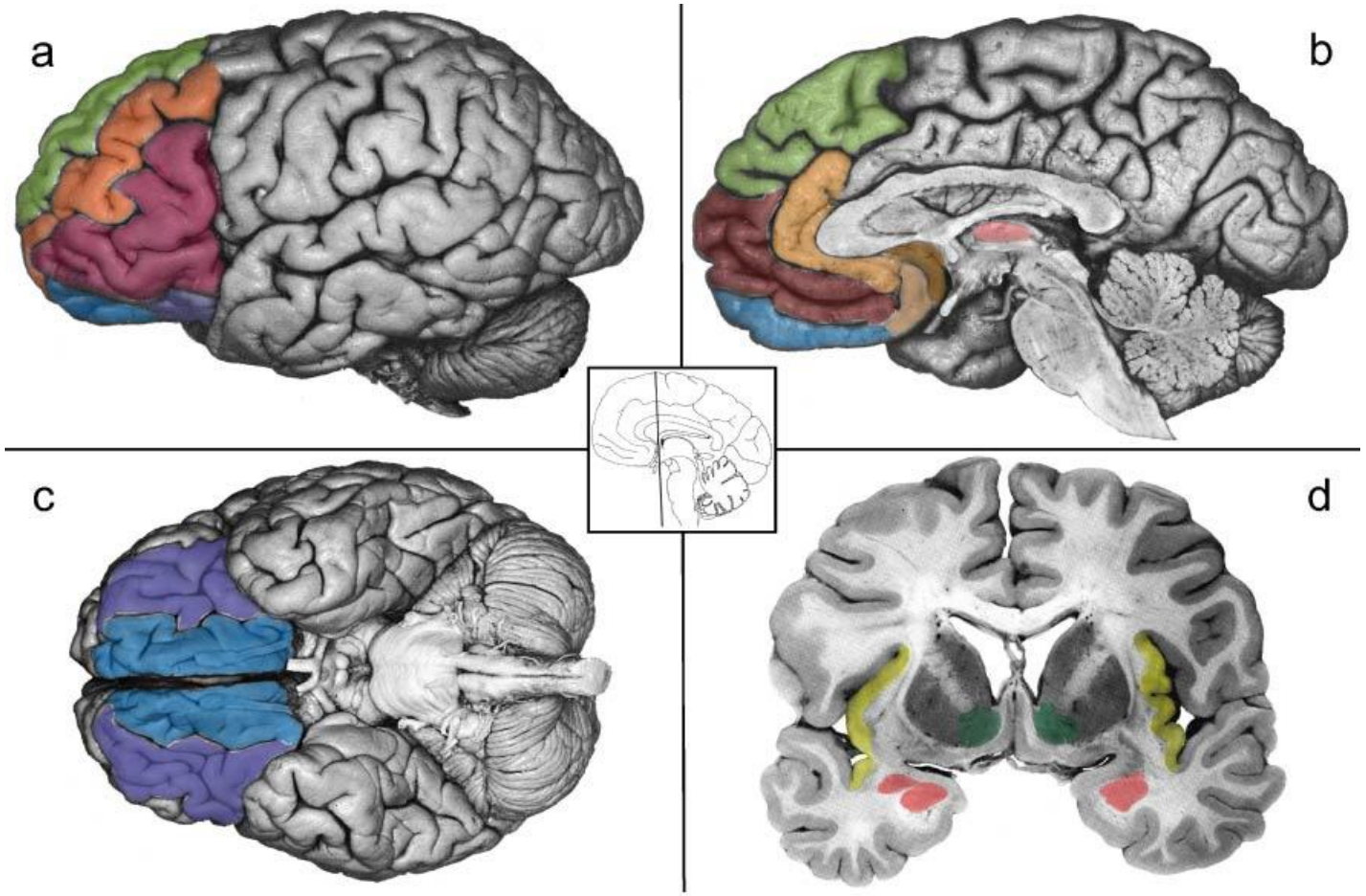
Major depressive disorder

Dr. Simon Surguladze PhD DSc

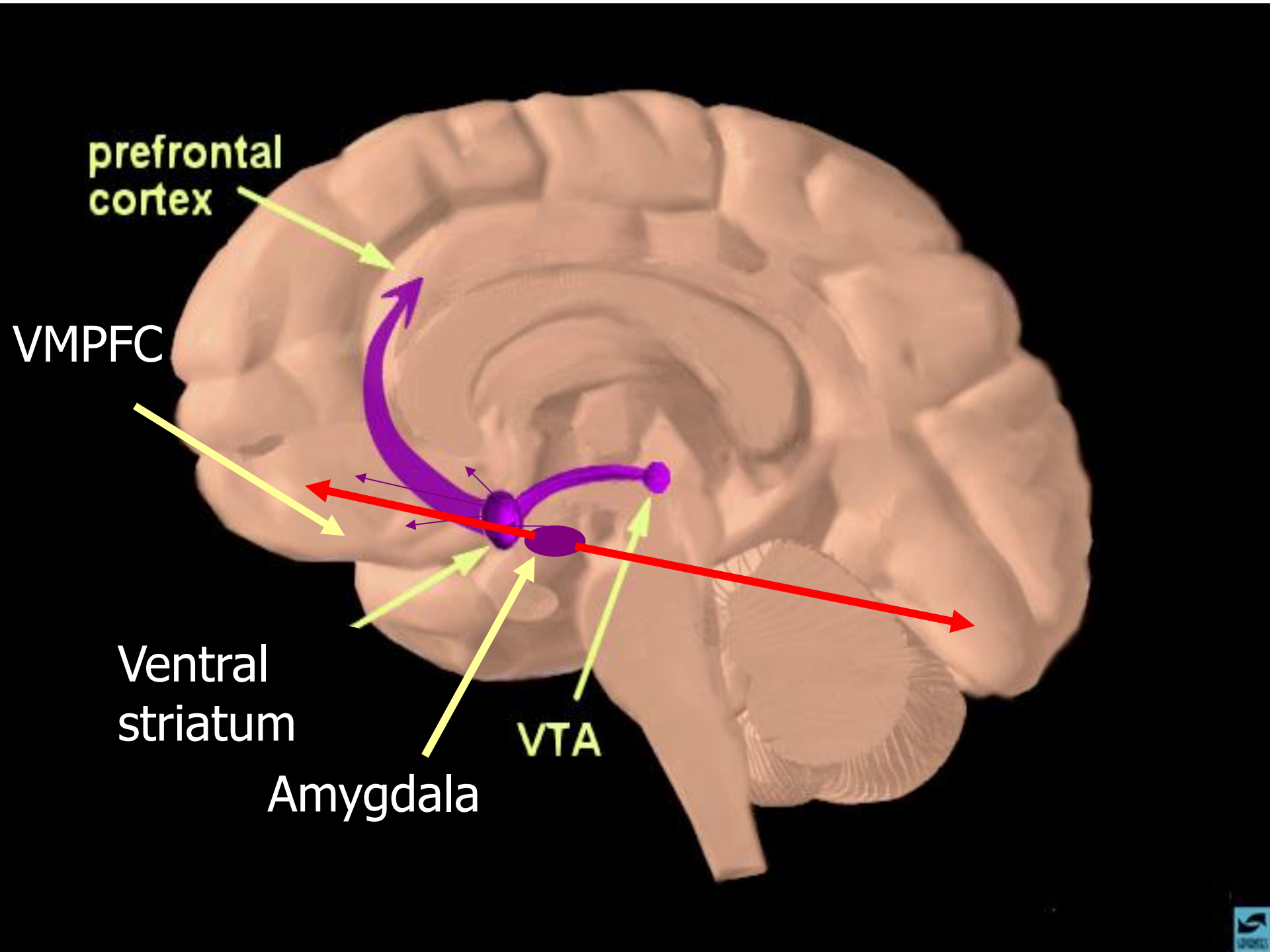
Levels of analysis of emotional processes

- Molecular biology
- Neurotransmitters
- Neuropathology
- Lesion studies
- Behavioural experiments
- Electrophysiology
- Neuroimaging: structural MRI, fMRI
- Neuroimaging of genomics

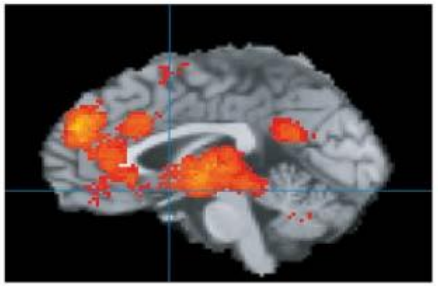


Barrett LF, et al. 2007.
Annu. Rev. Psychol. 58:373–403

Annual Reviews

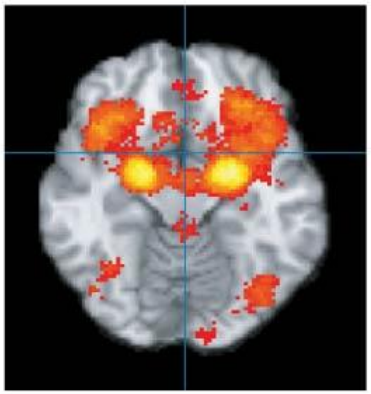

prefrontal cortex
VMPFC
Ventral striatum
Amygdala
VTA

a



b

c



Barrett LF, et al. 2007.
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Annual Reviews

Symptoms

Depressed mood

Anxiety

Anhedonia

Helplessness, hopelessness

Suicidality

Guilt

Low self esteem and confidence

Psychotic symptoms

Nihilistic delusions

Cognitive and biological symptoms

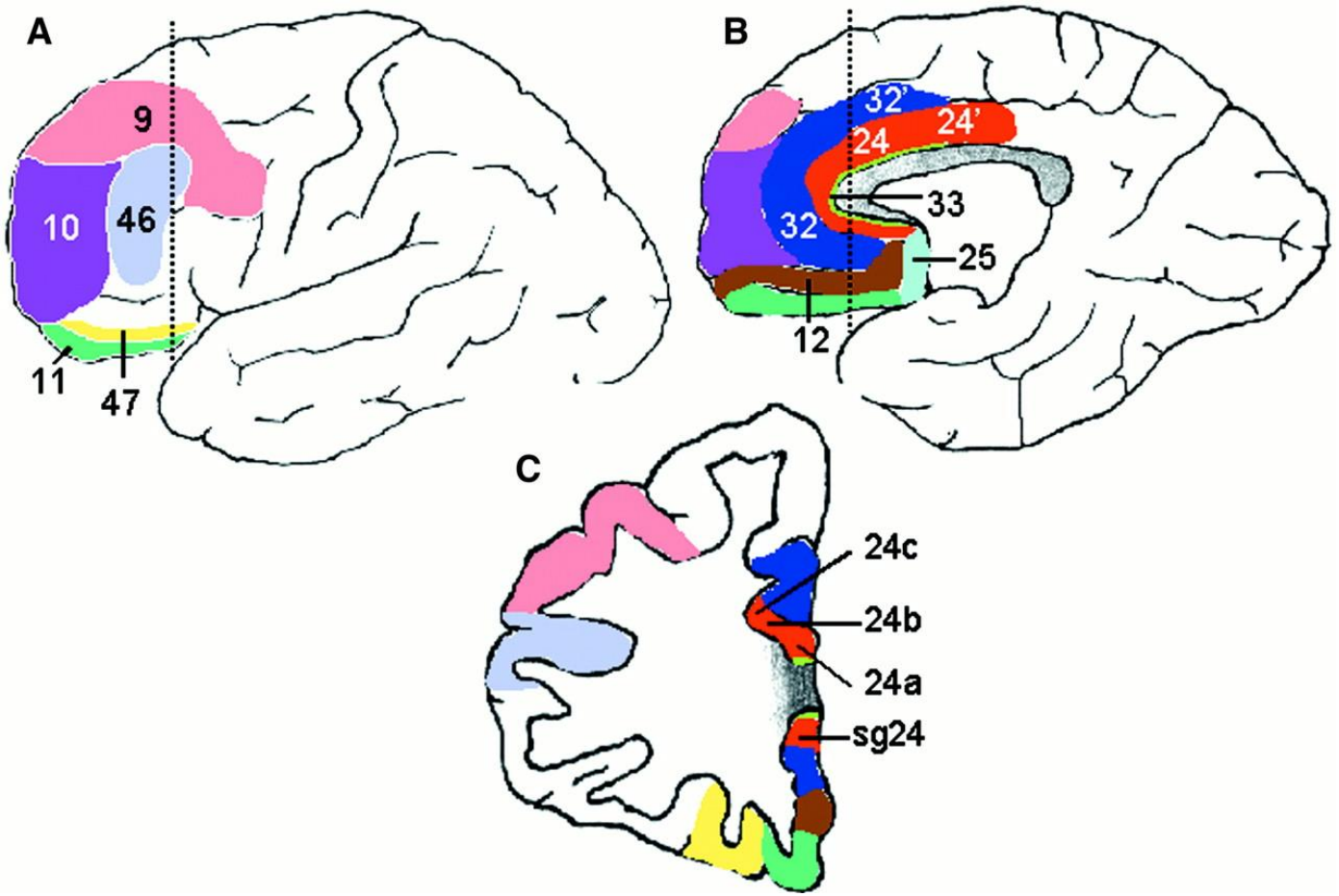
Poor sleep, appetite and concentration

Reduced libido

Low energy and motivation

Psychomotor retardation

Frontal lobe areas and the neuropathology of mood disorder



Harrison, P. J. Brain 2002 125:1428-1449; doi:10.1093/brain/awf149

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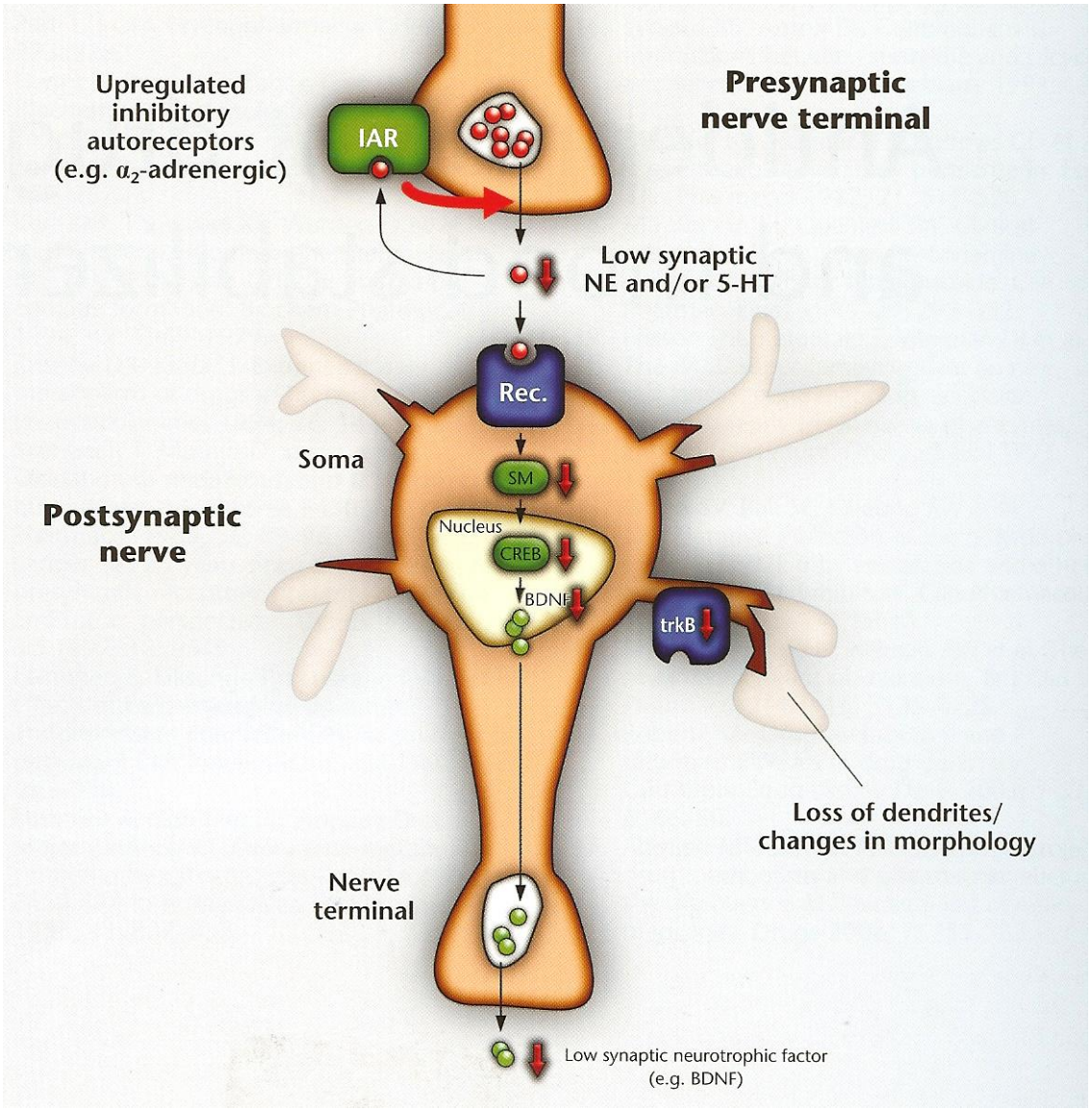
BRAIN
A journal of neurology

Neuropathology

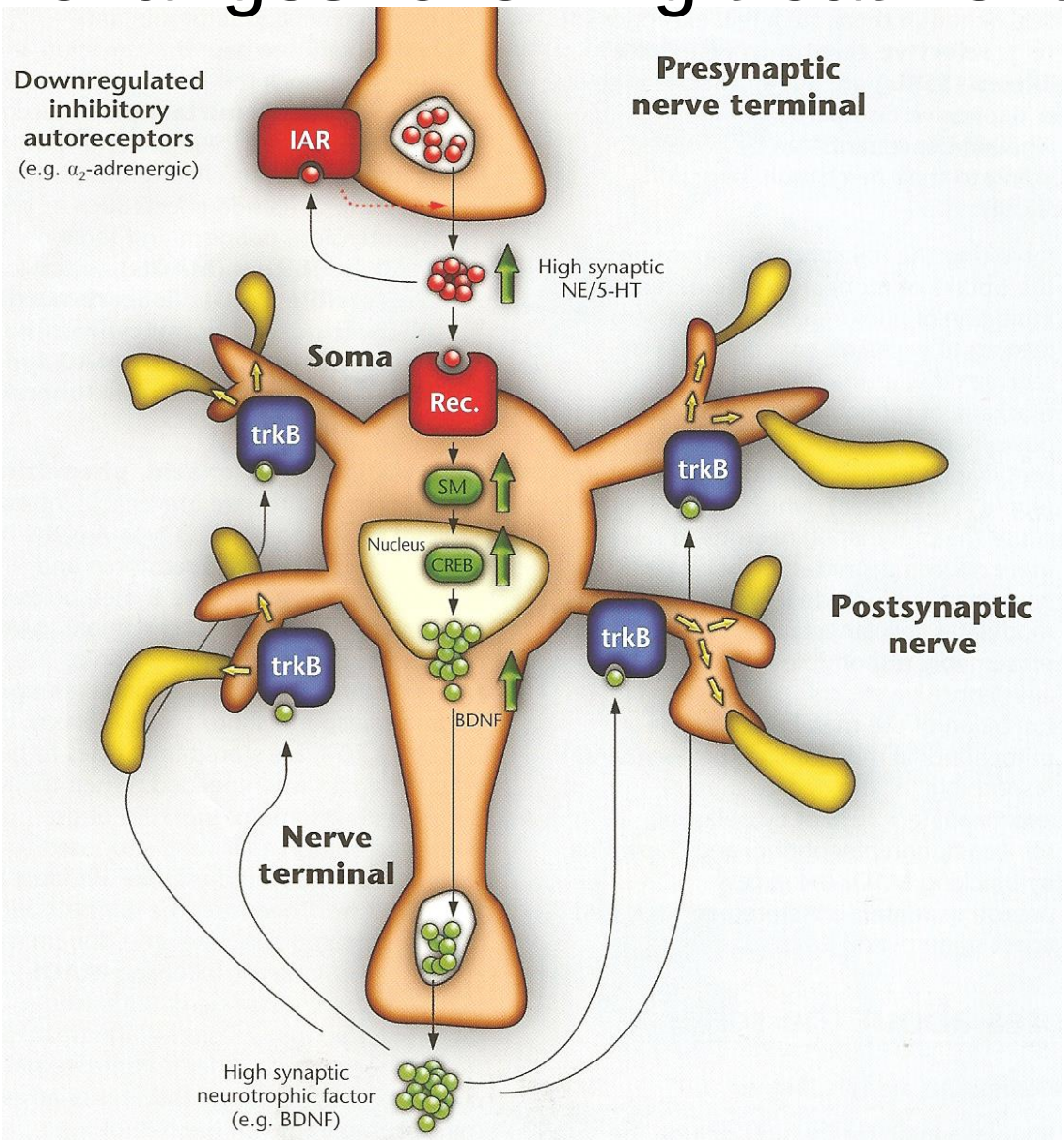
- Subgenual ACC:
  - Reduced glial density and glial number
- Supragenual ACC:
  - Reduced glial density and neuronal size
- Orbital and DLPFC:
  - Reduced glial density and neuronal size
- Hippocampus:
  - decreased arborization of apical dendrites, and a reduced density of dendritic spine

Major depressive disorder depressive state – no treatment



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

Major depressive disorder cellular changes following treatment



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

Emotional bias in MDD patients

Negative indirect (go/no-go; emotional stroop)

Negative / reduced positive direct (faces)

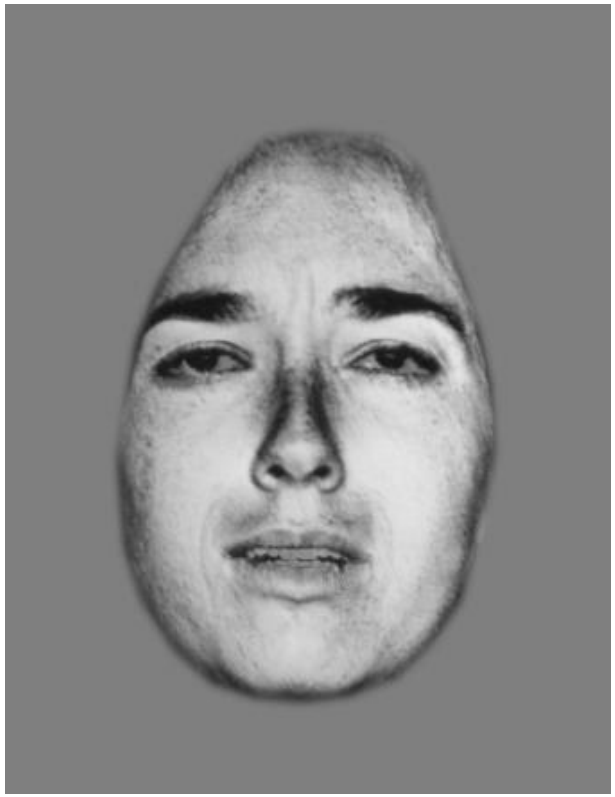
Some studies – generalised deficit OR – no impairment

Behavioral study of emotional bias in MDD

- Neutral
- 25% sad
- 50% sad
- 100% sad
- 25% happy
- 50% happy
- 100% happy

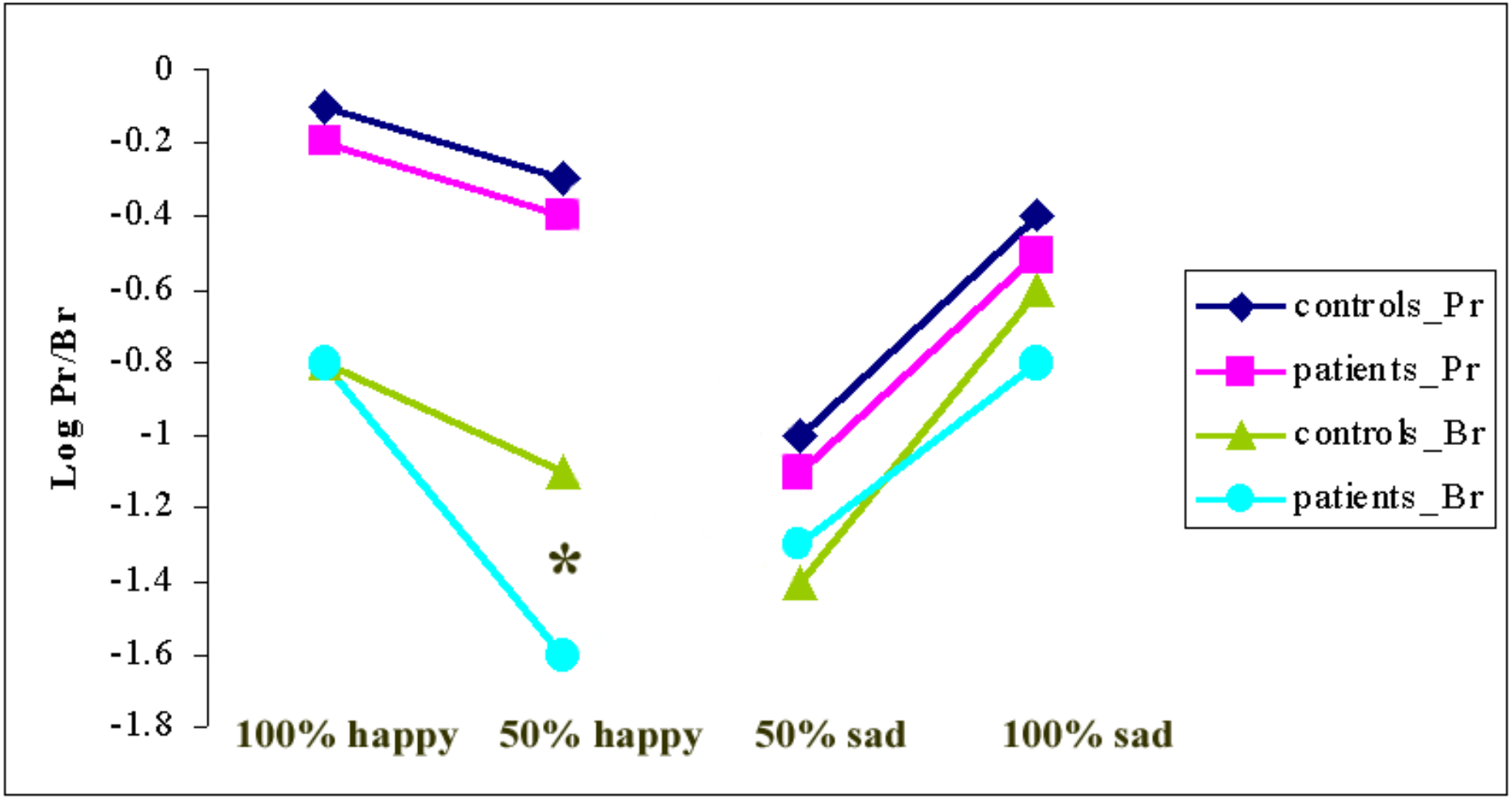
Ten different identities for each emotion
All stimuli presented for 100ms and 2000ms
ISI 1500ms

Surguladze et al. (2004)



neutral happy sad

neutral happy sad



Compared with healthy subjects, patients demonstrated a significantly greater response bias away from labeling 50 % happy expressions as happy ($t(54)=4.5$; $p<0.001$).

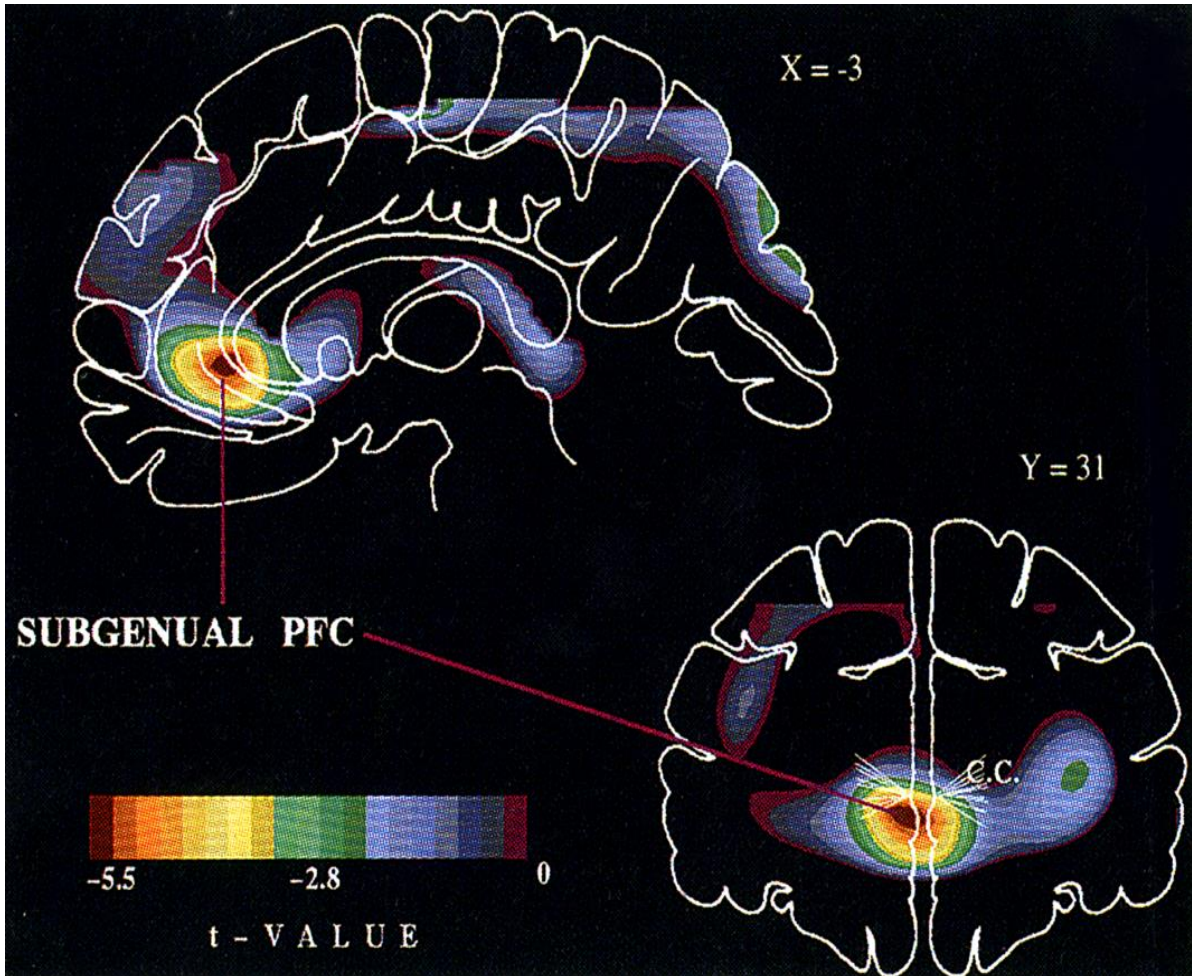
Functional abnormalities

↑ amygdala and ventral striatal blood flow at rest
positive correlation - amygdala metabolism
and depression severity

↑ subgenual resting activation

↑ amygdala activation to masked facial expressions

↓ habituation of amygdala response

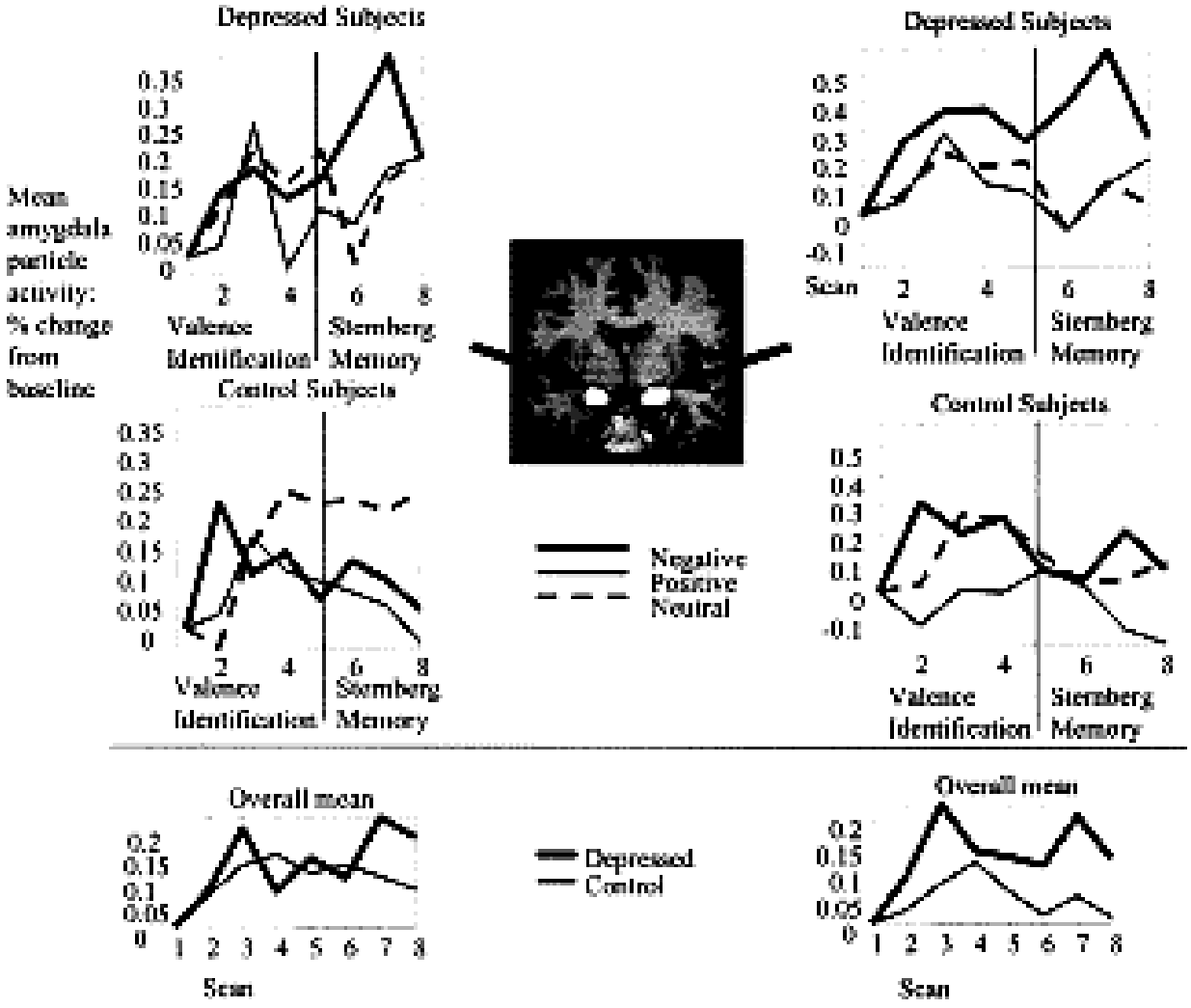

X = -3
Y = 31
SUBGENUAL PFC
g.c.
-5.5
-2.8
0
t - VALUE

Emotional state and emotion regulation

Relative increase in metabolism in ventral cingulate gyrus in depressed state

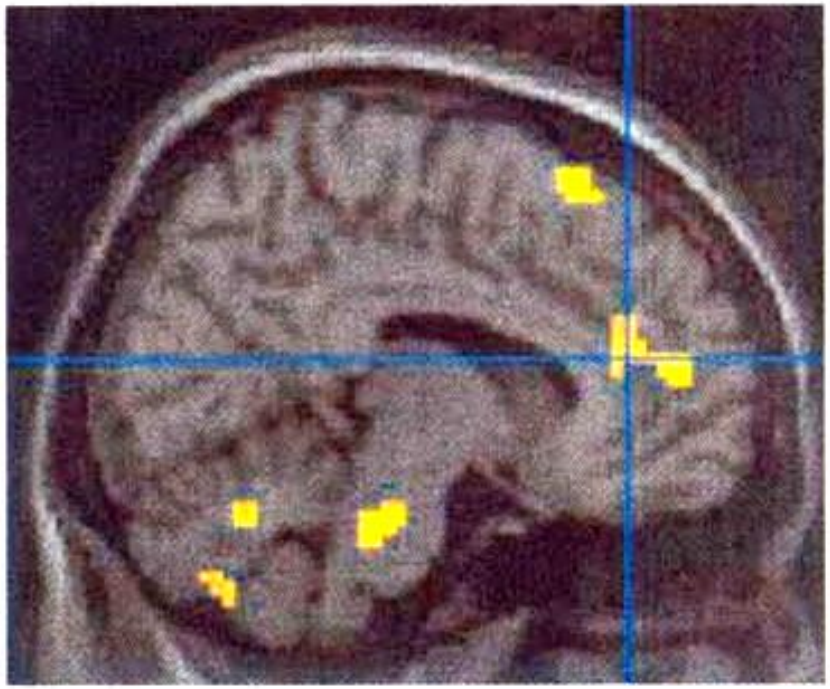
↓ prefrontal and dorsal anterior cingulate gyrus activity

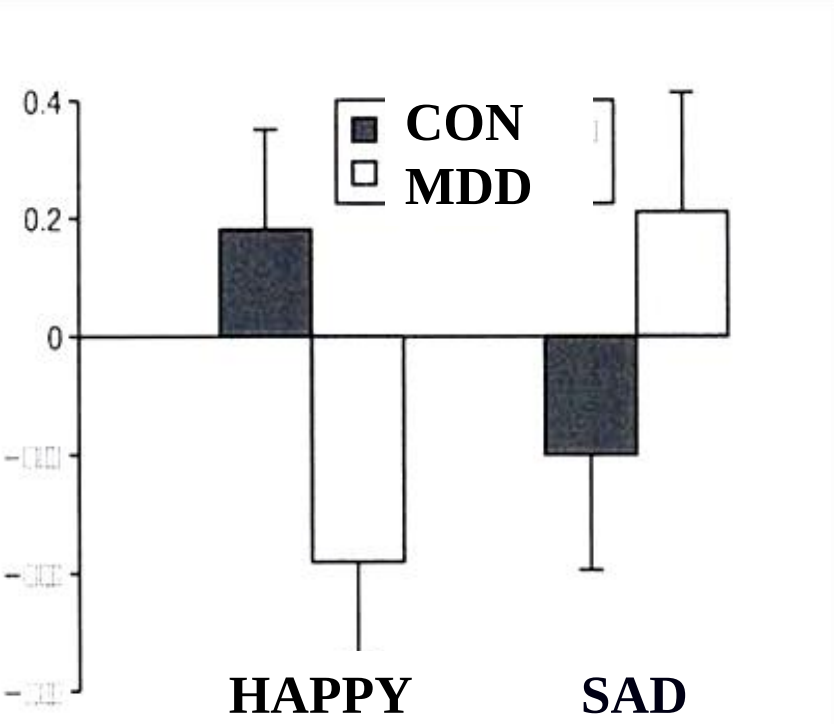
On recovery ↓ in ventral cingulate metabolism but ↑ in metabolism in dorsal anterior cingulate gyrus and dorsolateral prefrontal cortex



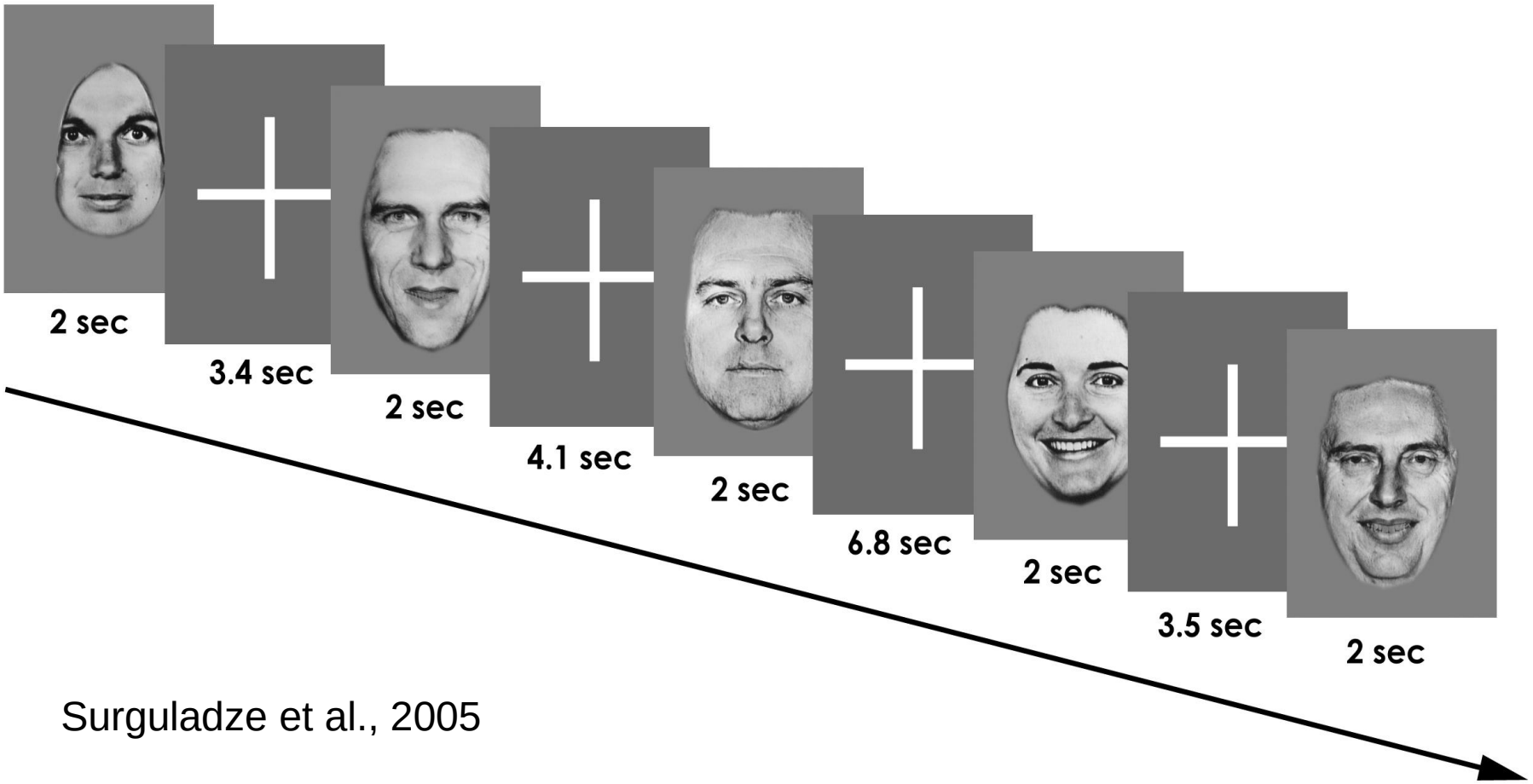
Sustained amygdala response to negative emotional words in depression. Siegle et al. (2002)

Elliott et al. (2002) Bias towards sad targets in MDD shown by increased anterior cingulate response





fMRI paradigm



Surguladze et al., 2005

Happy faces

Figure 1

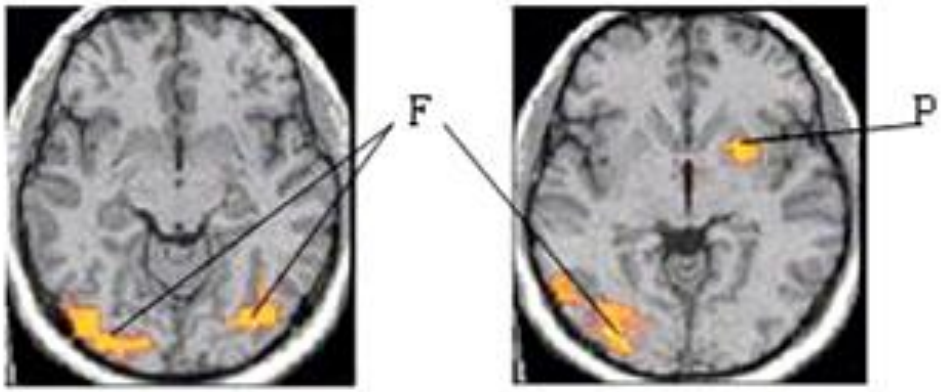
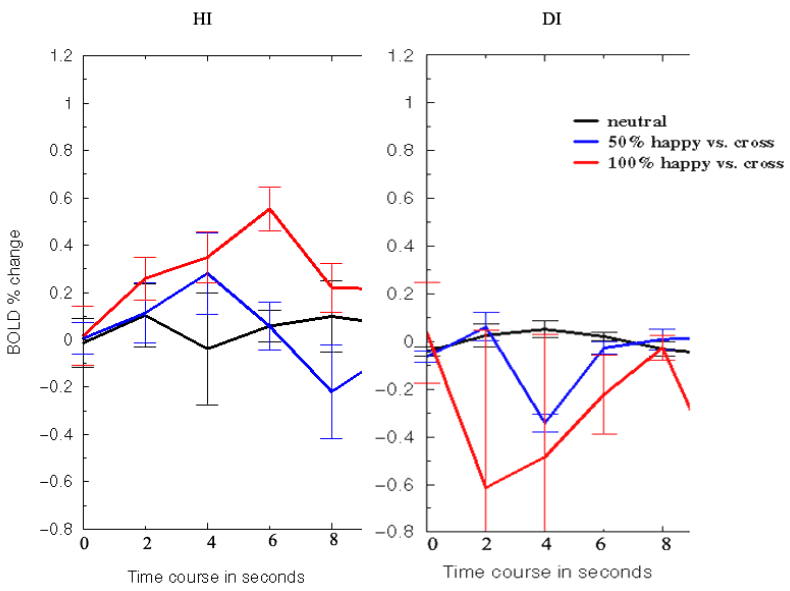
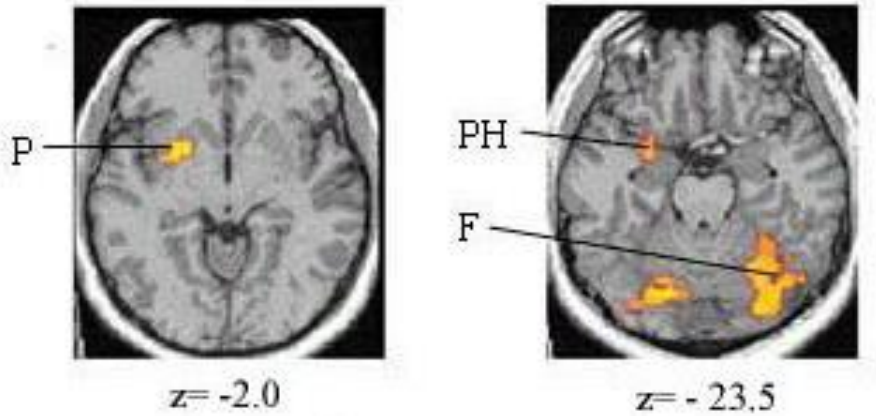


Figure 2.



Surguladze et al., 2005

Sad faces



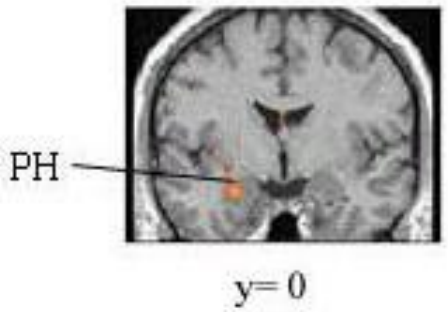
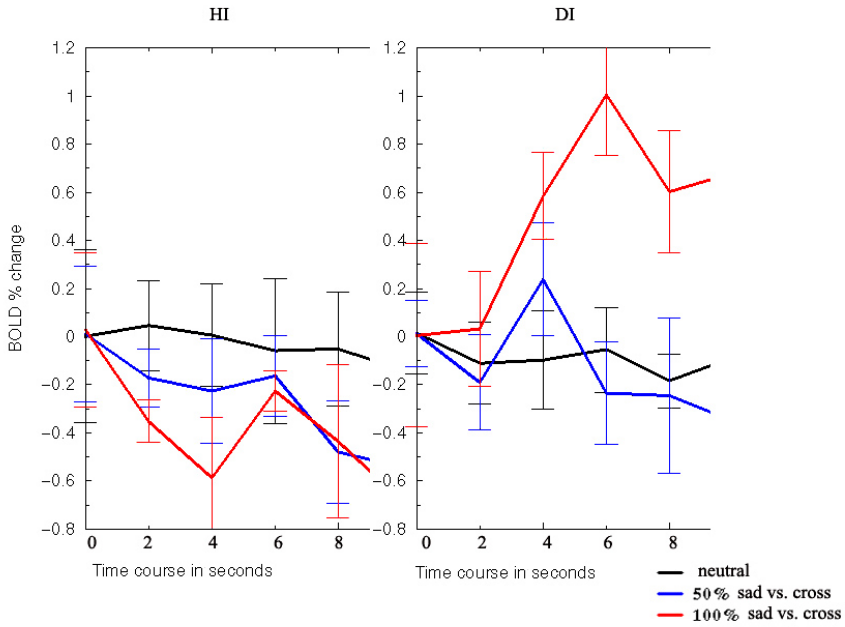
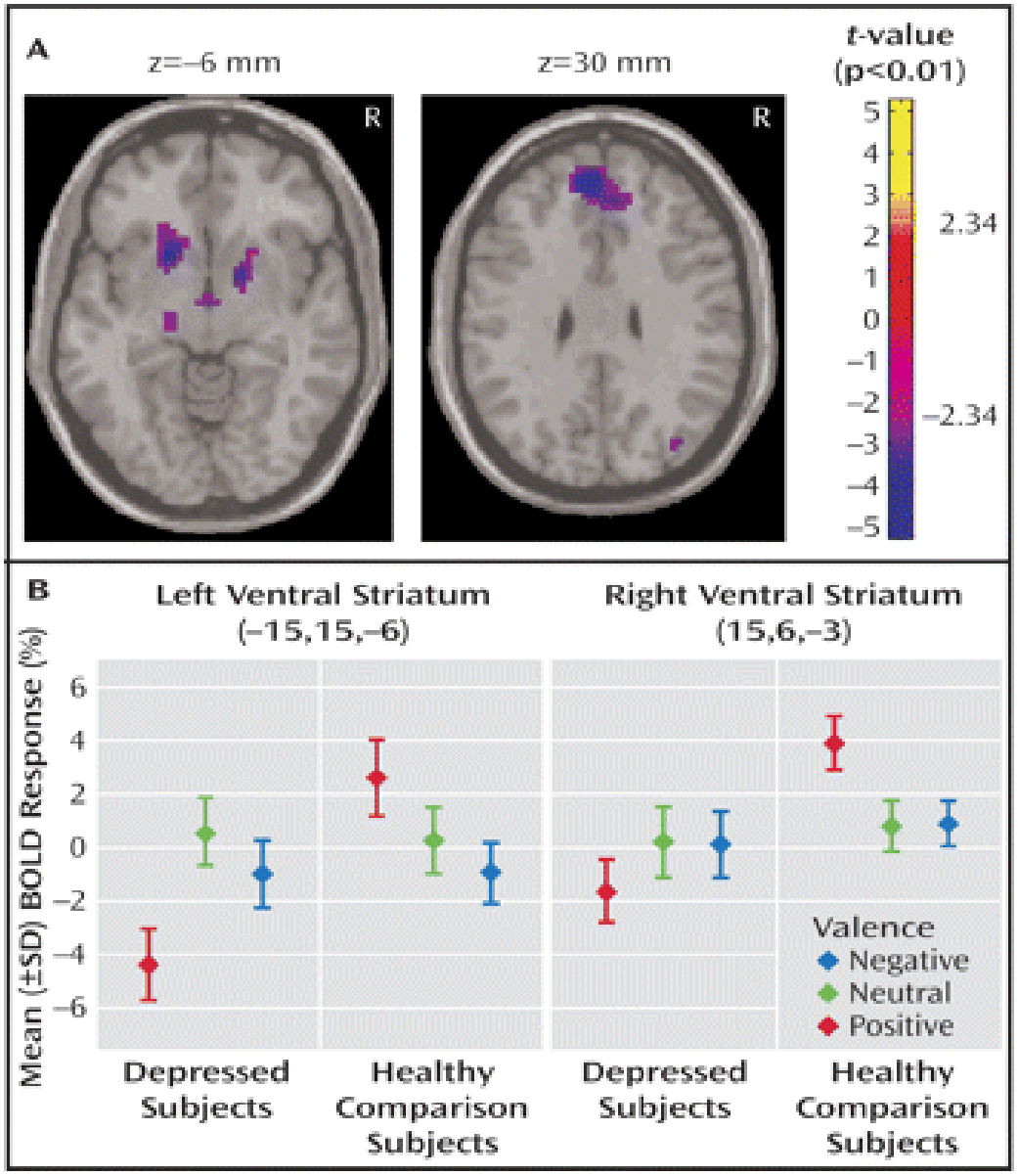


Figure 4.



Surguladze et al., 2005



Lack of Ventral Striatal Response to Positive Stimuli in Depressed Versus Normal Subjects

Epstein et al., American Journal of Psychiatry 2006

Summary

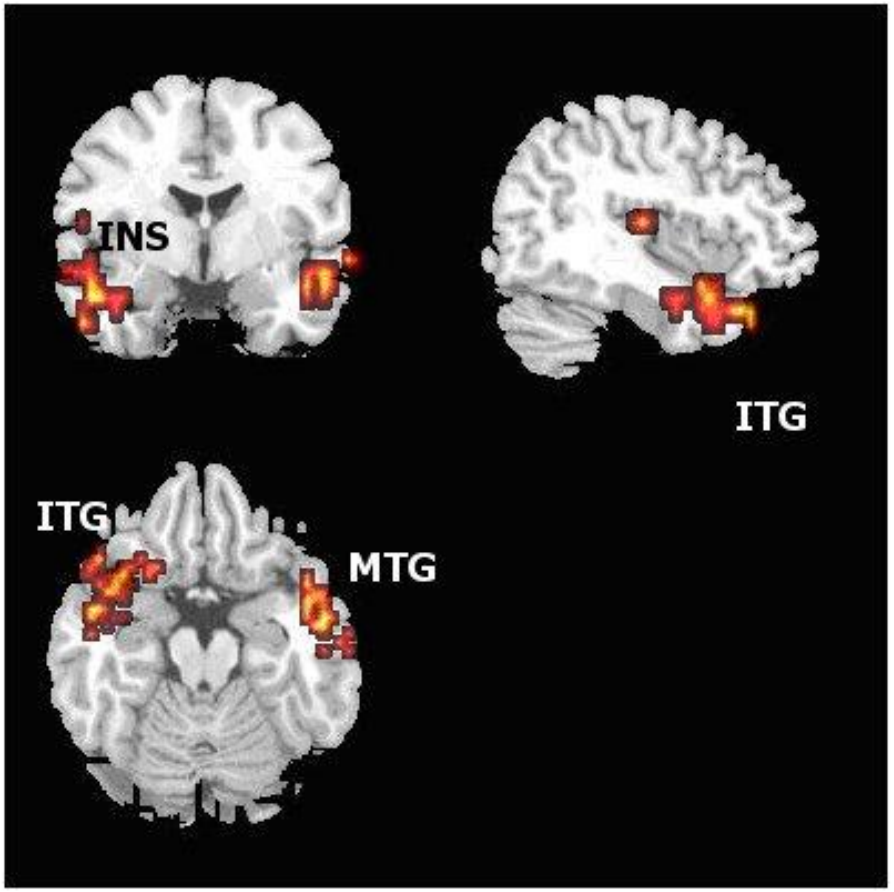
BIAS AWAY FROM HAPPY and TOWARDS NEGATIVE SIGNALS

Hyperactivation of amygdala

Significant DECREASE in activity within ventral striatum and visual cortex to increasing intensity of happiness

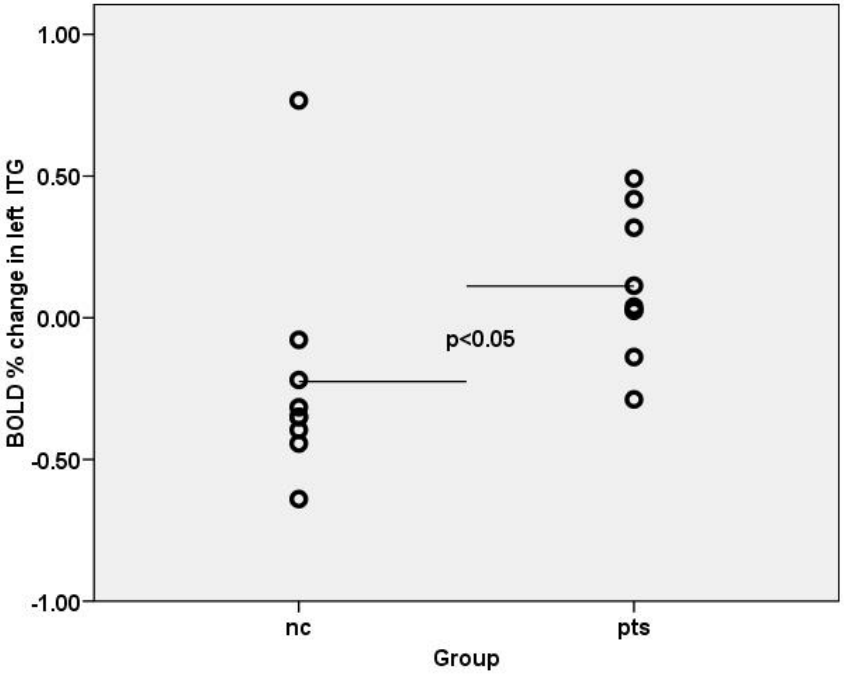
Significant INCREASE in activity within visual cortex to increasing intensity of sadness

Depression is associated with increased sensitivity to signals of disgust

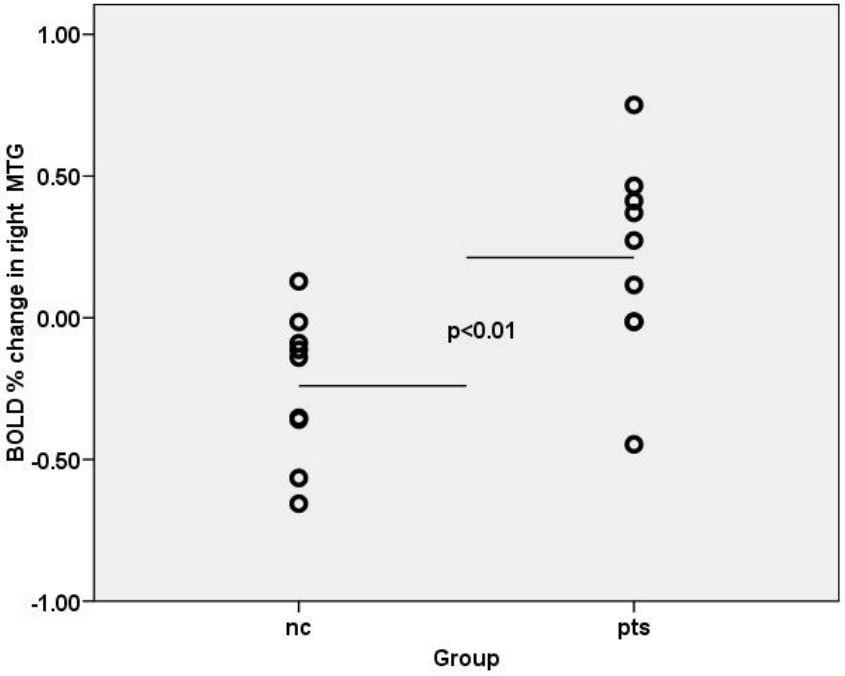


Surguladze, S.A., et al. *Journal of Psychiatric Research* (in press)

Increased activation to disgust

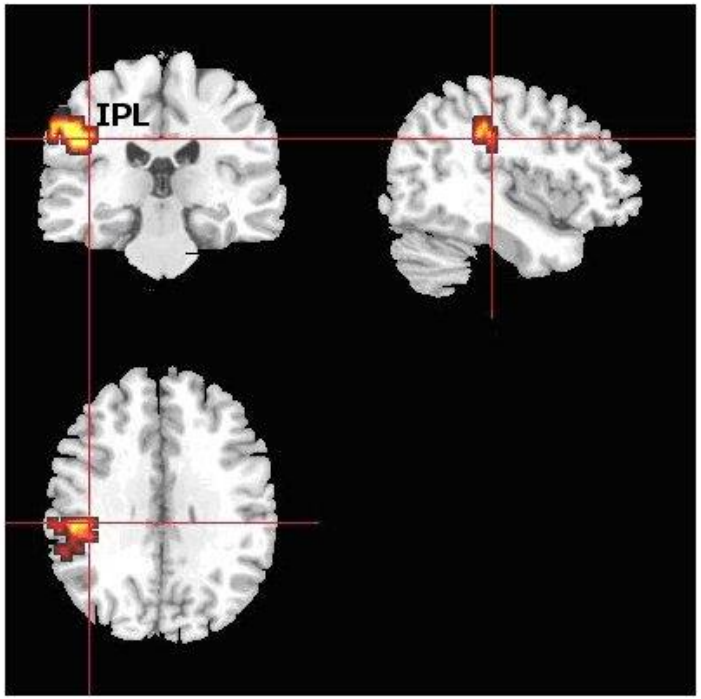


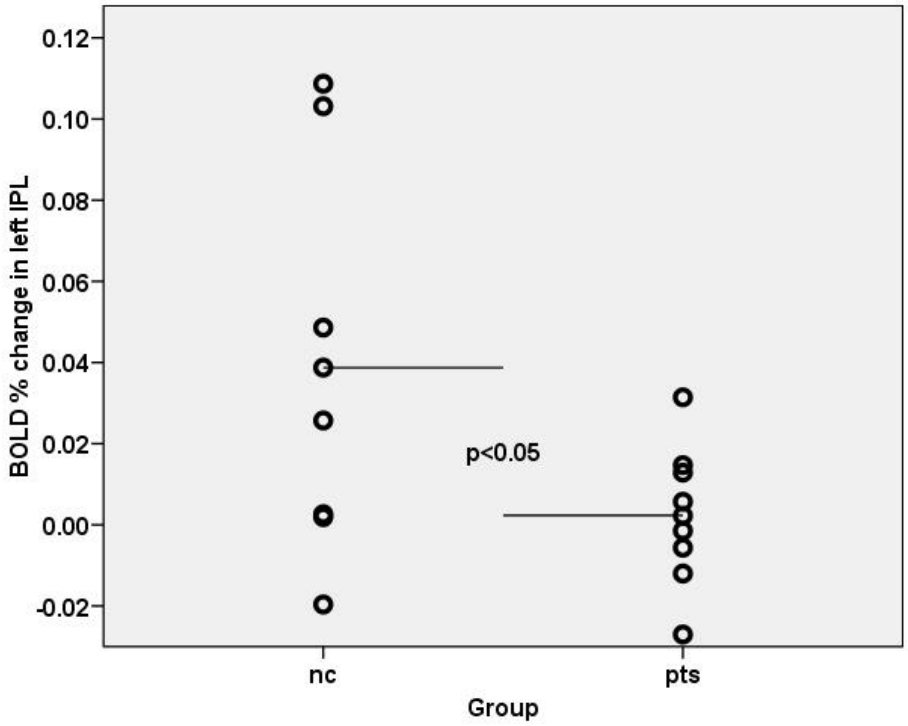
Left ITG/insula



Right MTG

Reduced attention to fear in depression

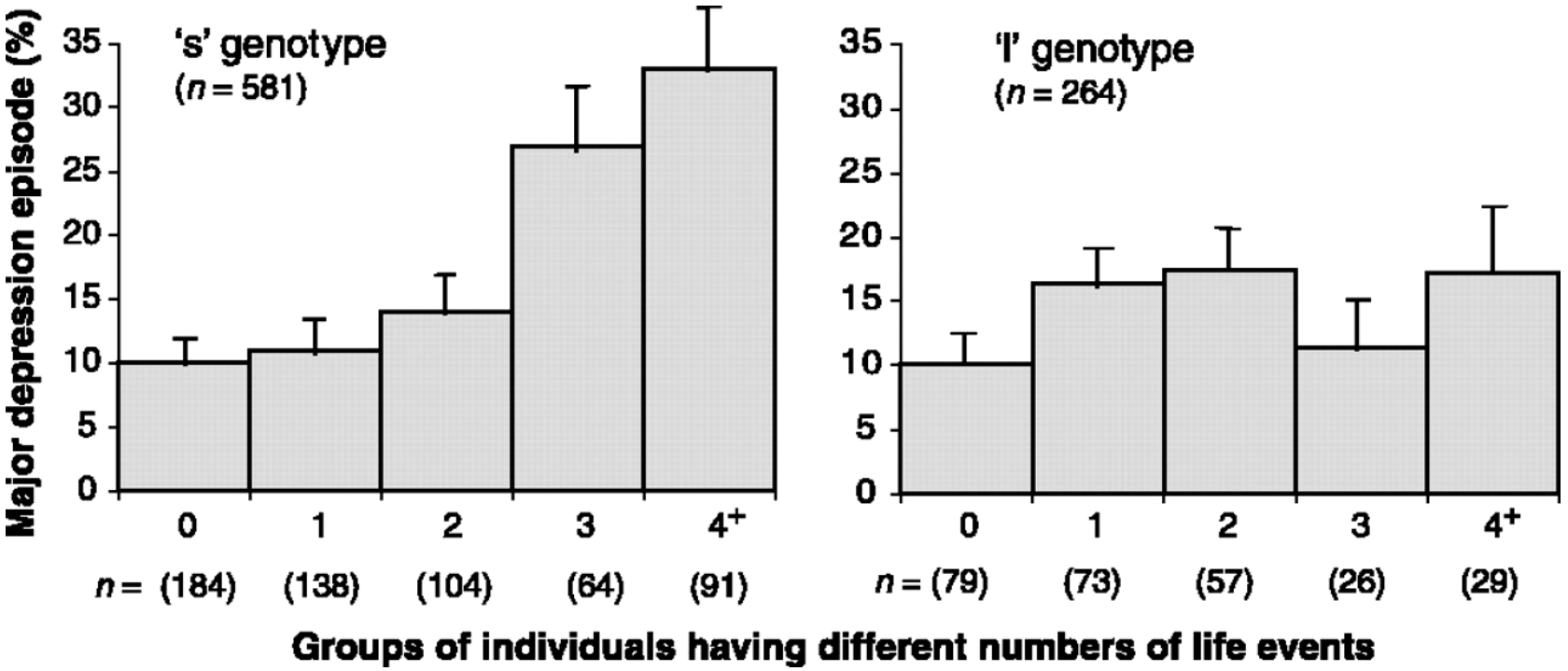




Neuroimaging of genomics

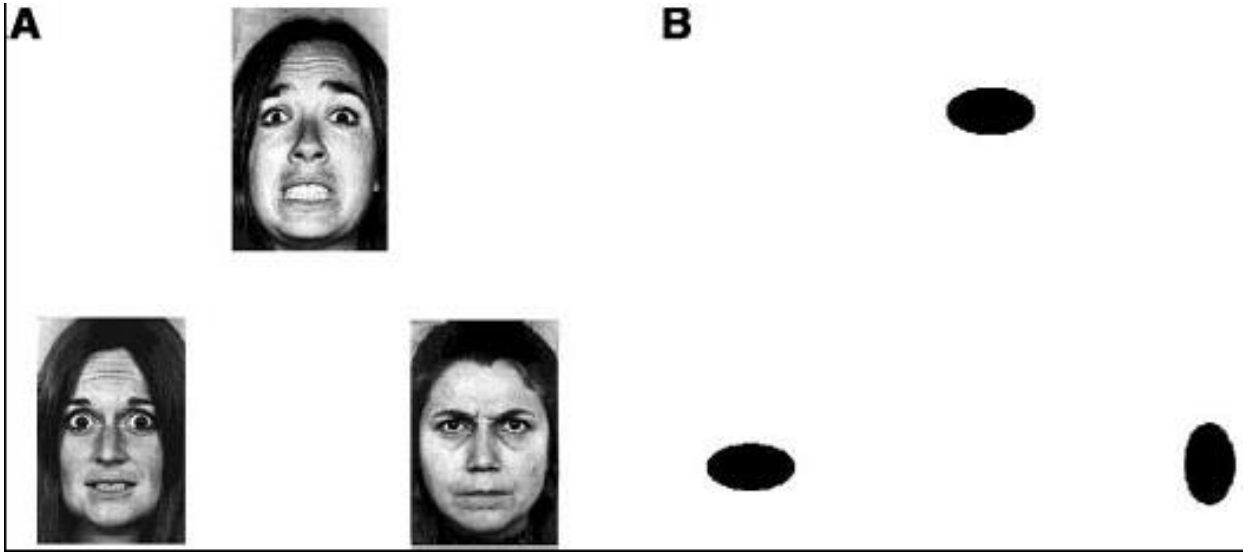
- 5-HTTLPR polymorphism (short allele) is associated with anxiety traits (Lesch et al, 1996)
- Human and animal studies have revealed that abnormal fear conditioning was associated with 5-HTT function
- The fear conditioning is dependent on the amygdala
- This suggests that amygdala may be critical in mediating the effects of 5-HT on emotional behaviour.

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene



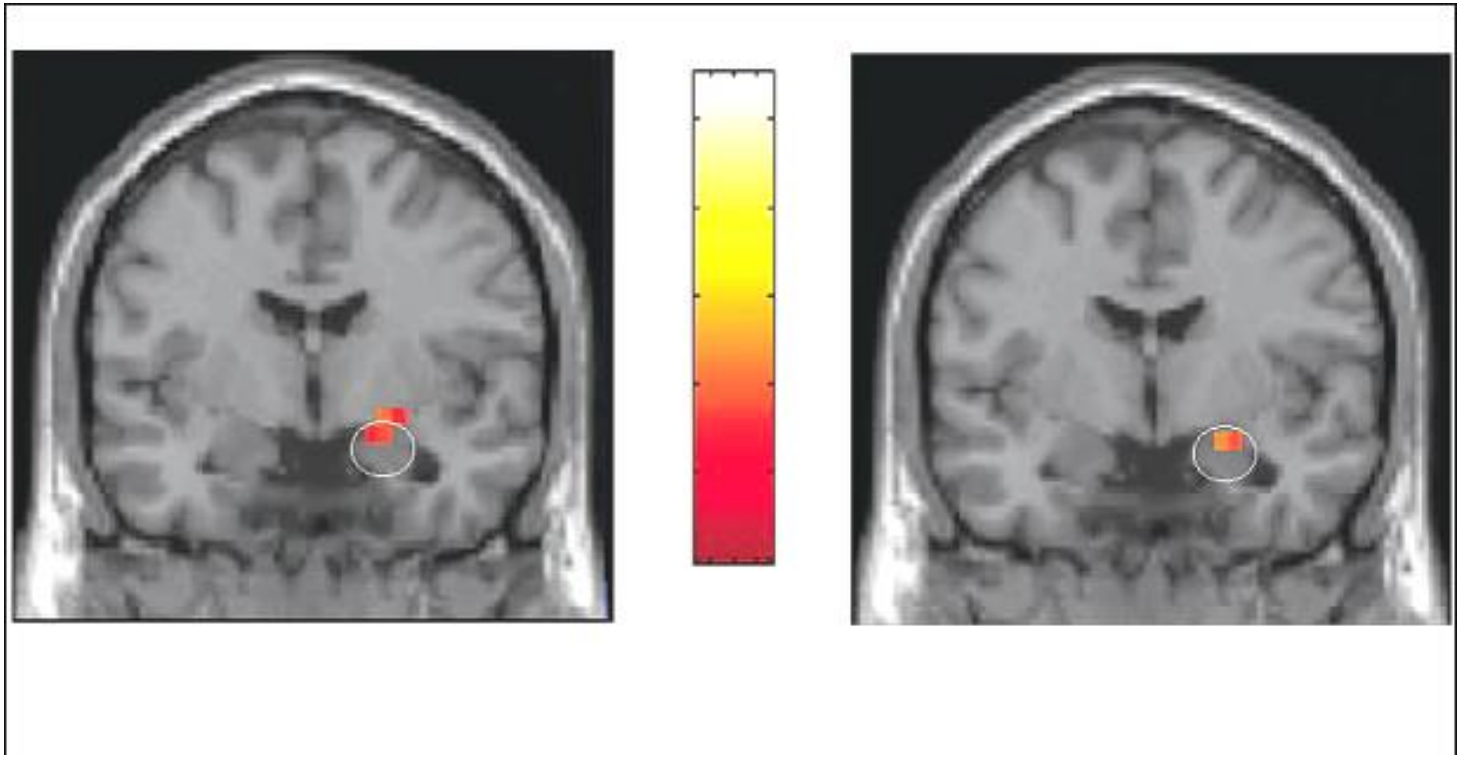
Caspi et al., *Science*, 2003

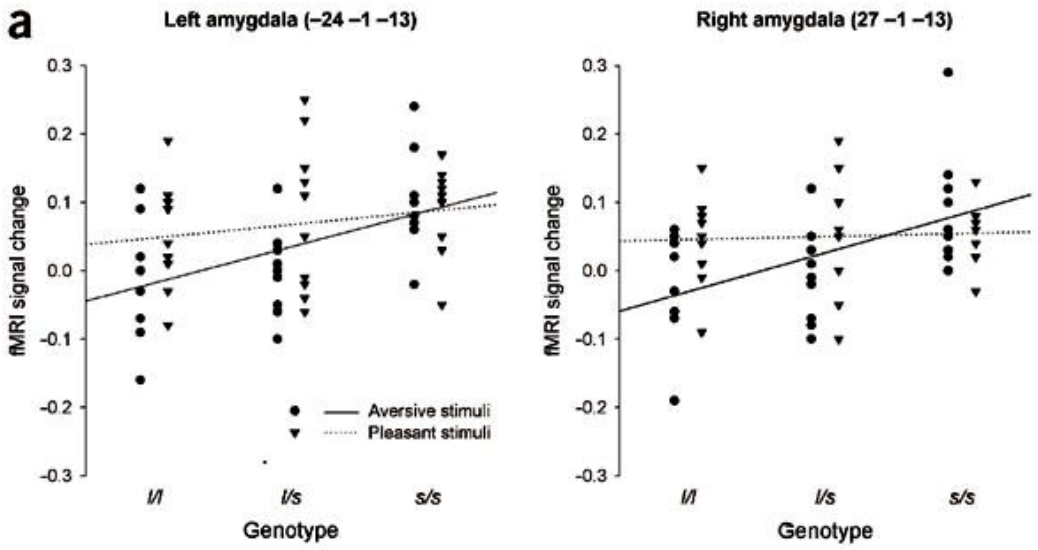
Serotonin transporter genetic variation and the response of the human amygdala

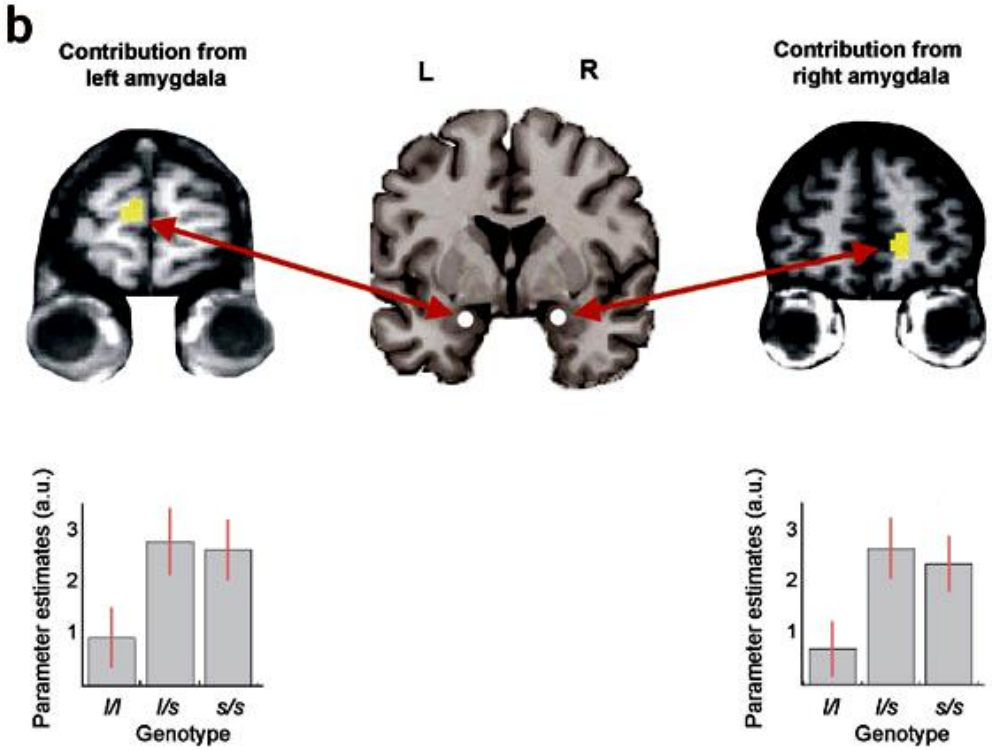


Hariri et al., Science 2002

Serotonin transporter genetic variation and the response of the human amygdala: s group > l group



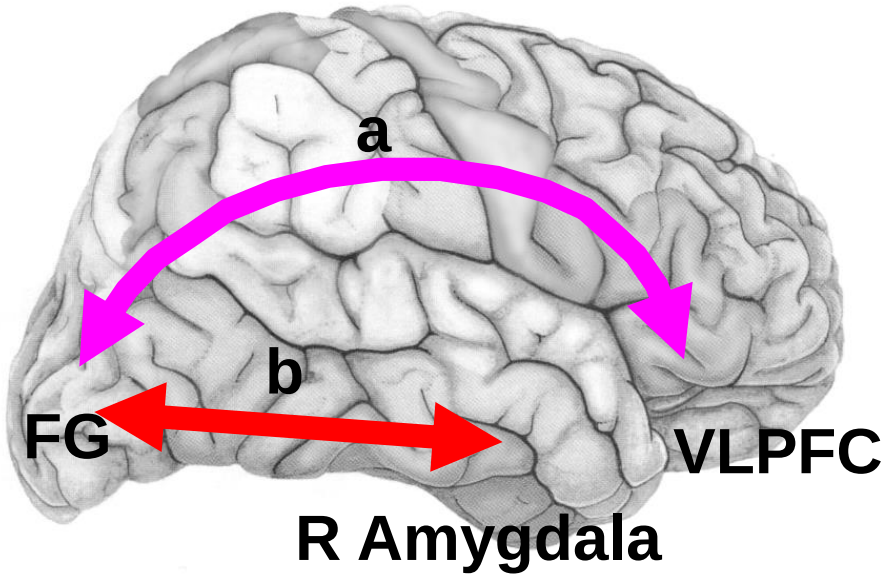




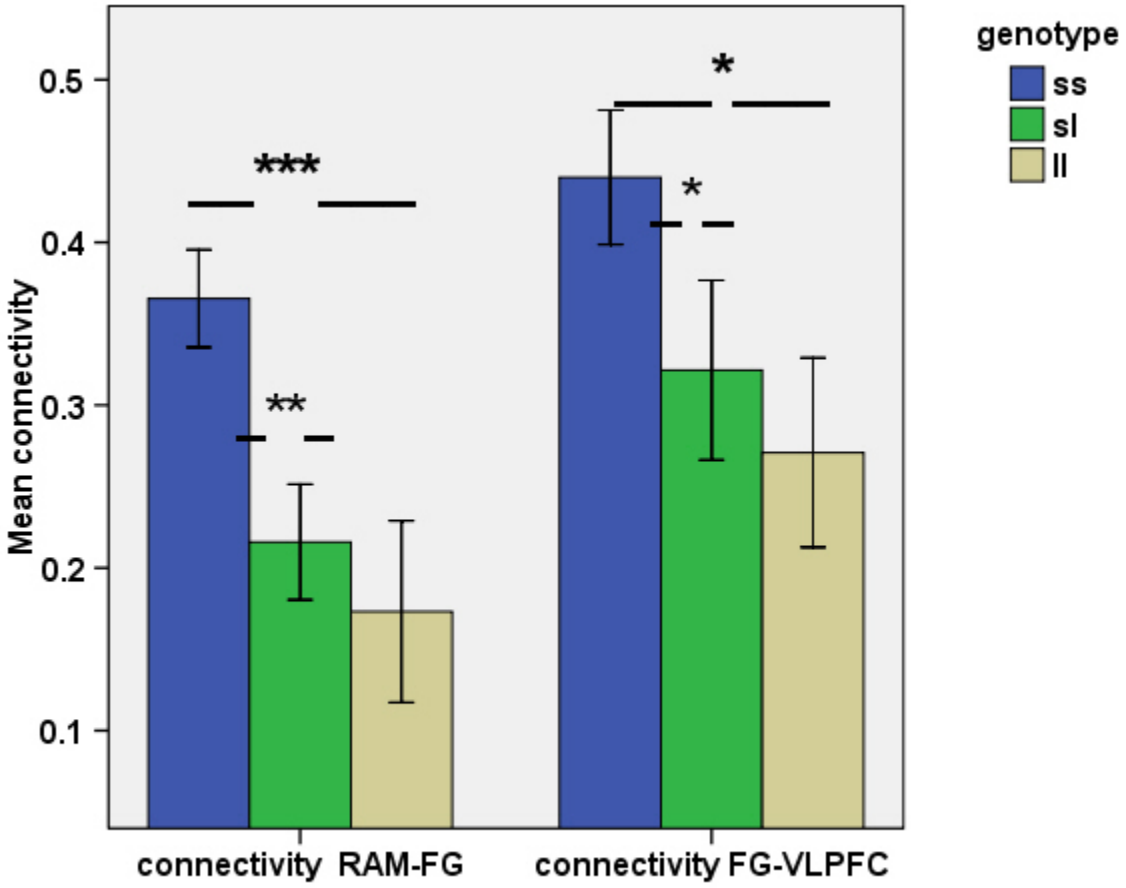
Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter

Heinz et al, Nature Neuroscience. 8(1):20-1, 2005 Jan.

Genetic variation in the serotonin transporter modulates neural system-wide response to fearful faces



In the right amygdala-right FG link the connectivity in *S/S* was significantly greater than either in *L/L* ($p<0.001$) or *S/L* ($p=0.001$). Within the right FG-right VLPFC link, the connectivity in the *S/S* group was significantly greater than either in *L/L* ($p=0.026$) or *S/L* ($p=0.038$).



Surguladze et al., *Genes, Brain & Behavior*, 2008