The Brain as a Regulator of Emotional Homeostasis
Primary Role of Amygdala in Fear Conditioning

- Impaired fear conditioning in Kluver-Bucy Syndrome
- LeDoux: “High Road” vs. “Low Road”
Major Connections of the Amygdala
Limbic Arousal and Regulation

- In humans we recognize the role of both medial and ventral lateral prefrontal cortex in inhibiting emotional responses
- Major medial PFC connections to the amygdala
MPFC connections to amygdala, HC and BG in non-human primates

from Price and Drevets, Neuropsychopharmacology, 2009
Match Affect

\[ z = -22 \]

Label Affect

\[ z = -22 \]

From Hariri et al. 1999
Cortical Influence During “Label”

From Hariri et al 1999
Amygdalar Response

From Hariri et al 1999
R. PFC Response

From Hariri et al 1999
Subconscious processing and amygdala

Emotional Regulation through conscious re-appraisal: Brain areas responsive to the regulation instructions

a. Left Inferior Frontal Gyrus (BA 44)

b. Left Superior Frontal Gyrus (BA 9)

c. Left Anterior Dorsal Medial Frontal Gyrus (BA 10)

d. Left Superior Dorsal Medial Frontal Gyrus (BA 6)

Two regions in left (L) and right (R) VMPFC demonstrate an inverse across-subjects correlation with the left amygdala.

Summary of regions involved in fear responses

- Amygdala involved in emotional arousal and conditioned fear; ACC and insula also active during increased fear states
- Ventromedial prefrontal cortex (vmPFC) involved with extinction of the fear response, modulated during reappraisal inverse to amygdala
- Both hippocampus and insular are associated with extinction of fear
- Ventrolateral PFC involved in labelling, conscious appraisal of affect, inversely correlates with amygdala
- Dorsal, superior and dorsomedial PFC correlates positively with amygdala activity- accentuates
- Dorsal ACC associated with anticipatory anxiety
- Rostral ACC associated with regulation and control of anxiety
Anxiety Disorders

- Not a simple relationship between regions and disorders
  - Excessive anxiety response (amygdala)
  - Undue attention, vigilance to anxiety stimuli
  - Decreased cortical processing of anxiety
  - Decreased cognitive control over anxiety
  - Decreased habituation/extinction of anxiety responses
  - Increased memory for anxiety experiences; poor contextualization of learned responses (overgeneralization)

- Genetic and environmental vulnerabilities
PTSD

- Numerous studies showing hyperactive responses in amygdala to both fear related stimuli and other stimuli, i.e., fearful faces (eg Rauch et al 2000; Whalen et al 1998)
- Attenuated responses in rACC (eg Shin et al 2001)
- Attenuated responses in medial PFC, negatively correlated with amygdala
Panic Disorder

- Similar to PTSD: amygdala hyperreactivity model, with decreased frontal control
- Increased rACC activity to panic imagery (eg Bystritsky 2001)
- Some evidence for increased resting glucose metabolism in brainstem, pons, and decreased GABAergic binding in pons and raphe
fMRI of Panic Imagery

(Bystritsky et al 2001)
Social anxiety and specific phobias

- Amygdala hyperreactivity
- Mixed findings in insula, rACC, dACC

FROM:
The Neurocircuitry of Fear, Stress, and Anxiety Disorders
Lisa M Shin and Israel Liberzon

Table 1. Summary of the Direction of Functional Neuroimaging Findings in Anxiety Disorders

<table>
<thead>
<tr>
<th></th>
<th>Amygdala</th>
<th>rACC</th>
<th>dACC</th>
<th>Hippocampus</th>
<th>Insular cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posttraumatic stress disorder</td>
<td>↑↓*</td>
<td>↓</td>
<td>↑*</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>↑↑*</td>
<td>↑</td>
<td>—</td>
<td>↑↓</td>
<td>—</td>
</tr>
<tr>
<td>Social phobia</td>
<td>↑</td>
<td>↑↓*</td>
<td>↑↓</td>
<td>—</td>
<td>↑</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<td>↑</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>↑↓*</td>
<td>↑</td>
<td>↑*</td>
<td>↑</td>
<td>—</td>
</tr>
</tbody>
</table>

rACC = rostral anterior cingulate cortex; dACC = dorsal anterior cingulate cortex.
↑ = increased function in the disorder (relative to control groups).
↓ = decreased function in the disorder (relative to control groups).
↑↓ = mixed findings.
* = based on a very small number of studies.
— = too little information available.
Genetic effects on anxiety risk

- 5-HTT promoter polymorphism on chromosome 17 - serotonin transporter gene, short form, associated with anxiety
- Used the same emotional face paradigm
- Subjects with the short allele activated the amygdala significantly greater than those with the long allele (Hariri et al, Science July 2002 Vol 297)
Amygdala response:

5HTT short allele > Long allele

Cohort 1

Cohort 2
5HTT and imaging
Summary of Limbic Circuitry

- Amygdala signals critical for fear/anxiety responses
- These are interpreted and regulated by frontal regions (MPFC, VLPFC, ACC)
- Most anxiety disorders associated with disruption in this system
- Increased amygdala responsiveness, varying degrees of impaired frontal regulation
Fronto-Striatal Circuits

Adapted from Alexander GE, DeLong MR, Strick PL 1986
Fronto-Striatal Circuits

Motor

Dorsolateral Pre-frontal

Lateral orbitofrontal

Anterior Cingulate

Cortex

Striatum

Pallidum/Sub. nigra

Thalamus

Cortex: SMA, APA, MC, SC

Striatum: Put, Vi-Gpi, Cl-SNr

Pallidum/Sub. nigra: Idm-Gpi, rl-SNr

Thalamus: Vlo, VLM

Dorsolateral Pre-frontal: DLC, PPC, APA

Lateral orbitofrontal: LOF, STG, ITG, ACA

Anterior Cingulate: ACA, HC, EC, STG, ITG

Adapted from Alexander GE, DeLong MR, Strick PL 1986
Working Memory Circuits

Mitchell DJ, Cusack R
Statistical maps for task 2 in which regional brain activation increased with increasing memory set size in healthy control subjects (A), in schizophrenic patients (B), and in controls compared with patients (C).

Fronto-Striatal Circuits

Motor
- Cortex: SMA
- Striatum: Put
- Pallidum/Sub. nigra: Vi-Gpi Cl-SNr
- Thalamus: Vlo, VLM

Dorsolateral Prefrontal
- Cortex: DLC
- Striatum: DI Caud (h)
- Pallidum/Sub. nigra: Idm-Gpi rl-SNr
- Thalamus: VApC, MDpc

Lateral orbitofrontal
- Cortex: LOF
- Striatum: Vm Caud (h)
- Pallidum/Sub. nigra: mdm-Gpi rm-SNr
- Thalamus: M-Vamic, MDmc

Anterior Cingulate
- Cortex: ACA
- Striatum: VS
- Pallidum/Sub. nigra: ri-Gpi rd-SNr
- Thalamus: Pm-MD

Adapted from Alexander GE, DeLong MR, Strick PL 1986
OCD

- Circuit involving the orbitofrontal cortex, the anterior cingulate/caudal medial prefrontal cortex, and the caudate nucleus
- Hyperactivity in ACC, OFC
- Deficiency in circuitry such that activated behavioral programs which should satisfy a signal to perform an action do not
- Possibly impaired interpretation of reward signals
Emotional Face Processing in OCD (S. Rausch)

Figure 2. Percent signal change for facial expressions versus fixation in left and right amygdala for OCD and HC groups. OCD, obsessive-compulsive disorder; HC, healthy control.
Disgust and Threat Responses in OCD (Shapiro 2002)
Mood Disorders and medial PFC

From Price and Drevets 2010
The cytoarchitectonic subdivisions of the human medial prefrontal (right) and orbital (left) cortex surfaces are distinguished here as being predominantly in the medial (red) and orbital (yellow) prefrontal networks. The orange areas are part of the dorsal prefrontal system. Modified from Öngür et al, 2003. From: Price and Drevets, 2009
Bipolar Disorder- Manic State: Altshuler et al 2005

**Figure 1.** Statistical parametric mapping results for control and manic subjects on NoGo minus Go task. **Top:** Activation in control subjects (n = 13) during NoGo minus Go condition (p = .0001, uncorrected, k = 10 voxels). **Bottom:** Manic patients (n = 11) show no activation during NoGo minus Go condition (p = .0001, uncorrected, k = 10 voxels).
fMRI in Mania
(Altshuler et al 2005)
Reversal Learning - Response inhibition

From Xue, Ghahremani and Poldrack 2008
Response Inhibition- Go-NoGo

From Durston et al 2008
Fronto-Striatal Circuits

Motor

Cortex

SMA

Put

SMA

Put

Motor

Cortex

SMA

Put

Dorsolateral Prefrontal

Cortex

SMA

Put

DLC

DLC

Put

Lateral orbitofrontal

Cortex

SMA

Put

DLC

LOF

Cl-SNr

CL-SNr

Put

Anterior Cingulate

Cortex

SMA

Put

DLC

LOF

DLC

Put

Adapted from Alexander GE, DeLong MR, Strick PL 1986
Reward Circuitry

- Reward system is a discrepancy calculator
- The absolute amount of reward is not important
- Expectations of outcome-positive vs negative experience
- Decision making is strongly affected by reward expectation
- Temporal discounting
Response to Reward during learning-monetary reinforcer

(Gharamani et al)
Drug users (cannabis) have heightened reward response during a gambling task

Nestor, Hester and Garavana
Social Rewards

- Social rewards may be primary reinforcers during early development
- Neonates orient preferentially to smiling faces (Legerstee et al., 1998)
- Reduced orientation to faces is seen early in autism (Dawson, et al., 1998; Osterling et al., 1994)
- Reward processing deficits could reduce social motivation
- Romantic and maternal love (Bartels & Zeki, 2004), attractive (Aharon et al., 2001) and happy faces (Phillips et al., 1998) and eye contact (Kempe et al., 2001), have shown reward-like responses in adults using fMRI
Monetary Reward Condition

- fMRI scans (3 Tesla) on 18 high-functioning ASD, 18 control children
- Separately model hemodynamic response to rewards and to learning

3.75 - 6.25 s

Monetary Feedback

“1” or “2”
Social Reward Condition

- Stimulus-response association is only probabilistic
- Seems random to subject
- Post test of explicit knowledge is at chance
Response to Rewards

Typical

Autism

Typical > Autism

Every occurrence of a reward (any type) vs. no-reward
Striatum is Involved in Language & Communication

- Artificial grammar learning (Lieberman et al., 2004)
- Subjects given sequences of letters with probabilistic sequences
- Presented novel sequences that follow the same rules
- Subjects can correctly classify them as right or wrong without knowing the rules or having learned the specific examples!

Lieberman et al., 2004 *J Cog Neuro*
Implicit Language Learning

TD - ASD

2Lang - rest

Exponential increase model as an index of learning
Social Cognition: Theory of Mind
Theory of Mind

Castelli et al, 2003 Brain
Imitation or “Mirror Neuron” deficit in Autism

- Mirror neurons: class of neurons first discovered in ventral premotor cortex (area F5) of the macaque (Gallese et al 1996; Rizzolatti et al 1996); Pars opercularis (BA 44), inferior frontal gyrus, is human homologue.

- Neurons fire during both the performance and observation of motor behavior; respond to intention: only fire for meaningful actions

- A dysfunctional mirror neuron system (MNS) in autism? (Williams et al 2001)

- MNS and limbic system may provide for the translation of an observed emotion into its internally felt significance
Chartrand and Bargh (1999) found a positive correlation between the Chameleon Effect and Dispositional Empathy.
Imitating and Observing emotions in autism

2 Separate Functional Runs
“Just look at the expression on each face”
“Imitate the expression you see on each face”

I. Watch faces
II. Imitate expressions

Angry
Fearful
Happy
Sad
Neutral

- 2 s +

faces

++

2 s
Activity During Imitation

TD Imitate

ASD Imitate

Imitate: TD > ASD

Motor areas

Visual areas

Mirror neuron area

TD > ASD

p<.05, corrected at cluster level

Center for Cognitive Neuroscience
Imitation: TD > Autism

- Anterior Insula
- Connection from mirror centers to emotion centers
- Ventral striatum: Reward Centers (happy faces)
- Amygdala: fear centers (negative faces)
Underconnectivity Model

Just et al 2004 Brain
Approaches to Mental Disorders

Separate Entities with potential co-morbidity

Vs. anatomical systems, different direction and loci of dysfunction

Mood Disorders
Anxiety Disorders
ADHD Disorders
OCD
Autism spectrum

Center for Cognitive Neuroscience
Some Reading

Joseph L Price and Wayne C Drevets Neurocircuity of Mood Disorders


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