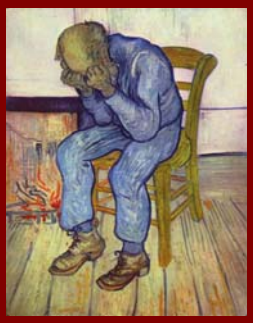
Depression: Voluntary or involuntary?

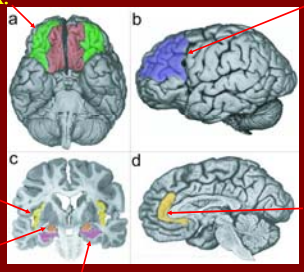


Depression: Neural circuitry & psychotherapeutic learning

- Neural circuitry supporting emotional cognition
- Stress-related neuroplasticity
- Treatment-related neuroplasticity

Tutorial: Neuroanatomy of Emotion

Key Brain Areas and Their Affect-related Functions



Orbitofrontal cortex: Affective evaluation; decoding punishment and reward value

Dorsolateral PFC: Approach- and/or withdrawal-related affect

Insula: Representation of the body's internal state; interoception

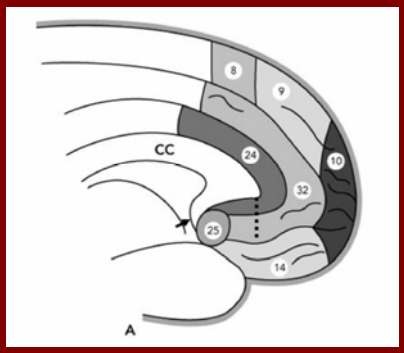
Anterior cingulate cortex (ACC): Top-down modulation; conflict detection; perception of "self"

Amygdala: Vigilance for motivationally salient events; threat detection; emotional memory

Hippocampus: Declarative memory; spatial navigation; contextual fear

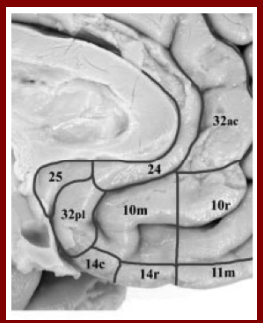
Insula and ACC: Integration of sensory, affective, cognitive, and autonomic processing

Medial Prefrontal Cortex (mPFC)



See supplemental data in Hamani, Mayberg, et al. 2011 *Biological Psychiatry.*

Medial Prefrontal Cortex (mPFC)

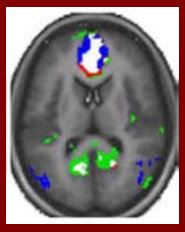


See supplemental data in Hamani, Mayberg, et al. 2011 *Biological Psychiatry.*

Emotional Cognition in Depression

- Inward-focused attention
- Rumination
- Difficulty with cognitive reappraisal & emotion regulation
- Negative cognitive bias
  - Interpretation bias
  - Memory bias

Inward attention at rest and during introspective tasks

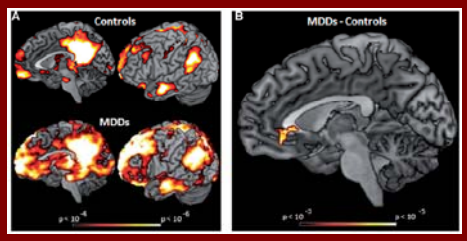


Buckner et al. (2008) *Annals NY Acad Sci*.

Increased subgenual PFC connectivity in depression

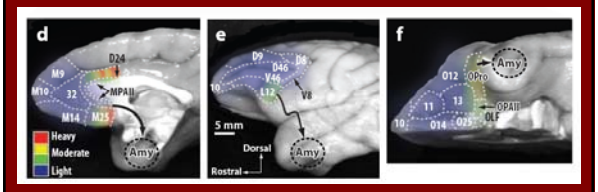
Grecius et al. (2007) *Biological Psychiatry*.

Increased subgenual PFC connectivity in depression



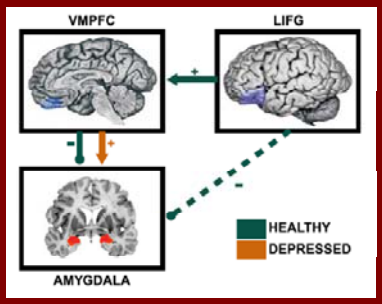
Berman et al. (2011) *SCAN*.

Anatomical projections from PFC to amygdala in rhesus monkeys



Ghashghaei, HT (2007) Neuroimage.
Also see Salzman & Fusi (2010) Annual Review Neurosci.

Loosening of regulatory control of PFC over subcortical circuitry



Johnstone et al. (2007) *J Neuroscience*.

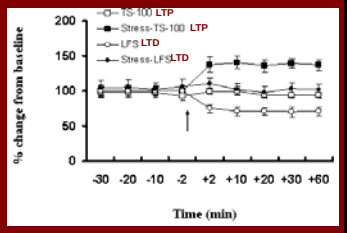
Neural alterations associated emotional cognition in depression

- Inward-focused attention (increased subgenual PFC connectivity?)
- Difficulty with emotion regulation (decreased frontal inhibition of amygdala?)
- Negative biases in learning & memory (amgydalar influence over hippocampal memory processes?)

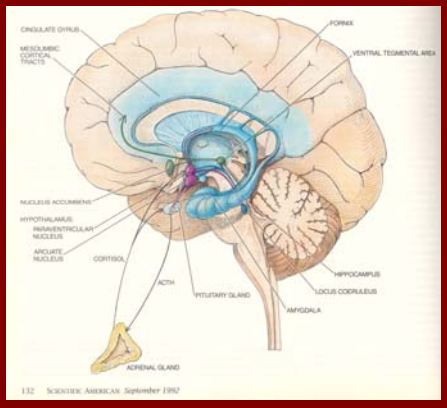
vmPFC stimulating electrodes

amygdala recording electrodes

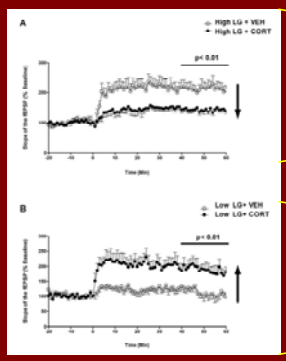
In rats, stress reverses PFC-amygdala plasticity



Maroun (2006) *European J Neuroscience*.



Hippocampal neurons

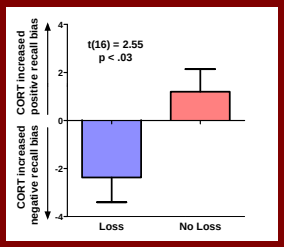


History of *high* maternal care: cort *decreases* synaptic strength

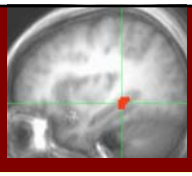
History of *low* maternal care: cort *increases* synaptic strength

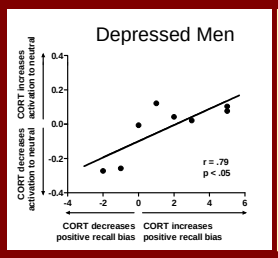
Champagne et al., 2008 J Neuroscience.

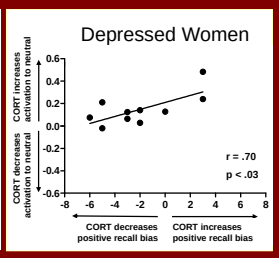
CORT altered memory bias in a negative direction only in depressed subjects with early loss



CORT's effects on hippocampus and memory are related







Abercrombie et al. (2011) *J Psychiatric Research*.

Stress-related neuroplasticity

- Stress alters PFC-amygdala plasticity
- Individual differences in the effects of stress & stress hormones
  - on learning
  - on hippocampal activation and/or plasticity

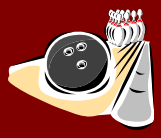
Therapeutic Learning

- Learning
  - Acquiring new information and/or skills
  - Altering/adapting behavior to meet environmental demands or contingencies
- Neuroplasticity
  - Experience-dependent changes in brain structure or function
- Promotion of learning and neuroplasticity
- Medications may enhance neuroplastic mechanisms; changes in neural circuitry need to be sculpted through learning

Practice & Repetition

- Behavior-induced structural brain changes occur
- Building new neural circuits requires REPETITION of the new behavior
- "Behavior" refers to thought as well as action
- How does this apply to CBT?

Depressogenic cognitions: The mental gutter



Cognitive Behavioral Therapy: Practice & Repetition

- *1. Notice automatic thoughts and habits*
- *2. Self-validation*
- *3. Apply new skill*

Changing behavioral and *mental* habits requires PRACTICE

- Insight re: the automatic thought or habit is not particularly useful unless the new skill is practiced repeatedly

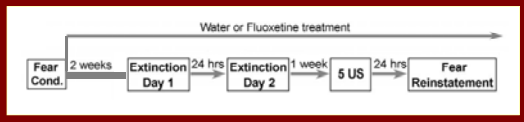
Pharmacological enhancement of therapeutic learning

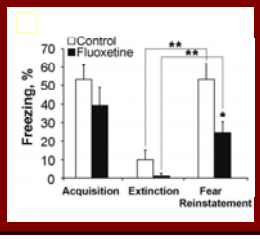
"The joint use of pharmacological and psychotherapeutic interventions might be especially successful because of a potentially interactive and synergistic—not only additive—effect of the two interventions.

Psychopharmacological treatment may help consolidate the biological changes caused by psychotherapy."

Eric R. Kandel, M.D., 1998

In the absence of extinction training, fluoxetine (Prozac) did not alter the amount of fear behavior (freezing) in mice. Rather, fluoxetine added durability to extinction learning.





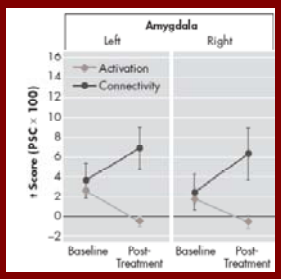
Karpova et al. (2011) *Science.*

Progress in our understanding of pharmacological enhancement of therapeutic learning

"The pharmacological effects of antidepressants need to be combined with psychological rehabilitation to reorganize networks rendered more plastic by the drug treatment."

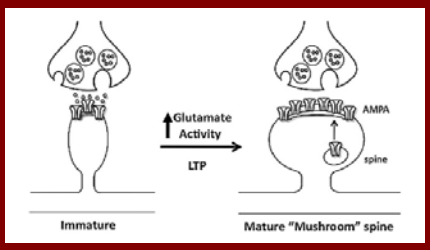
Karpova et al. (2011) *Science.*

Increase in ACC-amygdala functional connectivity with 6 wks sertraline

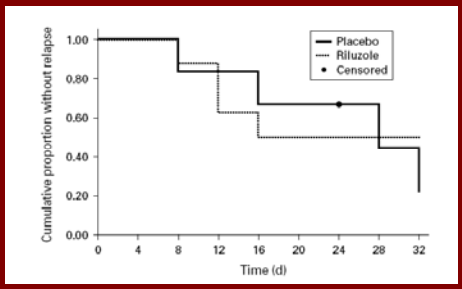


Anand, et al. (2007) *J Neuropsychiatry & Clin Neurosci.*

Ketamine increases synaptic and structural plasticity



Duman et al. (2012) *Neuropharmacology*.



Mathew et al. (2010) *International J Neuropsychopharm.*

Therapeutic Learning & Neuroplasticity

- Insight not enough; must practice new thoughts & behaviors
- Medication may promote neuroplasticity in crucial neural circuit, but functional adaptation may require practicing new thoughts/behaviors
- Pharmacological augmentation of therapeutic learning in depression: On the horizon!

What is depression? Despair & impairment associated with (malleable) neural circuitry