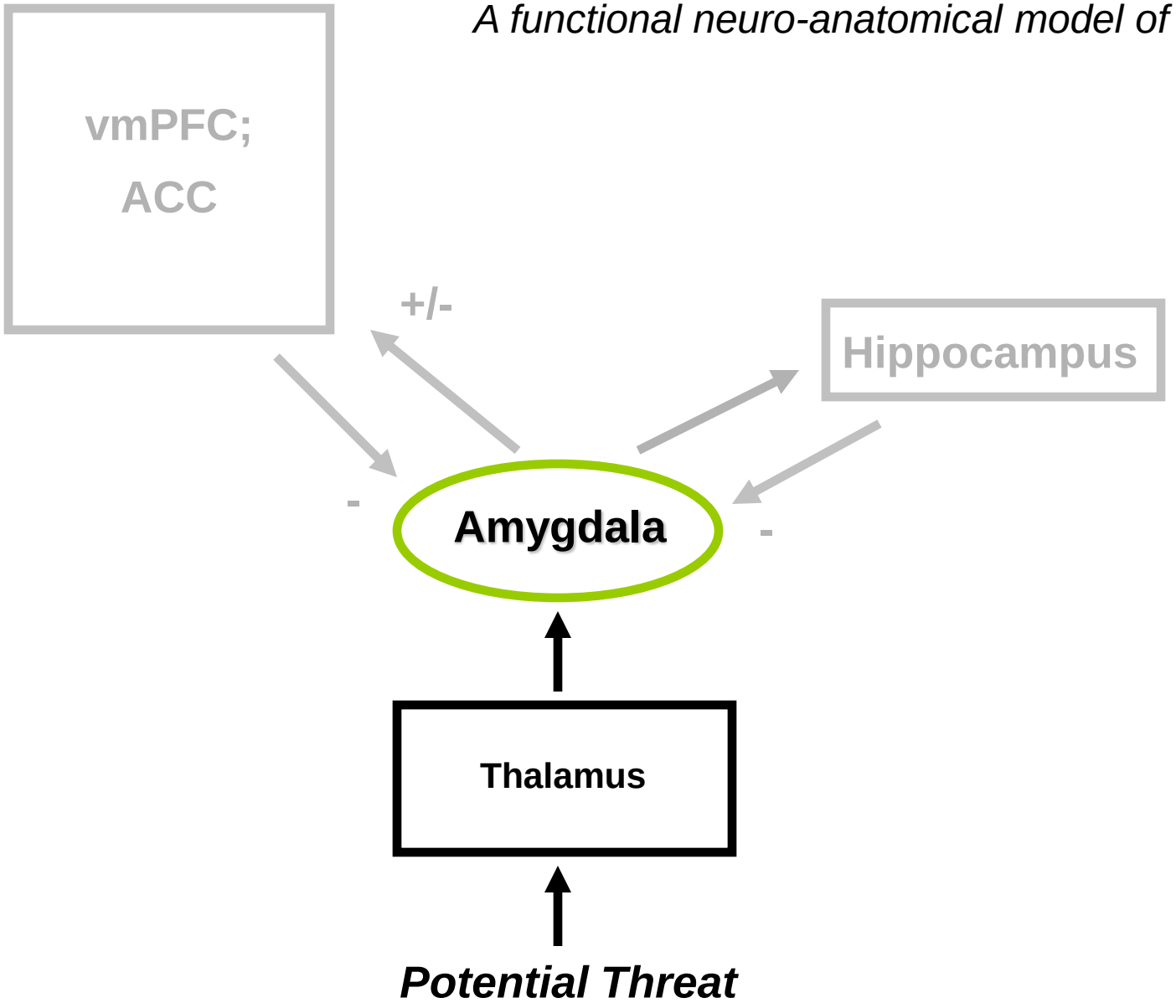
- Reduced levels of neuronal N-acetylaspartate in the dorsal anterior cingulate region in **OCD**, which was negatively correlated with their blood oxygen level-dependent activation of the region (Yucel et al., 2007)

Meta-analysis across anxiety disorders



Etkin & Wager, 2007 Am J Psychiatry

A functional neuro-anatomical model of PTSD



After Rauch et al 1998

Symptom provocation studies of PTSD

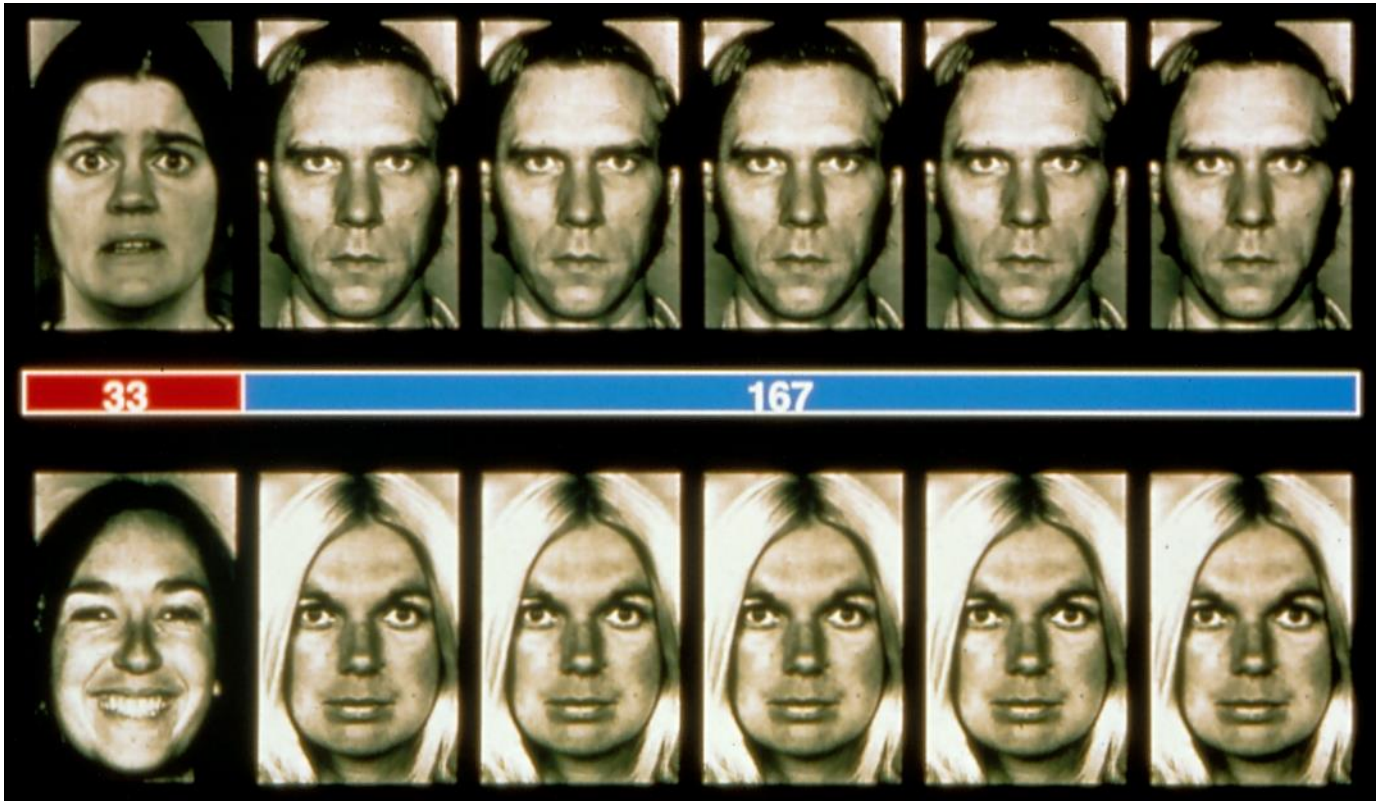
- Reminders of trauma: PTSD vs non-PTSD
  - exaggerated amygdala activation (Shin et al 1997, 2004; Liberzon et al 1999; Hendler et al 2003)
  - attenuated vmPFC / ACC activation (Bremner et al 1999a,1999b; Shin et al 1999, 2004; Lanius et al 2001; Lindauer et al 2004)

Masked-Faces Paradigm

FEAR
Target

NEUTRAL
Mask

msecs

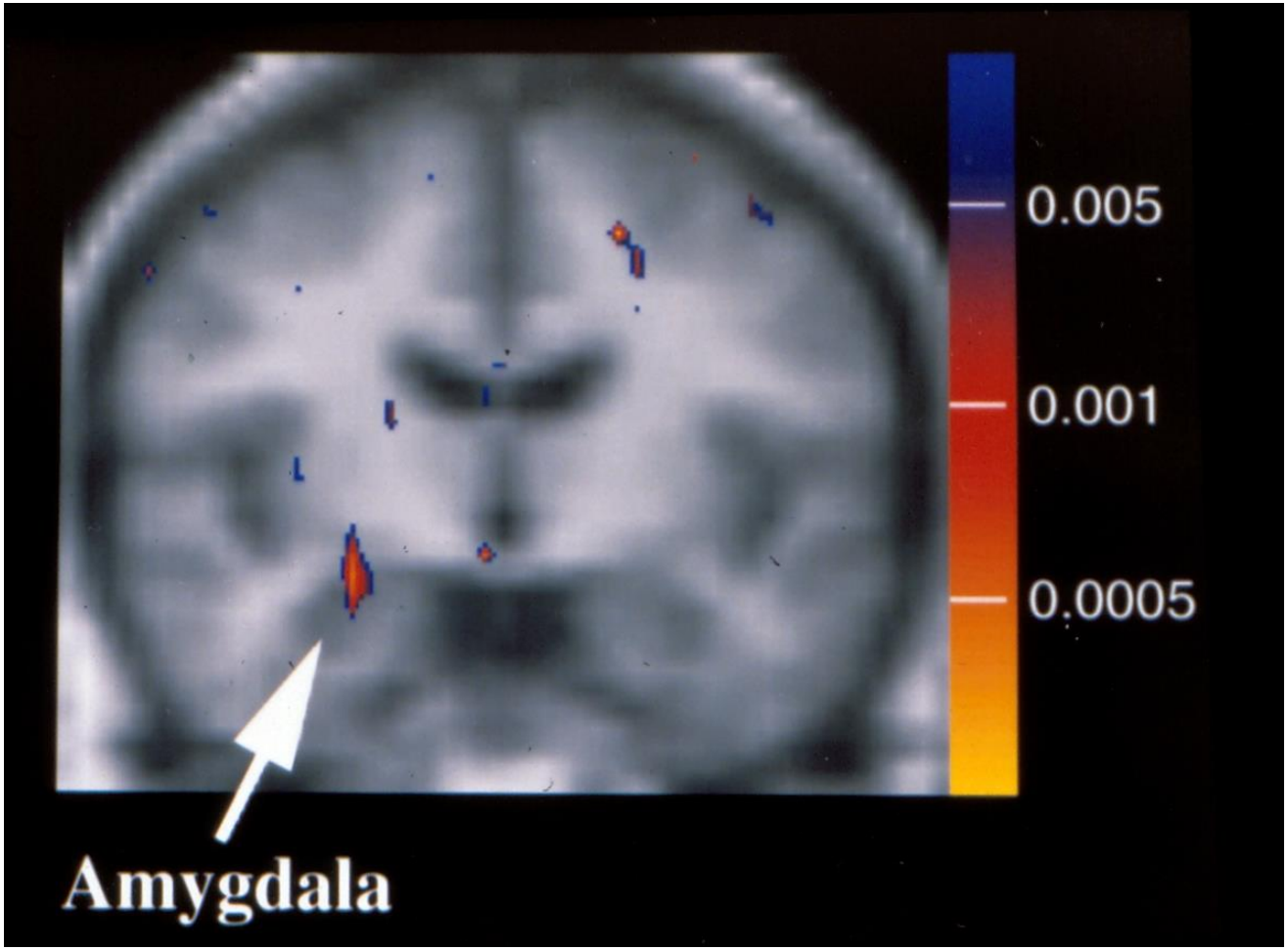


Target
HAPPY

Mask
NEUTRAL

Masked-Faces Results

PTSD > controls



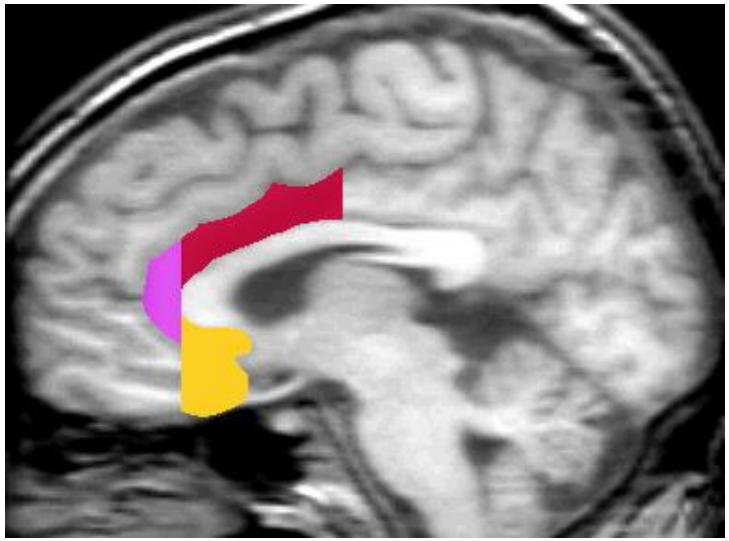
Rauch et al. *Biol Psychiatry.* 2000;47:769.

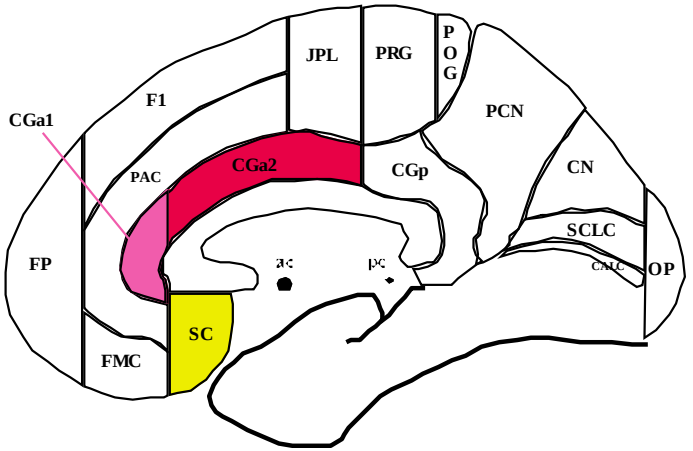
Parcellation of Anterior Cingulate Cortex in PTSD

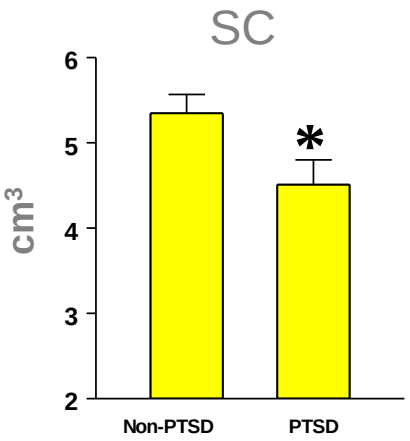
- 18 Female Combat Nurses from Vietnam War (9 PTSD; 9 Non-PTSD)
- PTSD vs. Non-PTSD
  - Reduced volume in rostral ACC
  - Reduced volume in subcallosal cortex
  - No difference in dorsal ACC

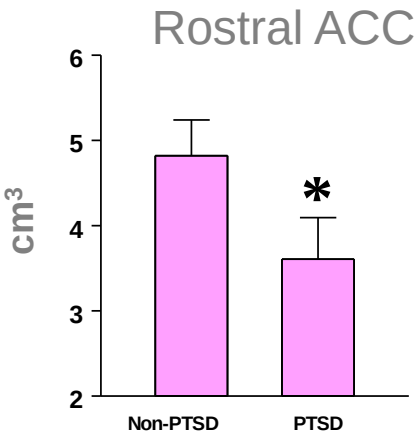
Rauch et al, *Neuroreport*, 2003

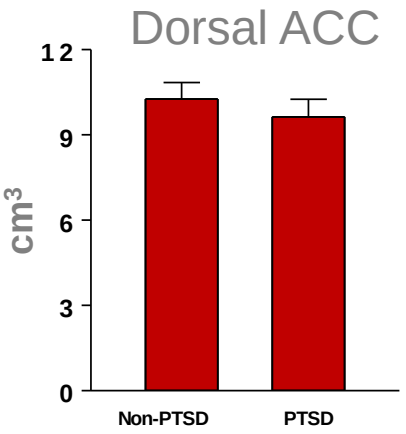
Reduced Cortical Volumes in Combat Nurses with PTSD





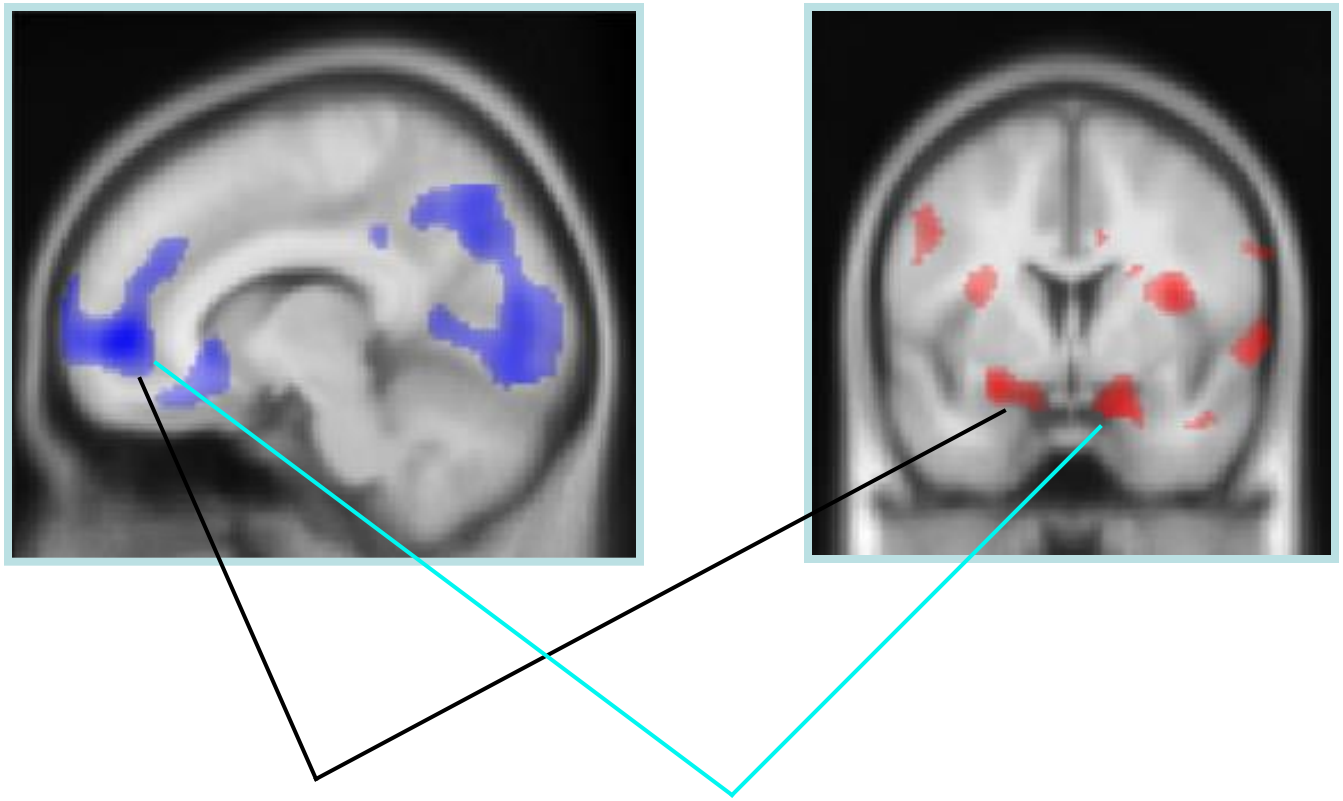






Rauch et al, *Neuroreport*, 2003

Functional Connectivity: Inverse Correlation (PTSD Group)

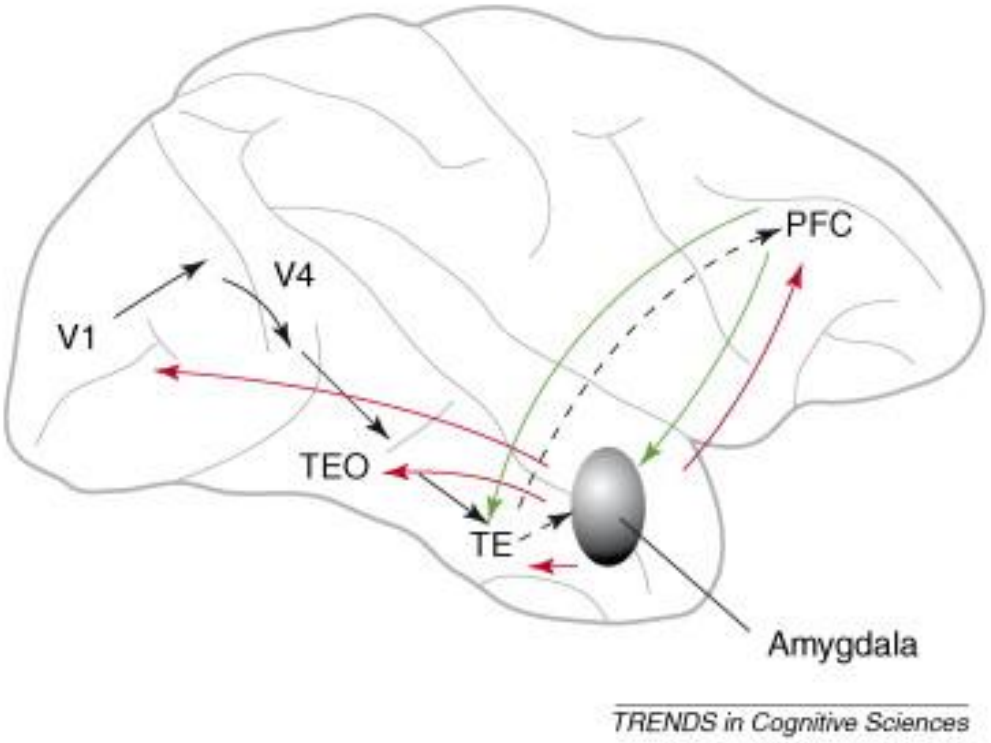


Shin et al 2004

r = -.69

r = -.64

Amygdala-PFC connections



Bishop, 2007 TICS

Neuroimaging Findings in Panic Disorder

- **Structural MRI** (Vythilingam ‘00; Massana ‘03)
  - Extra-hippocampal temporal cortical abnormalities
- **Neutral State** (Reiman ‘86; Nordahl ‘90)
  - rightward shift in hippocampal activity
- **Pre/Post-Treatment** (Nordahl ‘98)
  - decreases in posterior OFC with imipramine tx
- **Symptom Provocation**
  (Woods ‘88; Stewart ‘88; Reiman ’89 Bystritsky ’01)
  - increases in anterior paralimbic areas & hippocampus

Neuroimaging Findings in GAD

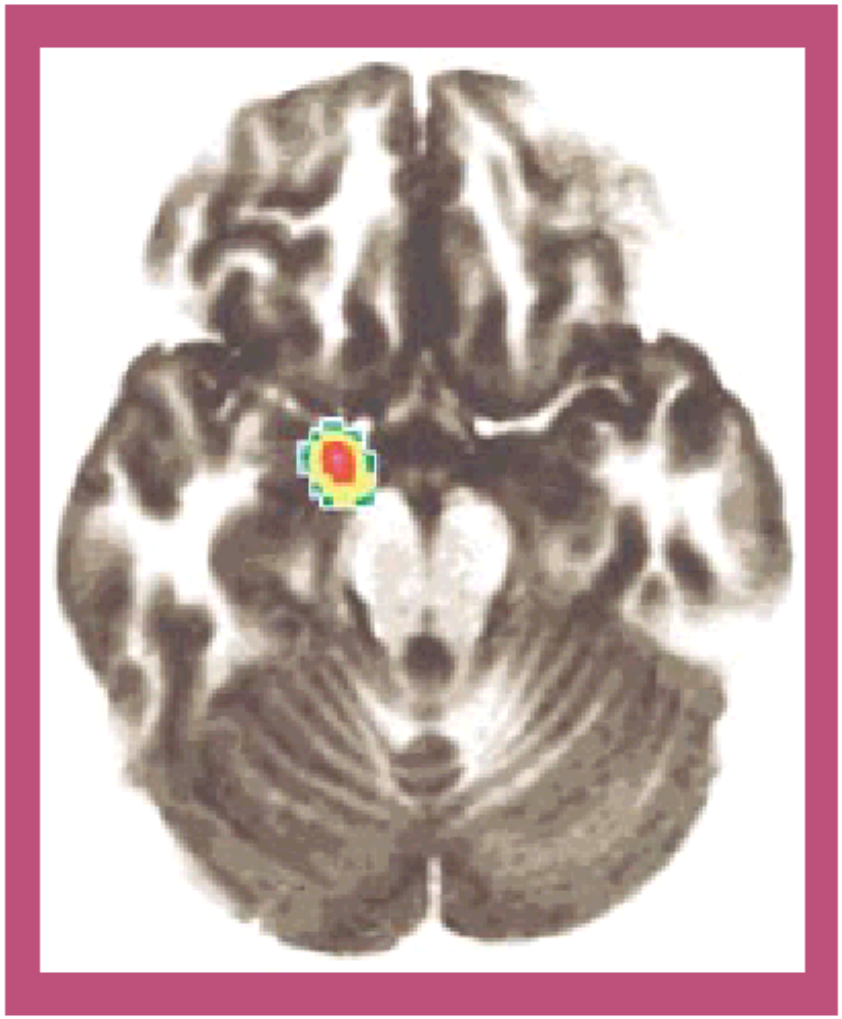
- **Structural MRI**
  - Increased amygdala volume (DeBellis et al 2000)
  - Increased GM and WM volume in superior temporal gyrus (DeBellis et al 2002)
- **fMRI**
  - Increased activation to emotional faces in amygdala, ventral prefrontal and anterior cingulate (McClure et al 2007)

Neuroimaging Findings in Social Phobia

- **Symptom provocation** (public speaking): increase in amygdala (Tillfors ’01; Lorberbaum ‘04)
- **Face paradigms** (fMRI): exaggerated increases in amygdala (Birbaumer ‘98; Schneider ‘99; Stein ’02; Straube ‘04)
- Subjects with **inhibited temperament** exhibit exaggerated amygdala responses to novel neutral faces (Schwartz ‘03); inhibited temperament appears to be a vulnerability factor for developing Social Phobia and Panic Disorder

Public vs. private speaking in Social Phobia

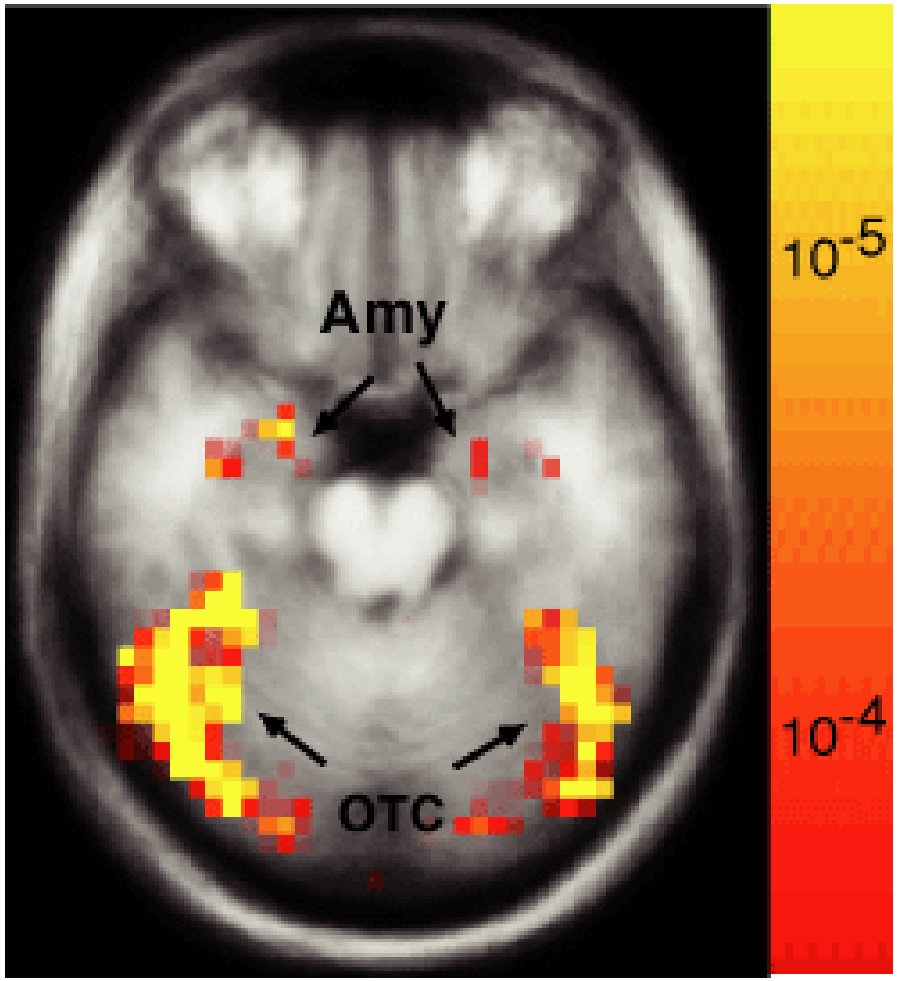
FIGURE 2. Composite PET Scan of Increased Normalized Relative Regional Cerebral Blood Flow (rCBF) in the Amygdaloid Complex During Public Versus Private Speaking for 18 Subjects With Social Phobia and Six Nonphobic Comparison Subjects[a]

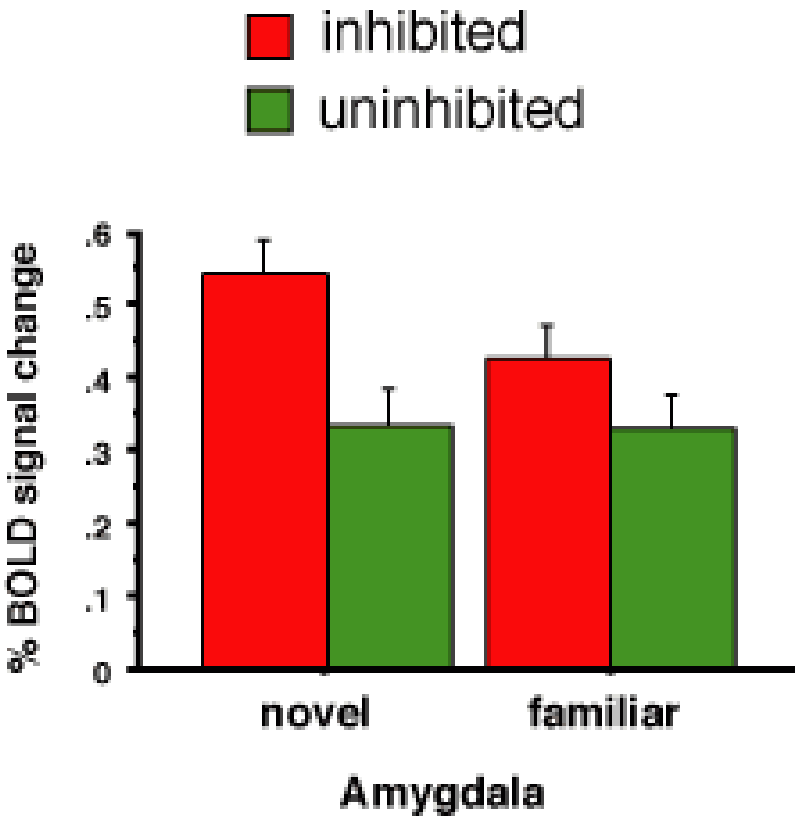


[a] Lighter colors signify greater differences. Scan is superimposed on a standard magnetic resonance reference image.

Tillfors et al 2001, Am J Psychiatry, 151:1220-1226

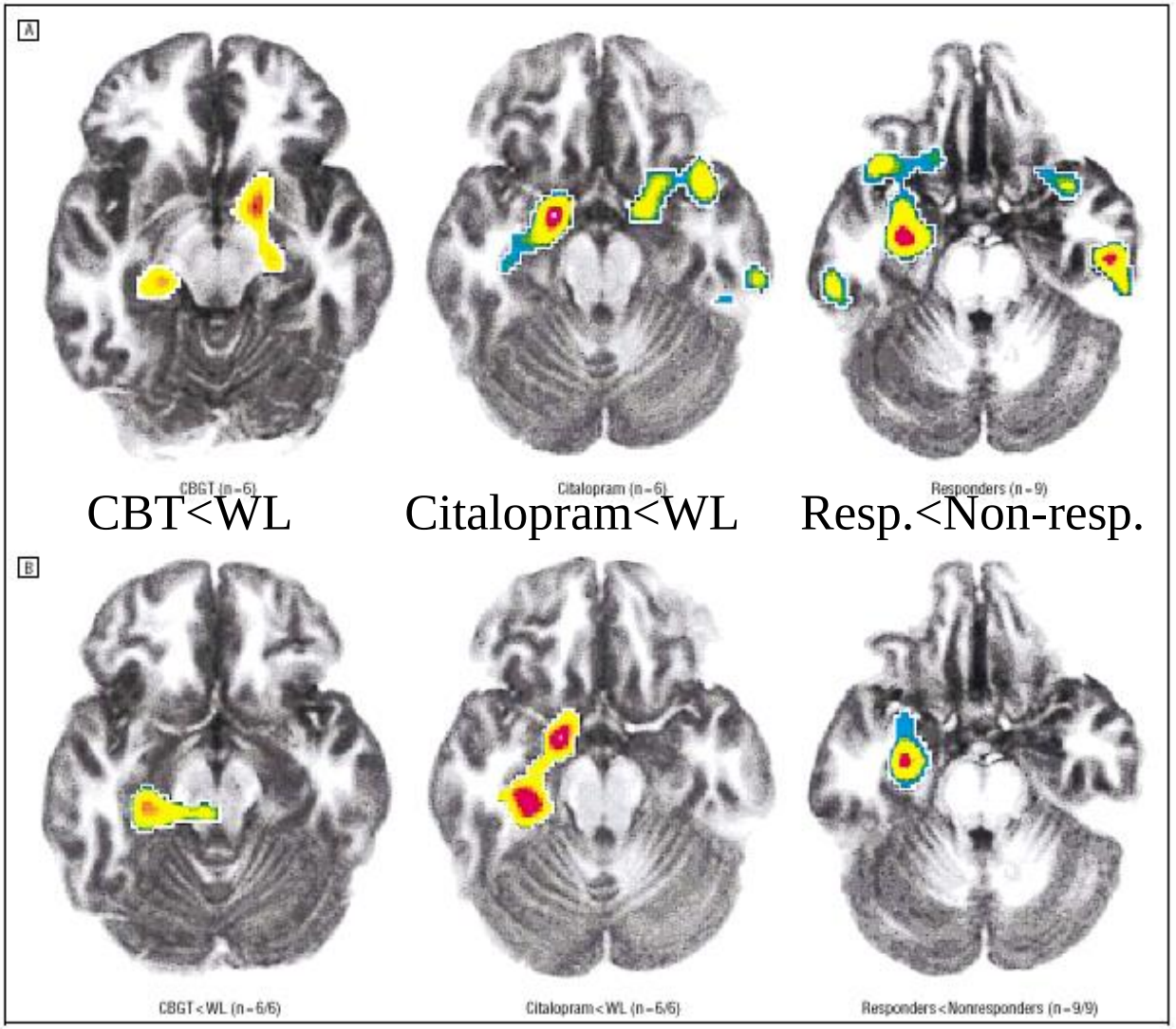
Greater Amygdala Responses to Novelty in Inhibited vs Uninhibited Temperament (vulnerability to social phobia)





Schwartz et al., Science, 2003

RCBF decreases: CBT Citalopram Responders



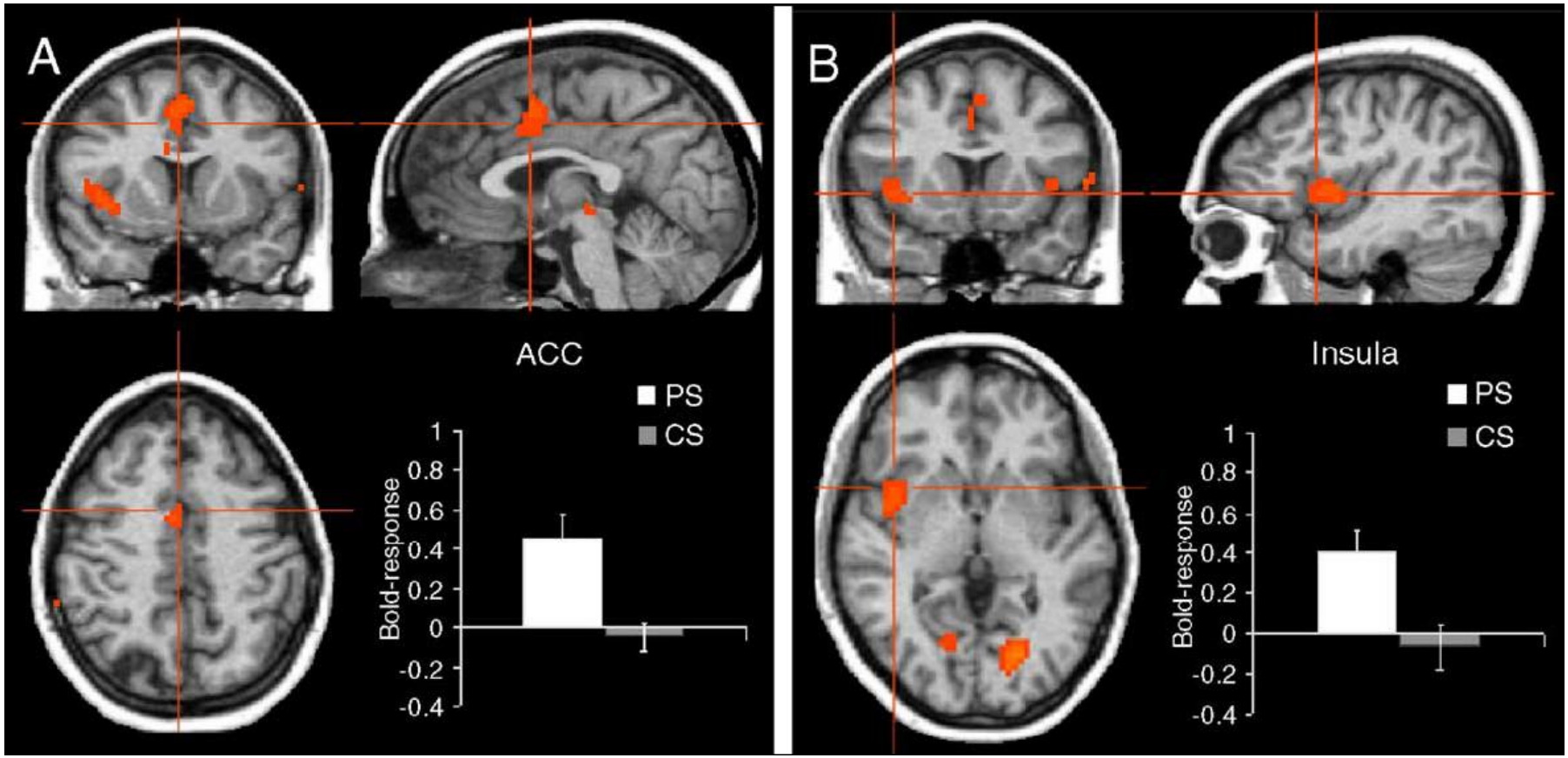
CBT<WL Citalopram<WL Resp.<Non-resp.

Figure 2. A, Transverse positron emission tomographic images, superimposed on a magnetic resonance reference image, showing significant decreases in the regional cerebral blood flow response to an anxiogenic public speaking task as a function of cognitive-behavioral group therapy (CBGT; left) or citalopram treatment (middle), and for responders regardless of treatment approach (right). Points of neural convergence were observed in the amygdala, hippocampus, and surrounding temporal cortical regions. B, Corresponding between-group differences in the amount of change in regional cerebral blood flow with treatment. Images show a greater reduction in the neural response to public speaking in CBGT relative to the waiting-list (WL) group (left), citalopram relative to the WL group (middle), and responders relative to nonresponders (right).

(Social phobia) Furmark et al (2002). Arch Gen Psychiatry, 59:425-433

CBT can change the brain!

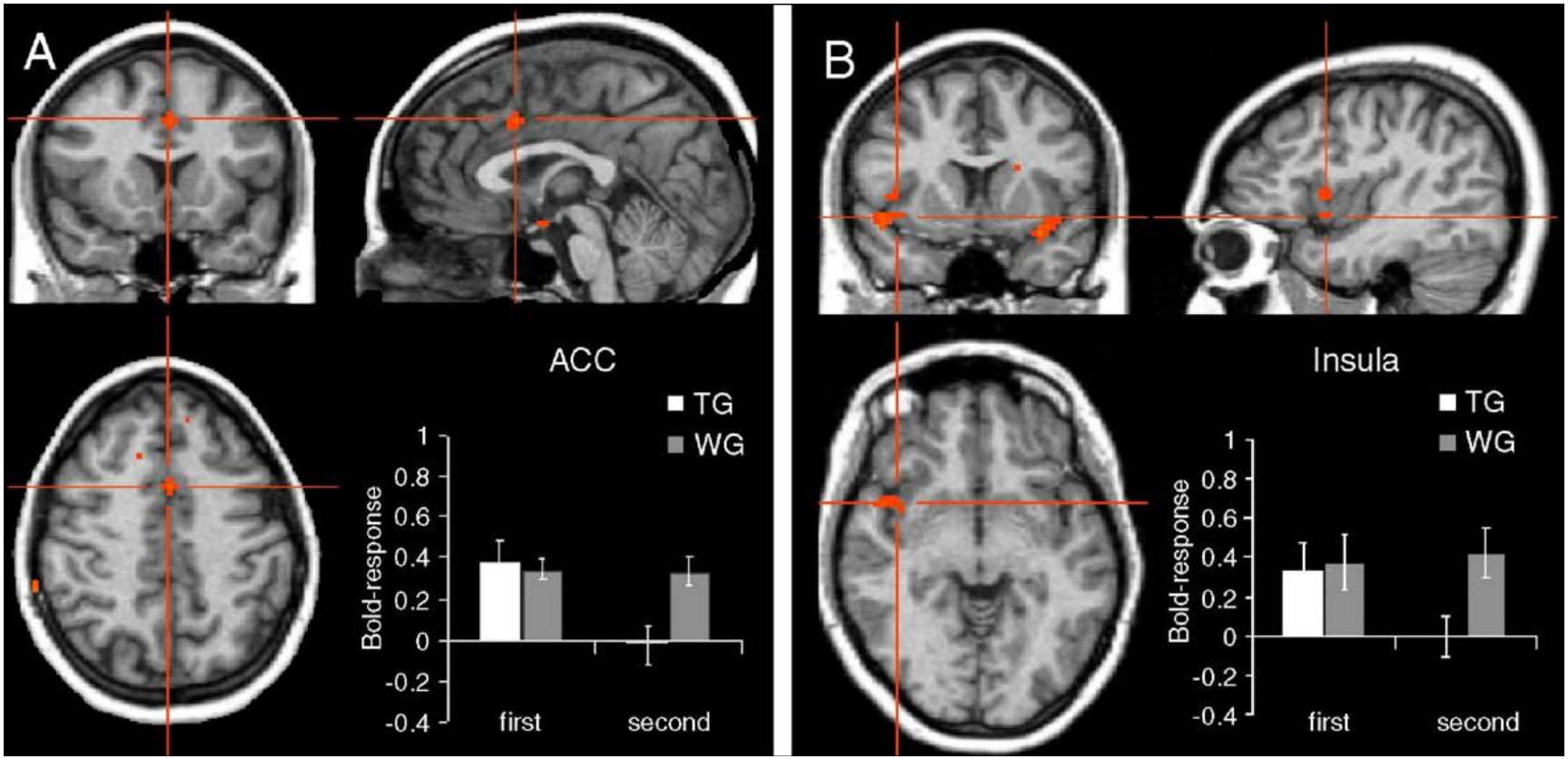
Spider vs neutral videos before treatment



Straube et al Neuroimage 2006

CBT can change the brain

Control > treated group after CBT



Straube et al Neuroimage 2006

But are all specific phobias the same?

- DSM-IV subtypes
  - Animal
  - Natural environment: storms, heights, water..
  - Situational: transport, tunnels, bridges, lifts..
  - Blood-injury: unique vasovagal response
    - Initial sympathetic response followed by parasympathetic response
    - Leads to fainting in 80% of cases
    - Highly familial

General conclusions

- Anxiety disorders are likely to share neural substrates dedicated to general threat detection and emotional arousal

- There may be some syndrome-specific neural substrates that may have evolved to deal with specific threats

- Current diagnostic boundaries do not reflect these neural correlates

    - Separate disorders may share same neural substrates

    - Heterogeneity within disorders

- Field is characterized by small sample sizes and lack of standardised paradigms