Reconciling the Body-Mind Connection

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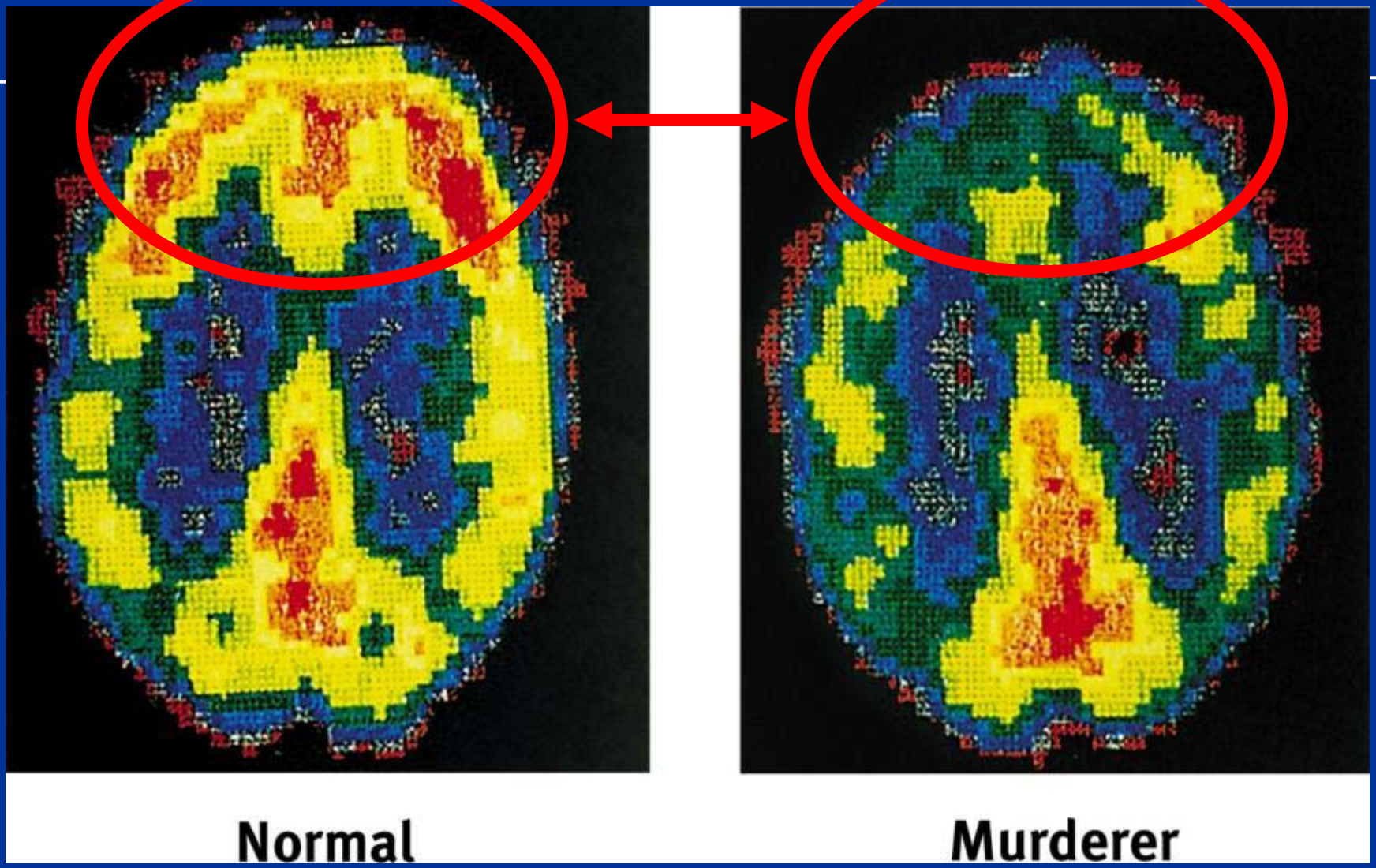
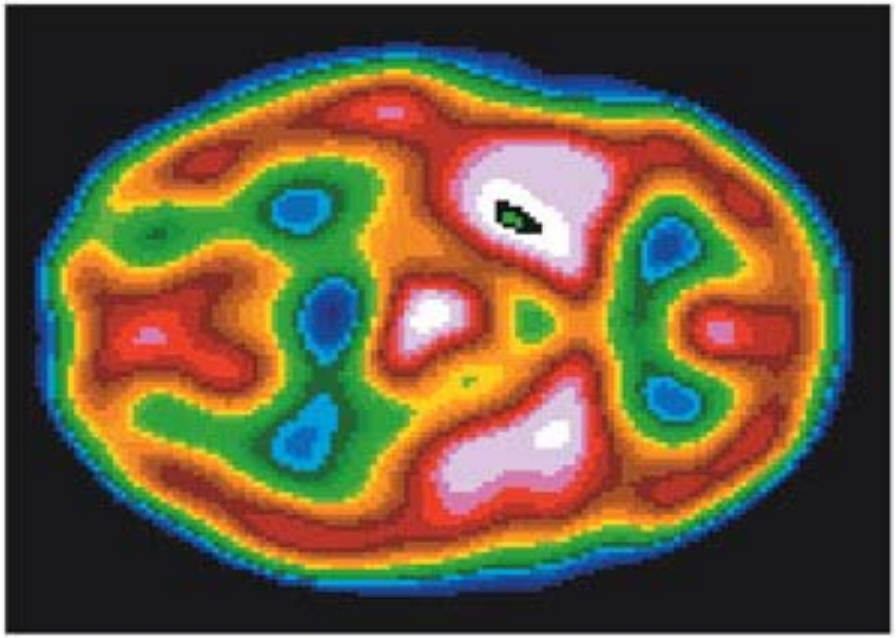


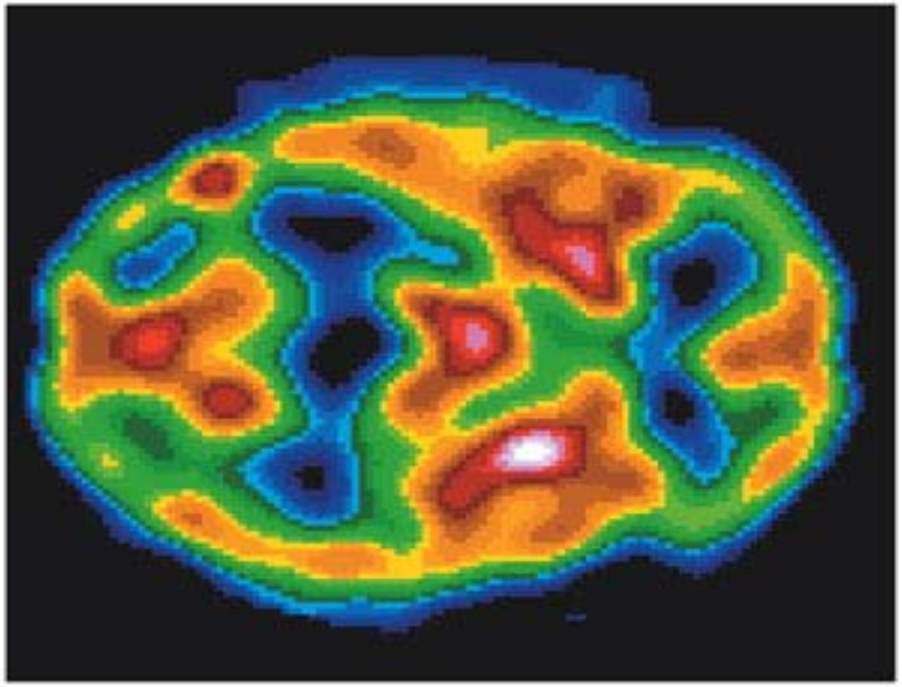
Figure 49.2 Murderous minds
Myers: Psychology, Eighth Edition

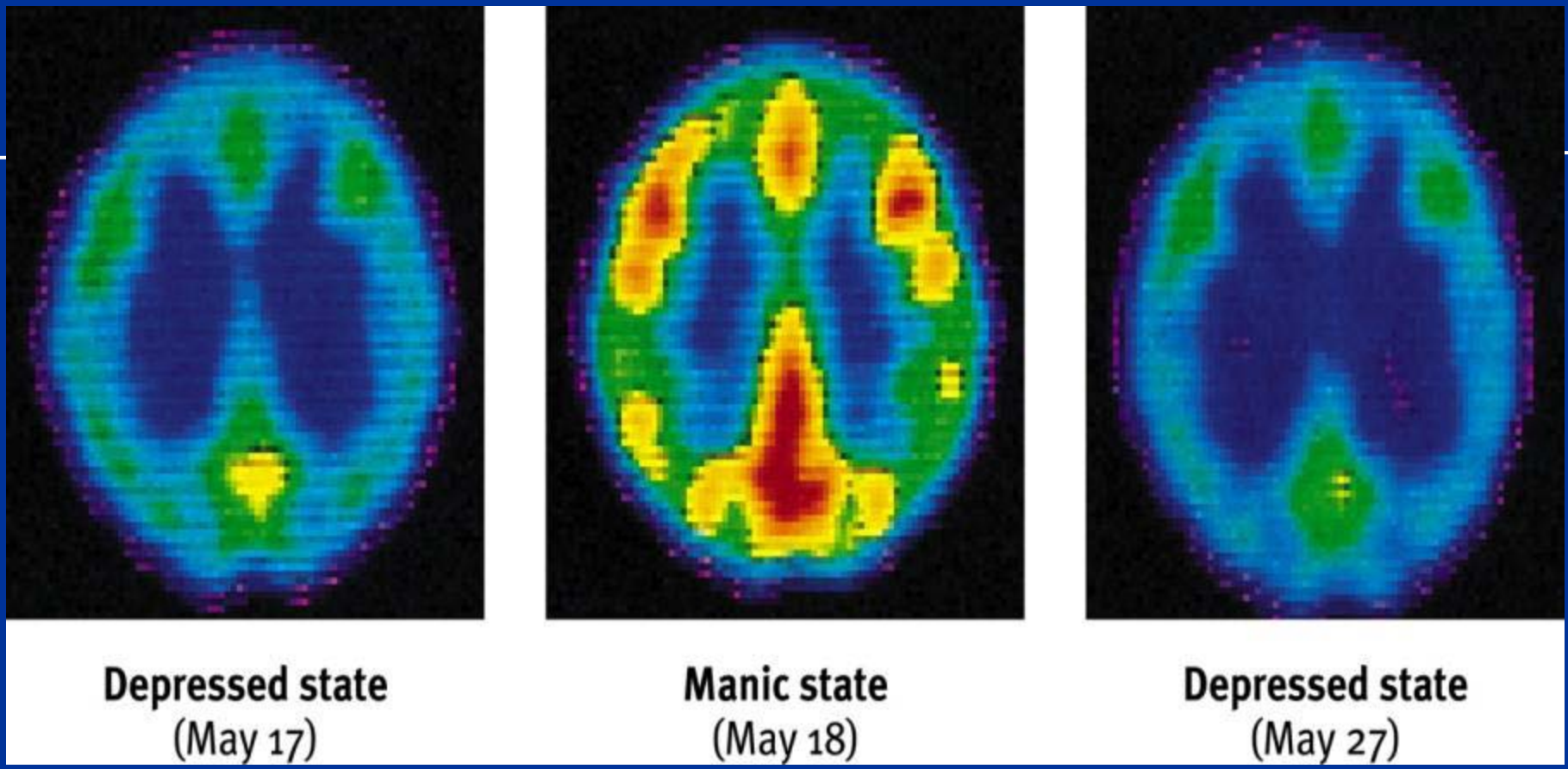
Brain activity in manic vs. depressive episode

Manic



Depressive





Red areas are where the brain rapidly consumes glucose. Brain shows less activity during depression than mania.

Figure 50.2 The ups and downs of bipolar disorder
Myers: Psychology, Eighth Edition

Definition

Major depressive disorder: malady of stress adaptation in the brain or a **disorder of stress response & adaptation** (Neuroplasticity).

(Duman et al, 1997; Duman et al, 1999; Gold et al, 1988;Skolnick,1999).

Multiple Core and Associated Symptoms *DSM and beyond*

Emotional symptoms

- Feelings of guilt
- Suicidal
- Lack of interest
- Sadness

Physical symptoms

- Lack of energy
- Decreased concentration
- Change in appetite
- Change in sleep
- Change in psychomotor skills

Associated symptoms

- Brooding
- Obsessive rumination
- Irritability
- Excessive worry over physical health
- Pain
- Tearfulness
- Anxiety or phobias

American Psychiatric Association (APA). DSM-IV-TR; 2000:352,356.

Major depressive disorder (MDD)

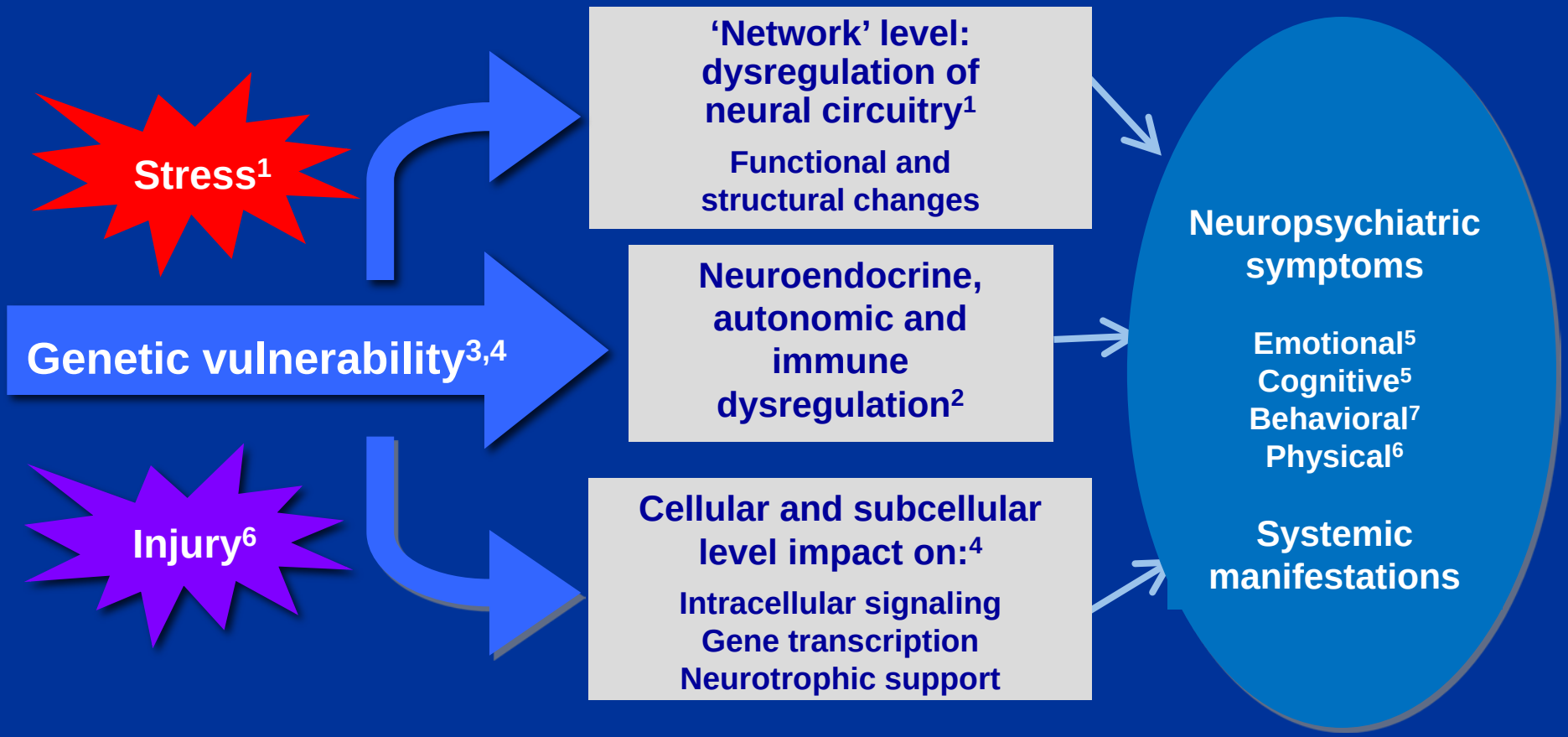
- MDD can be a **chronic, recurrent, and progressive** [1,2]
- MDD is associated w/ alterations in functional & **structural changes in the brain**[2-4]
- MDD, stress, & pain are all associated w/ similar suppression of neurotrophic factors & compromised **neuroplasticity**[2-4]
- **Remission not response** is the ultimate goal of treatment[5,6]

1. Kendler KS, et al. *Am J Psychiatry.* 2000;157(8):1243-1251.
2. Maletic V, et al. *Int J Clin Pract.* 2007;61:2030-2040.
3. Duman RS. *Biol Psychiatry.* 2004;56:140-145.
4. Maletic V. *Prim Psychiatry.* 2005;12(suppl 10):7-9.
5. Keller MB, et al. *Arch Gen Psychiatry.* 1992;49(10):809-816.
6. APA. *Am J Psychiatry.* 2000;157(4 suppl):1-45.

Agenda

- Biology
- Response vs Remission
- Duloxetine

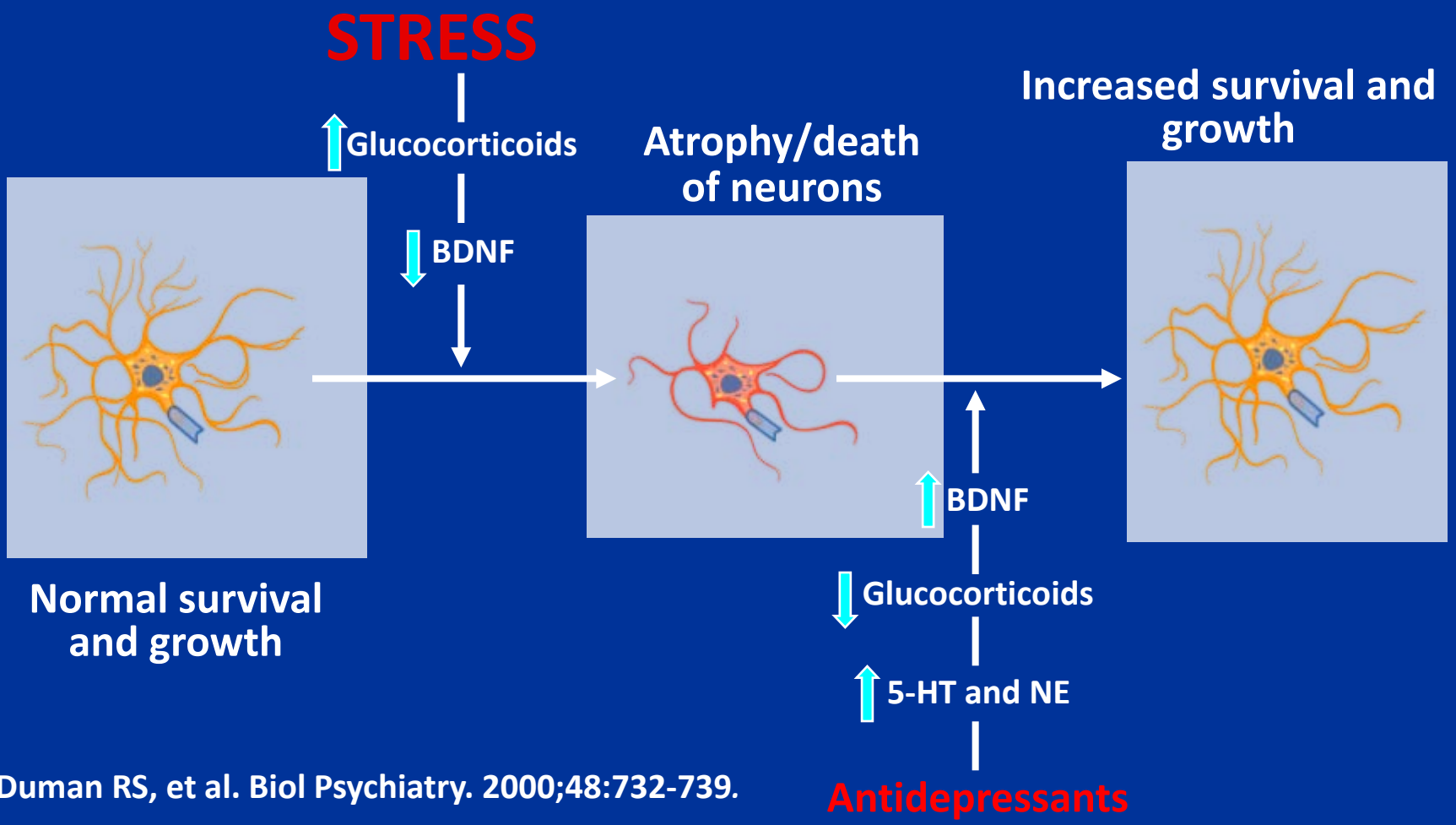
Micro to Macro Effects



1. Sheline YI, et al. *Biol Psychiatry.* 2001;**50**:651–658. 2. Raison CL, et al. *Trends Immunol.* 2006;**27**:24–31. 3. Gatt JM, et al. *J Integr Neurosci.* 2007;**6**:75–104. 4. Carlson PJ, et al. *NeuroRx.* 2006;**3**:22–41. 5. Drevets WC. *Curr Opin Neurobiol.* 2001;**11**:240–249. 6. Blackburn-Munro G, et al. *J Neuroendocrinol.* 2001;**13**:1009. 7. American Psychiatric Association (APA). DSM-IV-TR; 2000:352,356.

Cellular, Functional and Structural Changes Associated with MDD and Pain

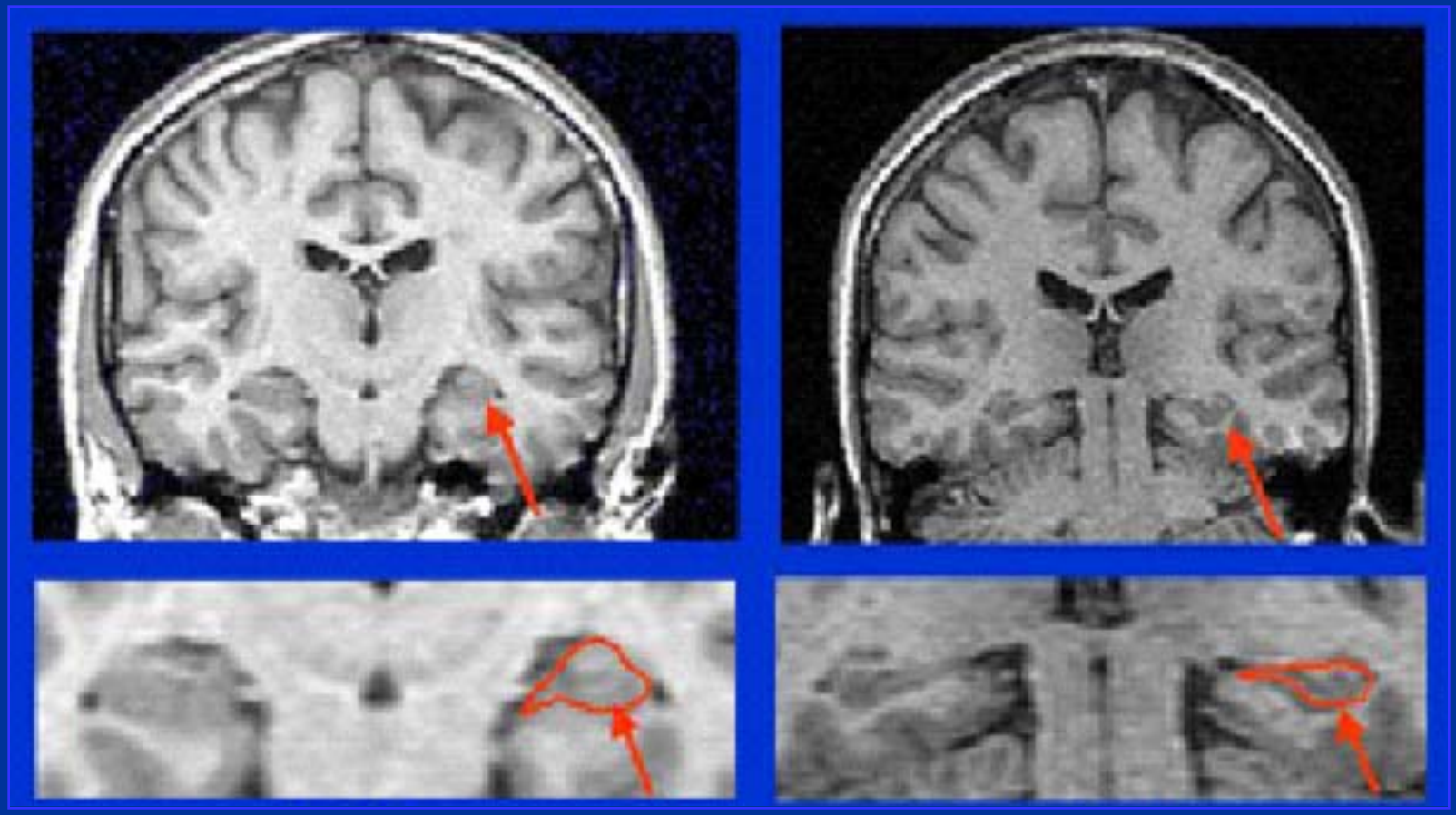
Psychobiology



Duman RS, et al. Biol Psychiatry. 2000;48:732-739.

Brain atrophy in depression?

Atrophy of the Hippocampus in Depression



Normal

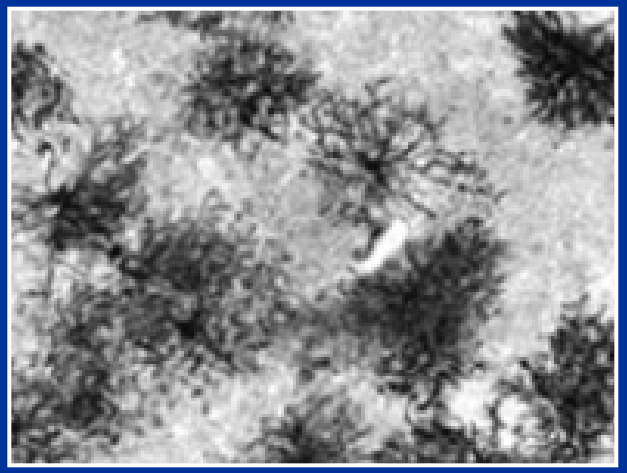
Depression

Bremner JD, et al. *Am J Psychiatry*. 2000;157(1):115-118.

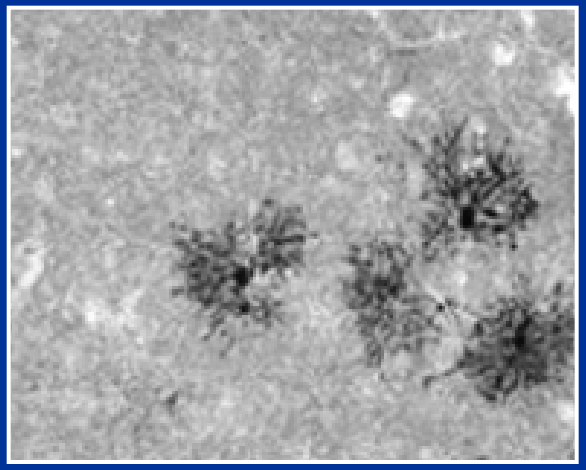
Glial Changes in the Prefrontal Cortex of a Depressed Patient

Glial immunoreactivity in the prefrontal cortex[1]

Control (27 years old)



MDD (32 years old)

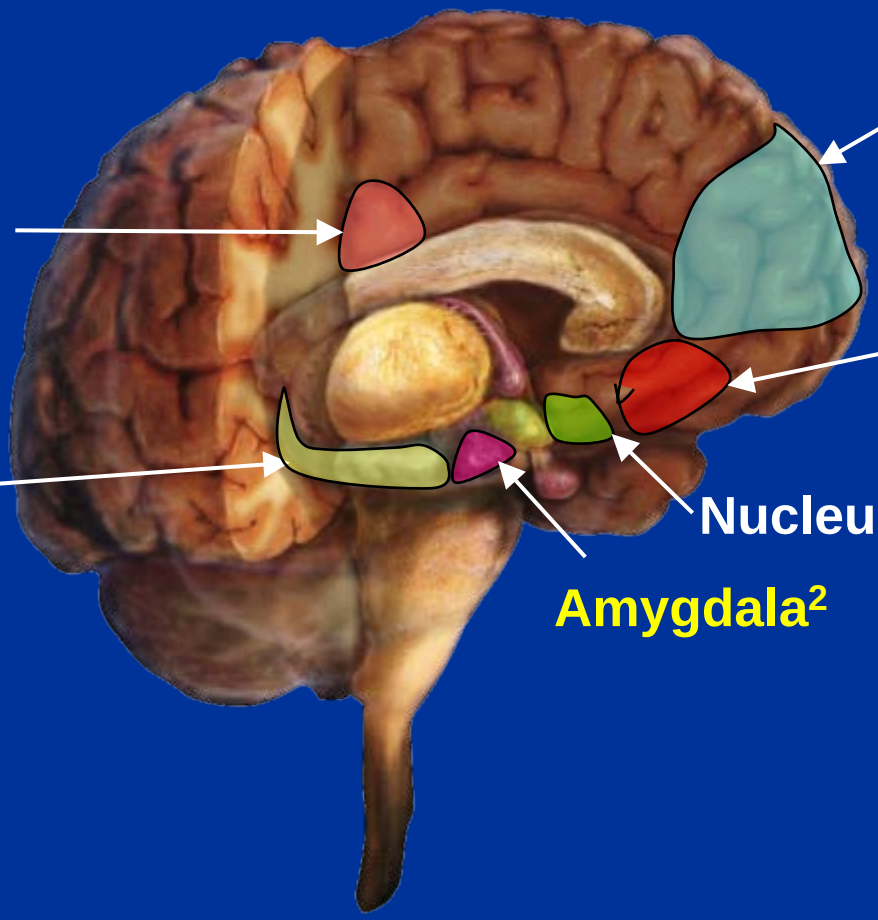


- Reduction in glial cell density and number is the most prominent feature of cell pathology in depression[1–4]

Images courtesy of Bentham Science Publishers.

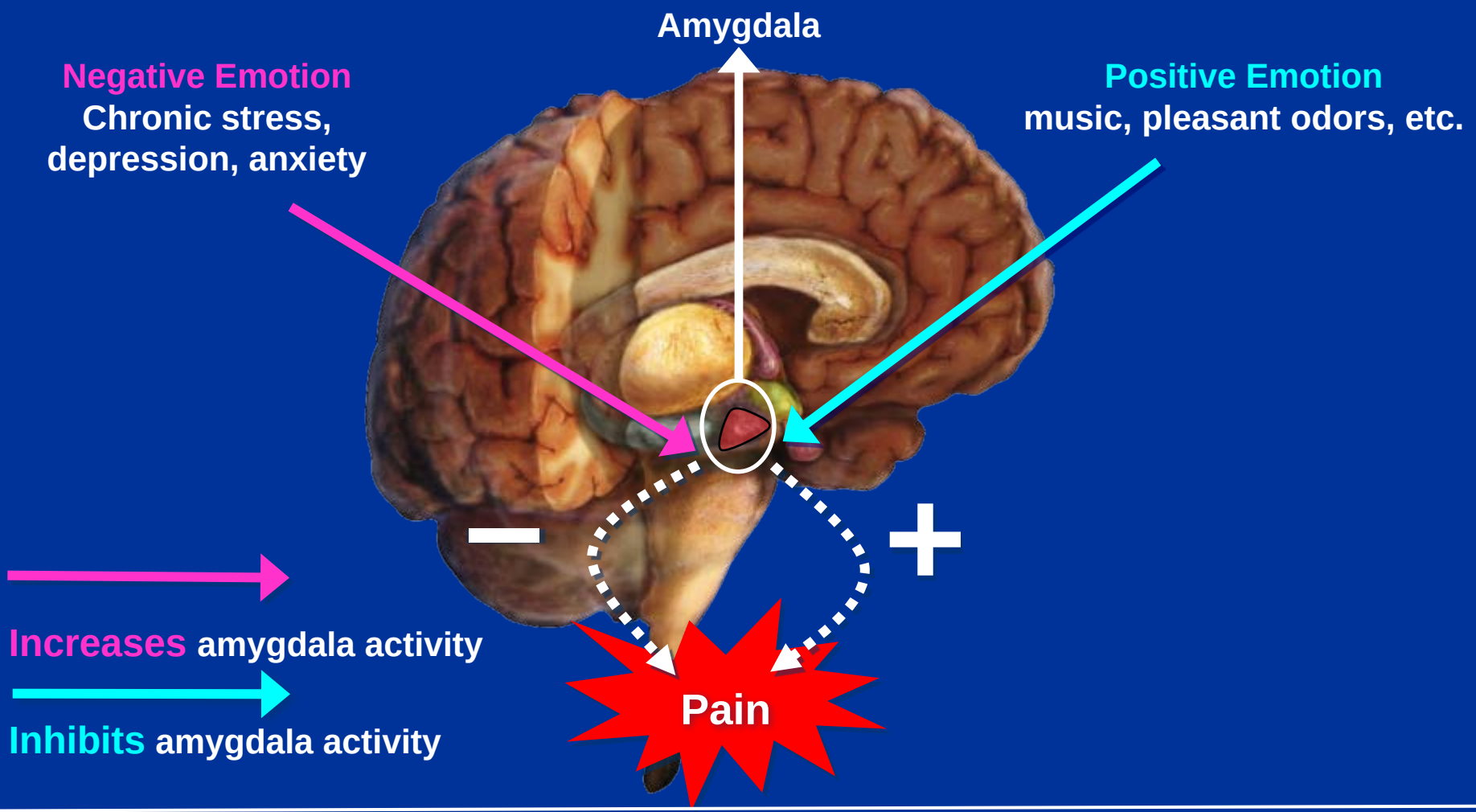
1. Rajkowska G, et al. *CNS Neurol Disord Drug Targets*. 2007;**6**:219–233. 2. Rajkowska G, et al. *Biol Psychiatry*. 1999;**45**:1085–1098. 3. Ongür D, et al. *Proc Natl Acad Sci USA*. 1998;**95**:13290–13295. 4. Si X, et al. *Neuropsychopharmacol.* 2004;**29**:2088–2096.

Areas of the Brain Implicated in MDD



1. Kennedy SE, et al. *Arch Gen Psychiatry*. 2006;**63**:1199–1208. 2. Drevets WC. *Curr Opin Neurobiol*. 2001;**11**:240–249. 3. Whittle S, et al. *Neurosci Biobehav Rev.* 2006;**30**:511–525. 4. Schlaepfer TE, et al. *Neuropsychopharmacology*. 2008;**33**:368–377. 5. Gaughran F, et al. *Brain Res Bull*. 2006;**70**:221–227.

The Amygdala as a Primary Modulator: Emotions and Stress Effects Amygdala Response to Pain (Hypothetical Model)



Modified from: Neugebauer V, et al. *Neuroscientist.* 2004;**10**:221–234.

Key brain areas involved in regulation of mood

(A) Ventromedial prefrontal cortex (VMPFC)[1]

– Modulates pain and aggression, and sexual and eating behaviors

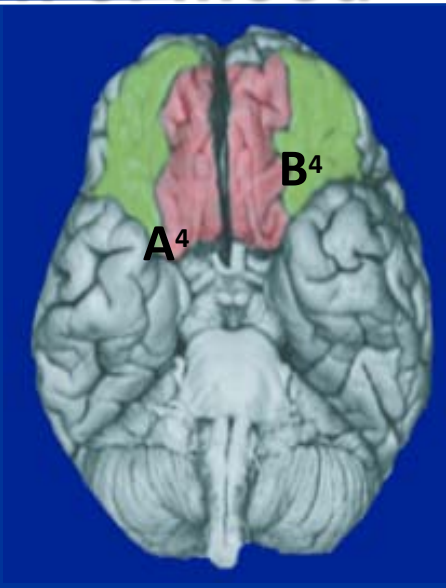
(B) Lateral orbital prefrontal cortex (LOPFC)[2]

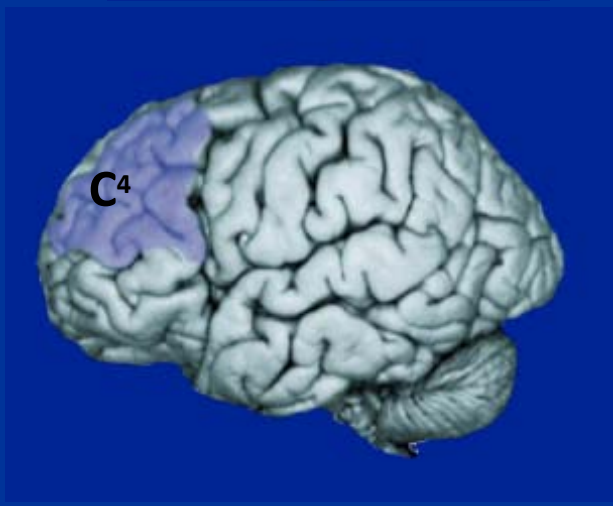
– Activity is increased in depression,

(C) Dorsolateral prefrontal cortex (DLPFC)[3]

– Cognitive control,

– Hypoactivity of DLPFC in depression

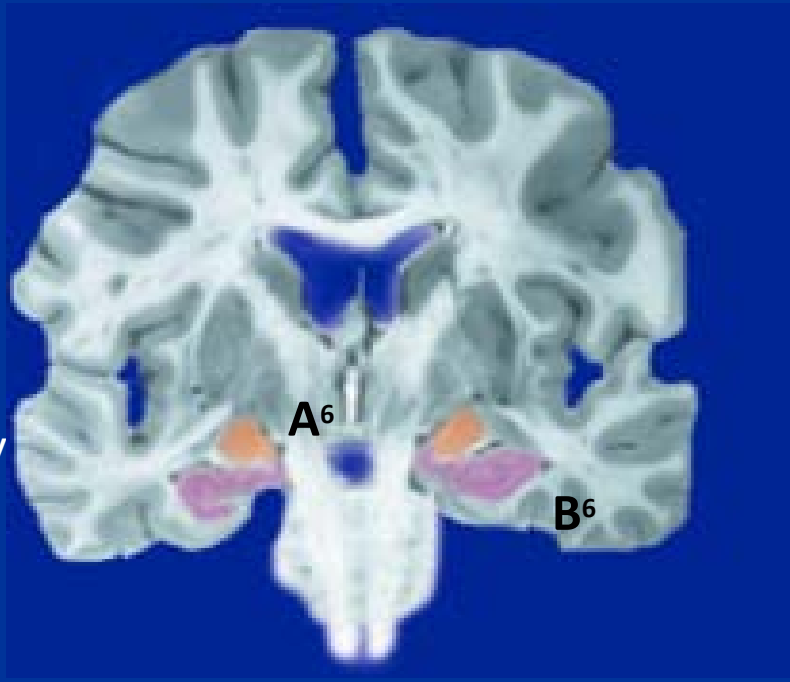




1. Öngür D, Price JL. *Cereb Cortex.* 2000;10(3):206-219.
2. Drevets WC. *Annu Rev Med.* 1998;49:341-361.
3. MacDonald AW III, et al. *Science.* 2000;288(5472):1835-1838.
4. Davidson RJ, et al. *Annu Rev Psychol.* 2002;53:545-574.

Key brain areas involved in regulation of mood(cont.)

- (A) Amygdala:
  - Role in emotional learning and memory
  - Activation of amygdala correlates with degree of depression[2]
- (B) Hippocampus: has a role in memory[3,4]
  - Rich in corticosteroid receptors[5]
  - Regulatory feedback to hypothalamic-pituitary adrenal axis



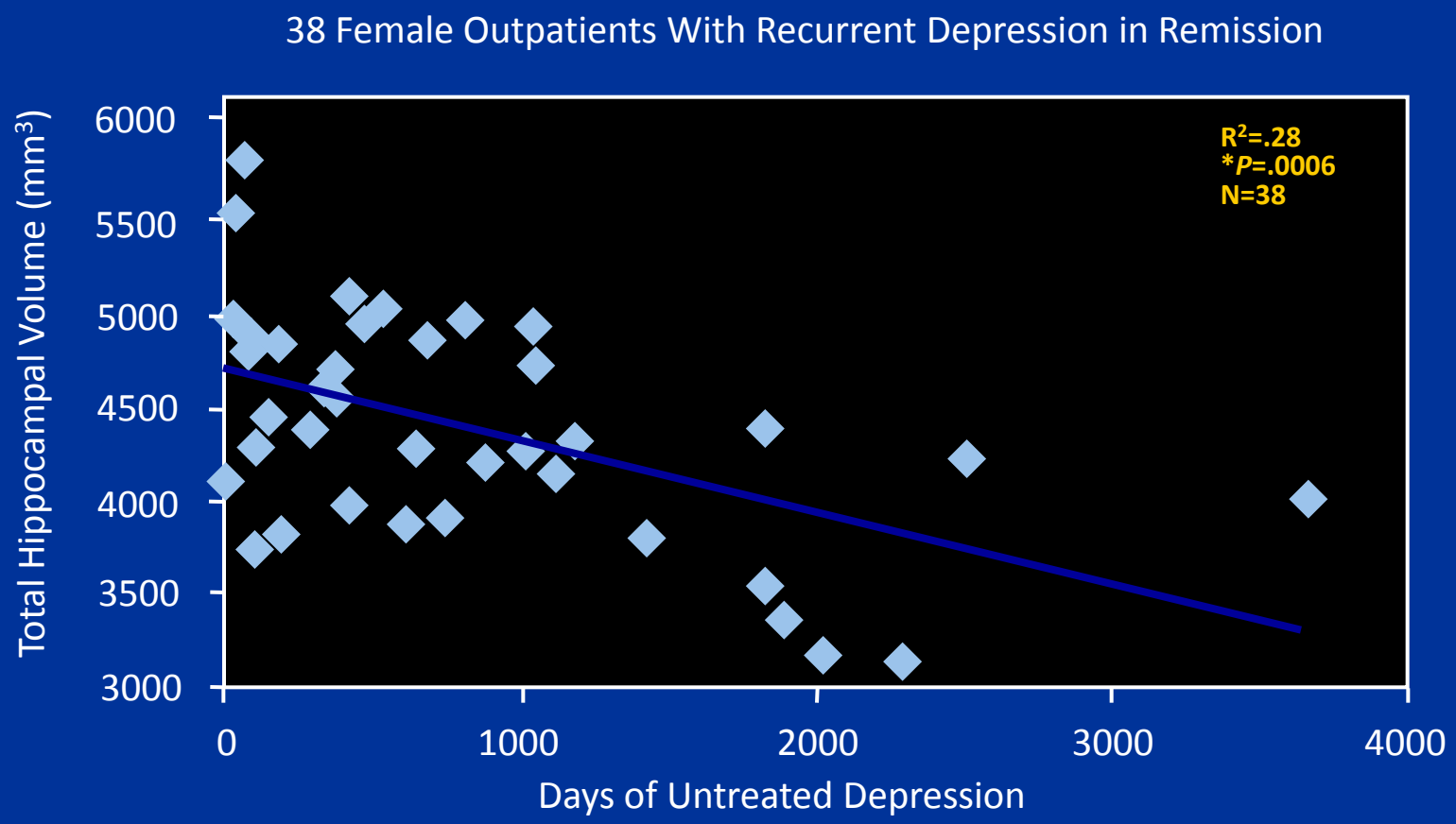
1. Davidson RJ. *Psychophysiology.* 2003;40(5):655-665.
2. Drevets WC. *Curr Opin Neurobiol.* 2001;11(2):240-249.
3. Squire LR, Knowlton BJ. In: Gazzaniga MS, ed. *The New Cognitive Neurosciences;* 2000:765-779.
4. Fanselow MS. *Behav Brain Res.* 2000;110(1-2):73-81.
5. Reul JM, De Kloet ER. *J Steroid Biochem.* 1986;24(1):269-272.
6. Davidson RJ, et al. *Annu Rev Psychol.* 2002;53:545-574.

Hippocampus: The “weak link”?

- A combination of excessive excitatory input from the VMPFC and increased levels of glucocorticoids may have a “toxic” effect on the hippocampus → apoptosis

1
Sheline YI. *Biol Psychiatry*. 2000;48(8):791-800.

Correlation between hippocampal volume and duration of untreated depression*

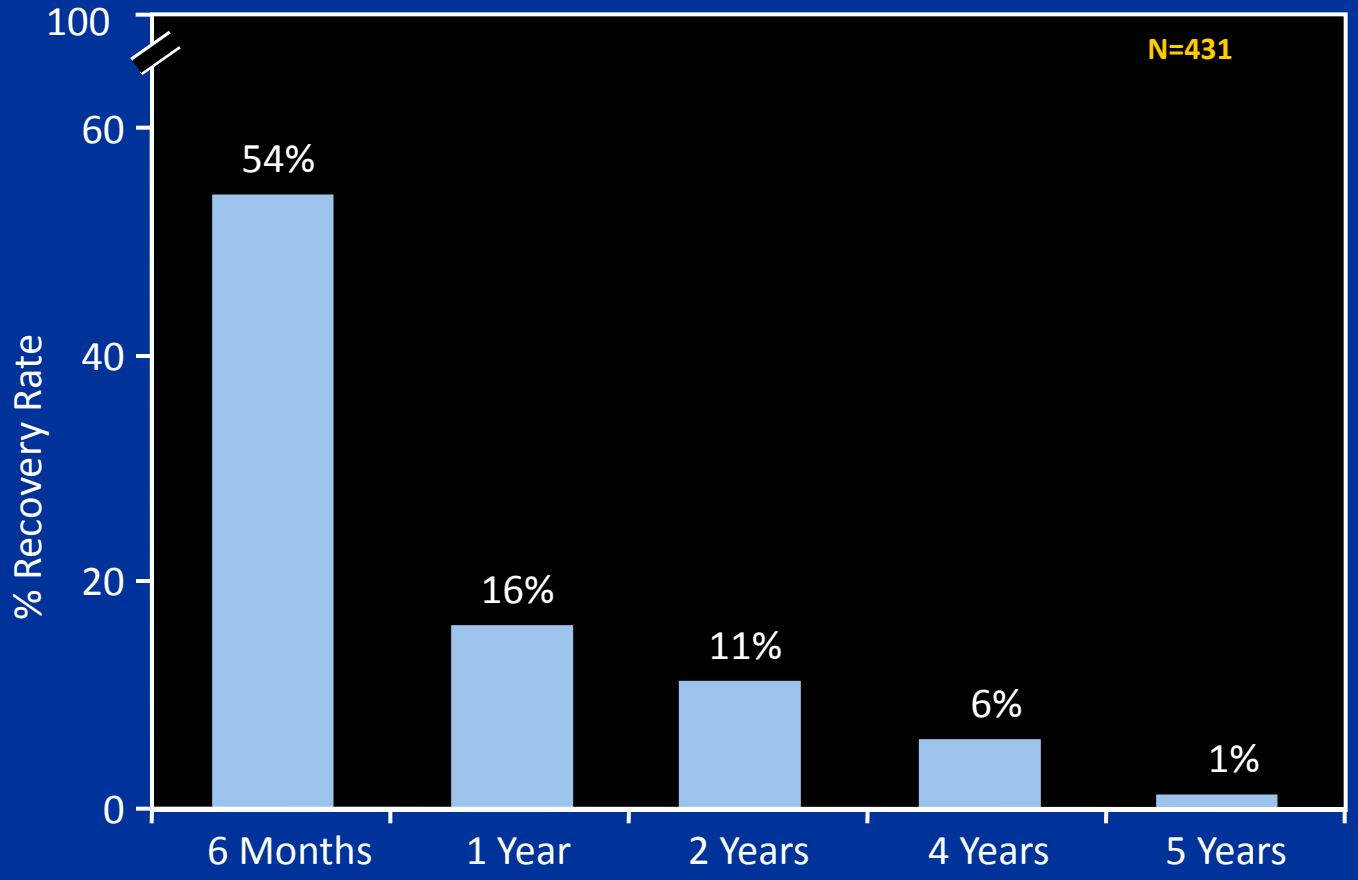


***Significant inverse relationship between total hippocampal volume and the length of time depression went untreated.**

Sheline YI, et al. *Am J Psychiatry*. 2003;160(8):1516-1518.

- Remission and response

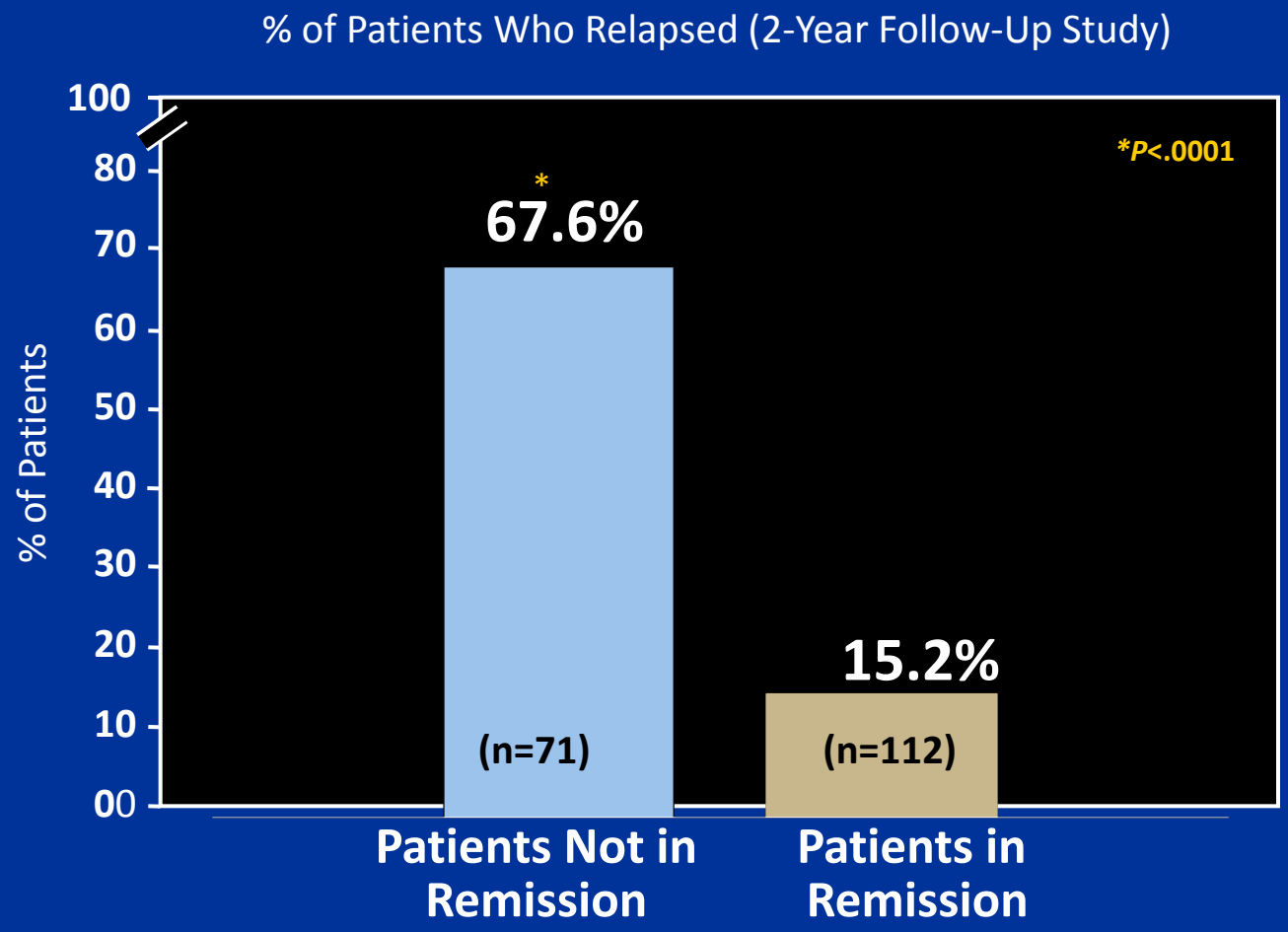
Rates of recovery diminish w/ duration of MDD



Recovery=8 weeks of Psychiatric Status Rating (PSR) 1 or 2.
Recovery=sustained remission.

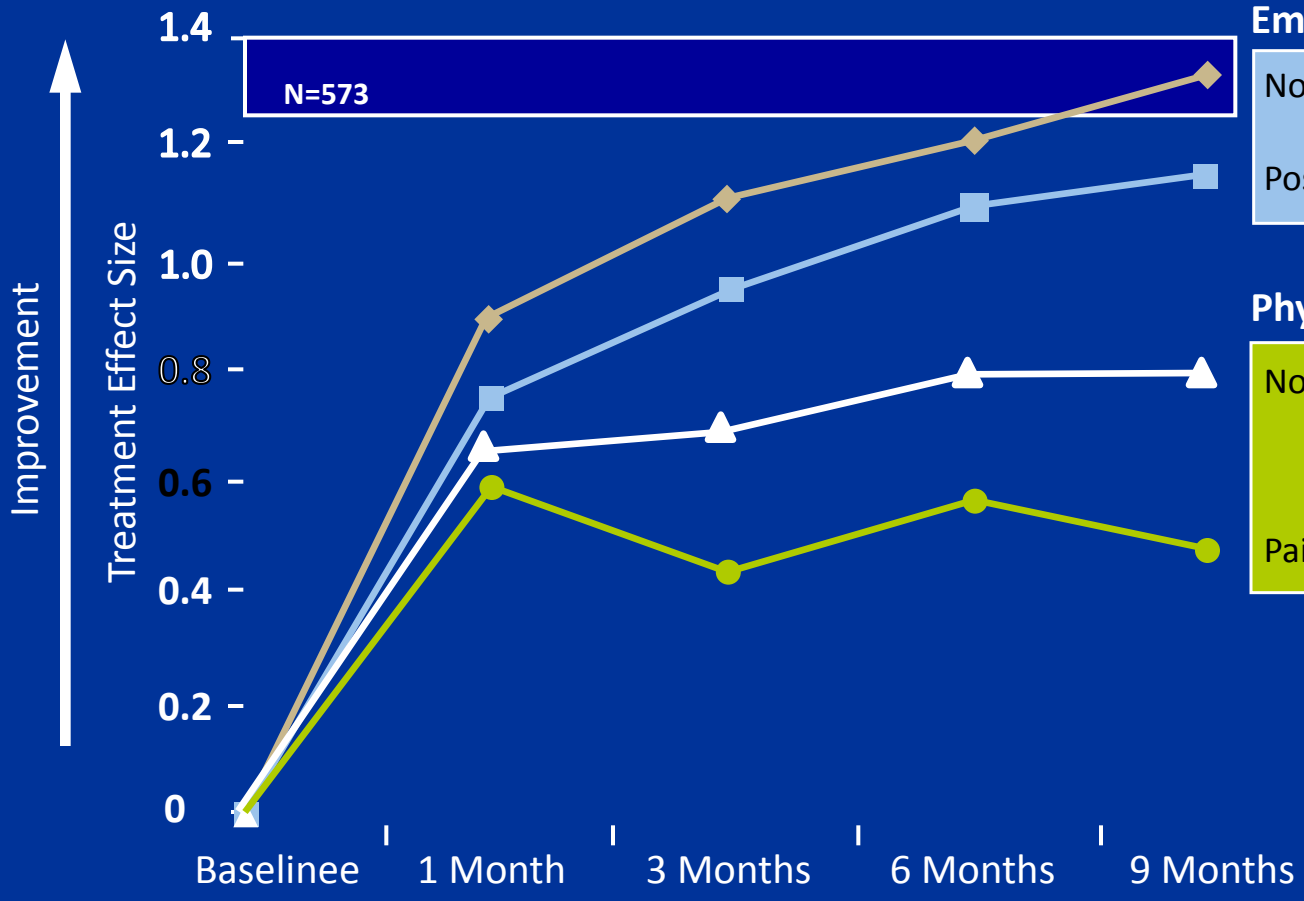
Keller MB, et al. *Arch Gen Psychiatry*. 1992;49(10):809-816.

What happens if remission is not achieved?



Pintor L, et al. *J Affect Disord.* 2003;73(3):237-244.

ARTIST: Over time, emotional and physical symptoms respond differently to therapy



Emotional Symptoms

Nonsomatic depressive symptoms

Positive well-being

Physical Symptoms

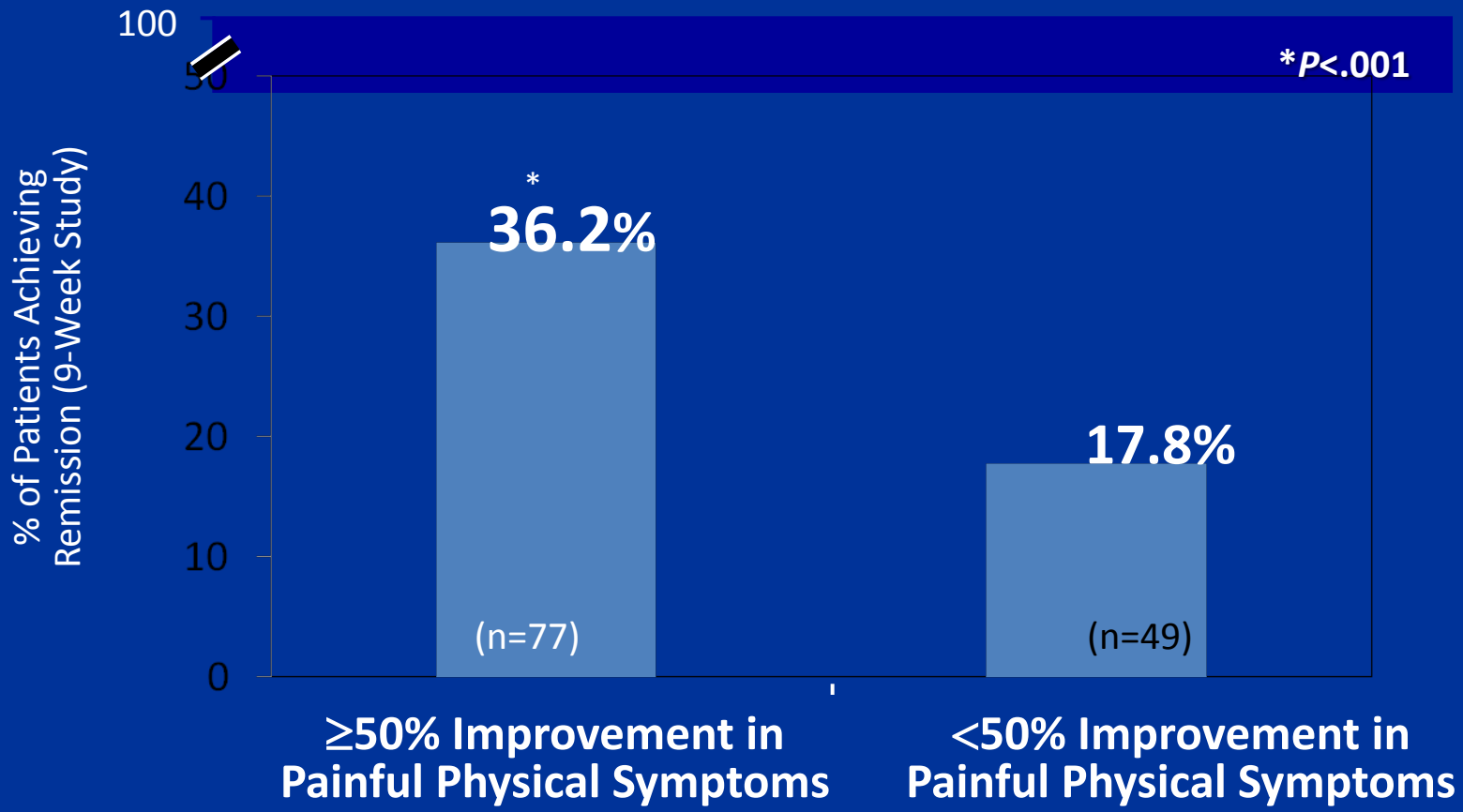
Nonpain somatic symptoms

Pain somatic symptoms

ARTIST=A Randomized Trial Investigating SSRI Treatment.

Adapted from: Greco T, et al. *J Gen Intern Med*. 2004;19(8):813-818.

Pain symptom improvement increases chances of remission

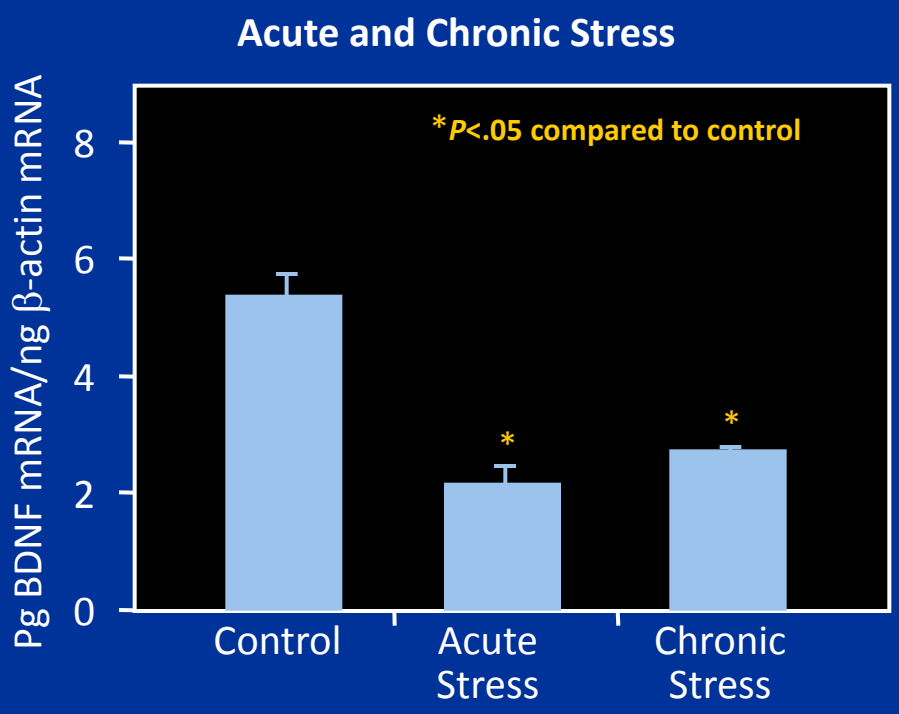


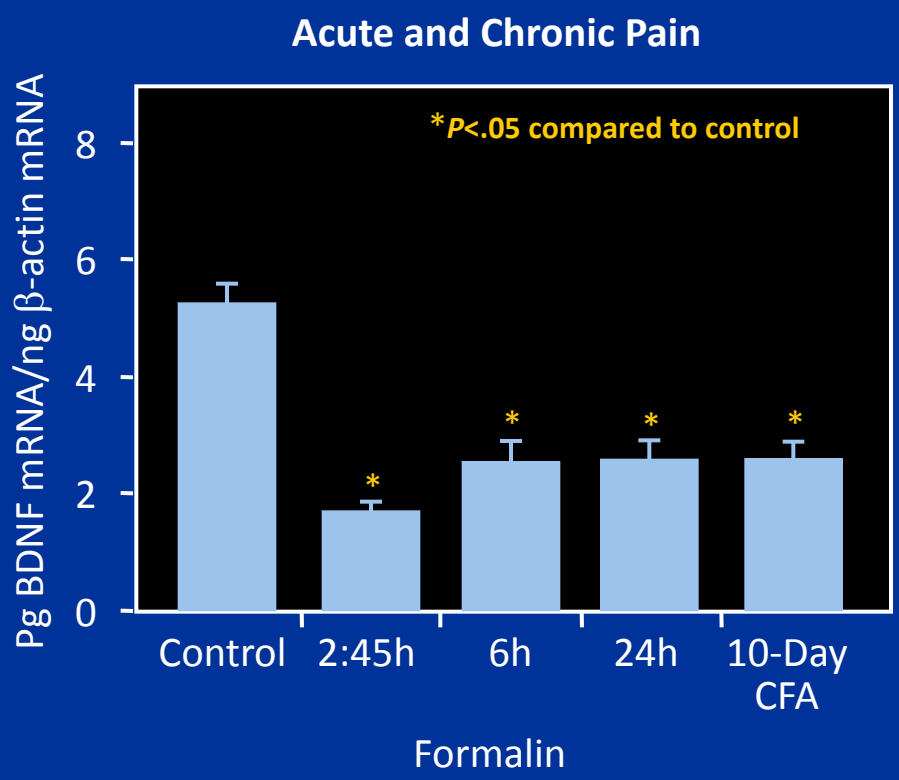
Remission defined as HAM-D_{17} Total Score ≤7. Painful physical symptom improvement was measured by the Visual Analog Scale (VAS) overall pain score.

Fava M, et al. *J Clin Psychiatry.* 2004;65(4):521-530.

Pain and stress lower BDNF gene expression in animal models

Changes in Hippocampal BDNF Synthesis





CFA=complete Freund's adjuvant.

Duric V, McCarson KE. *Neuroscience.* 2005;133(4):999-1006.

Restoring homeostasis and harmony

- Continuous AD use may be associated with increased 5-HT and/or NE in the prefrontal cortex and limbic system
- Effective AD treatment may be associated with decreased activity in the VMPFC

1. Mayberg HS, et al. *Biol Psychiatry*. 2000;48(8):830-843.
2. Brody et al. *Biol Psychiatry*. 2001;50:171-178.
3. Duman RS. *Neuromolecular Med.* 2004;5(1):11-25.