Depression and Affective Neuroscience

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depression

- genetic vulnerability
- intrapsychic factors
- early life stress
- SES
- loss

- psychotherapy
- medication
- brain stimulation
- social support
- exercise
- nutrition
motivation

activation of emotion

generation of emotion

adapted from Berton and Nestler 2006 Nat Rev Neurosci
FRONTAL
planning
- WHAT and HOW to do

PARIETAL
the body and objects in space - WHERE things are

TEMPORAL
recognition of objects and people - WHO things are

VMPFC, ANTERIOR TEMPORAL
memory, emotion, reward - meaning, or, WHY to do or not to do

Marcel Mesulam, 2000
Principles of Behavior and Cognitive Neurology
A. ATLAS BUNDLE LIST

Bundles in left and right hemispheres

Arcuate fasciculus
- Direct Segment (red)
- Anterior Segment (green)
- Posterior Segment (yellow)

Inferior Longitudinal fasciculus (purple)
Inferior Fronto-Occipital fasciculus (violet)
Uncinate fasciculus (cyan)

Cingulum
- Cingulate long fibers (brown)
- Cingulate short fibers (light green)
- Temporal fibers (blue)

Corticospinal tract (orange)

Fornix (black)

Thalamic radiations
- Anterior radiations (gray)
- Superior motor radiations (teal)
- Superior parietal radiations (pink)
- Posterior radiations (light blue)
- Inferior radiations (ocre)

Interhemispheric bundles

Corpus Callosum
- Rostrum (fuchsia)
- Genu (dark blue)
- Body (dark green)
- Splenium (dark brown)
Kelley et al. 2005

The diagram illustrates the connectivity and functional integration of various brain regions, including PREFRONTAL CORTEX, MOTOR CORTEX, HIPPOCAMPUS, DORSAL STRIATUM, PALLIDUM, AMYGDALE, THALAMUS, HYPOTHALAMUS, and MIDBRAIN DOPAMINE CELLS. Arrows depict the direction of neural signals, with labels indicating specific functional connections:

- Executive function, impulse control, decision-making
- Motor planning
- Voluntary somatic motor output
- Habit learning
- Reward/motor integration and association
- Locomotor, digestive, defensive, reproductive behaviors (behavioral control columns)

Key nodes include:

- Acb CORE
- Acb SHELL
- MD Thalamus
- "Taste" Thalamus
- PV Thalamus
- LH
- PVN
- DMH
- VMH
- Arcuate
- NTS
- Primary ascending gustatory pathways
- Reward, unpredicted events

Nodes also indicate sensory and emotional processing inputs, such as multimodal sensory input, emotional processing, reward learning, and gustatory visceral input.
“resting state” networks

areas presumed to be connected
continuously active
dynamically interactive
correspond to functional studies

Yeo et al 2011 J Neurophysiol
default mode network

mind-wandering
daydreaming
stimulus-independent thought
simulation
episodic/autobiographical memory

Buckner et al 2008
DMN correlated with spontaneous cognition

Andrews-Hanna et al 2010 J Neurophysiology
attention network
switching attention

executive control/frontoparietal network
working memory
staying on task
maintaining focus

salience network
encoding “value”
monitoring errors
subjective experience (“aha” moments, craving, and more)
salience

working memory (fronto-parietal and dorsal attention)

sensory, auditory, motor

visual

DMN

 Doucet et al 2011 J Neurophysio
DMN

PCC
VMPFC

Salience network

ACC
dAIC

CEN

PPC
DLPFC

Dynamic switching

Internally directed action

Externally directed action

Uddin 2015 NATURE REVIEWS | NEUROSCIENCE

Medial view
Lateral view

Social inclusion
Social exclusion

Eisenberger 2012 Nat Rev Neurosci
Salience network implicated across many psychiatric disorders

gray matter loss across 6 diagnoses (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety) - the dorsal anterior cingulate, right insula, left insula

Goodkind et al 2015 JAMA Psychiatry
Emotion, instinct, drive

Attention, perception, regulation

Two-way or ‘circular’ causation

Tertiary-process cognitions
Largely neocortical

Secondary-process learning
Basal ganglia and upper limbic

Primary-process emotions
Raw affects deeply subcortical

Top-down cognitive regulations

Bottom-up learned influences
on ruminations and thoughts

Top-down learned control

Bottom-up instinctual influences
on learning and development

Panksepp and Solms 2012 Trends Cog Sci
# Table 1

Postulated relationships between basic emotional systems, common emotional processes, and major psychiatric disorders

<table>
<thead>
<tr>
<th>Basic emotional system (Panksepp, 1998a)</th>
<th>Emergent emotions</th>
<th>Related emotional disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEEKING (+ and −)</td>
<td>Interest</td>
<td>Obsessive compulsive</td>
</tr>
<tr>
<td></td>
<td>Frustration</td>
<td>Paranoid schizophrenia</td>
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<tr>
<td></td>
<td>Craving</td>
<td>Addictive personalities</td>
</tr>
<tr>
<td>RAGE (− and +)</td>
<td>Anger</td>
<td>Aggression</td>
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<tr>
<td></td>
<td>Irritability</td>
<td>Psychopathic tendencies</td>
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<tr>
<td></td>
<td>Contempt</td>
<td>Personality disorders</td>
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<tr>
<td></td>
<td>Hatred</td>
<td></td>
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<tr>
<td>FEAR (−)</td>
<td>Simple anxiety</td>
<td>Generalized anxiety disorders</td>
</tr>
<tr>
<td></td>
<td>Worry</td>
<td>Phobias</td>
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<tr>
<td></td>
<td>Psychic trauma</td>
<td>PTSD variants</td>
</tr>
<tr>
<td>PANIC (−)</td>
<td>Separation distress</td>
<td>Panic attacks</td>
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<tr>
<td></td>
<td>Sadness</td>
<td>Pathological grief</td>
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<tr>
<td></td>
<td>Guilt/shame</td>
<td>Depression</td>
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<tr>
<td></td>
<td>Shyness</td>
<td>Agoraphobia</td>
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<tr>
<td></td>
<td>Embarrassment</td>
<td>Social phobias, autism</td>
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<tr>
<td>PLAY (+)</td>
<td>Joy and glee</td>
<td>Mania</td>
</tr>
<tr>
<td></td>
<td>Happy playfulness</td>
<td>ADHD</td>
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<tr>
<td></td>
<td>Erotic feelings</td>
<td>Fetishes</td>
</tr>
<tr>
<td></td>
<td>Jealousy</td>
<td>Sexual addictions</td>
</tr>
<tr>
<td>LUST (+ and −)</td>
<td>Nurturance</td>
<td>Dependency disorders</td>
</tr>
<tr>
<td></td>
<td>Love</td>
<td>Autistic aloofness</td>
</tr>
<tr>
<td>CARE (+)</td>
<td>Attraction</td>
<td>Attachment disorders</td>
</tr>
</tbody>
</table>

**Key Brain Areas**
- SEEKING/Expectancy System: Nucleus Accumbens – VTA, Mesolimbic and mesocortical outputs, Lateral hypothalamus – PAG
- RAGE/Anger: Medial amygdala to Bed Nucleus of Stria Terminalis (BNST), Medial and perifornical hypothalamic to PAG
- FEAR/Anxiety: Central & lateral amygdala to medial hypothalamus and dorsal PAG
- LUST/Sexuality: Cortico-medial amygdala, Bed nucleus of stria terminalis (BNST), Preoptic hypothalamus, VMH, PAG
- CARE/Nurture: Anterior Cingulate, BNST, Preoptic Area, VTA, PAG
- PANIC/Seperation: Anterior Cingulate, BNST & Preoptic Area, Dorso medial Thalamus, PAG
- PLAY/Joy: Dorso-medial diencephalon, Parafascicular Area, PAG

**Key Neuromodulators**
- DA (+), glutamate (+), opioids (+), neurotensin (+), orexin (+), Many other neuropeptides
- Substance P (+), Ach (+), glutamate (+)
- Glutamate (+), DBI, CRF, CCK, alpha-MSH, NPY
- Steroids (+), vasopressin, & oxytocin, LH-RH, CCK
- oxytocin (+), prolactin (+), dopamine (+), opioids (+/-)
- opioids (-), oxytocin (-), prolactin (-), CRF (+), glutamate (+)
- opioids (+/-), glutamate (+), Ach (+), cannabinoids, TRH?
SEEKING (↓ PLAY) (↑ RAGE)

RAGE ↓ PLAY ↑ FEAR

FEAR ↓ PLAY, LUST, SEEKING ↑ RAGE

LUST

CARE ↓ GRIEF

PANIC/GRIEF ↓ PLAY ↑↓ SEEKING ↑ FEAR

PLAY

fundamentally dynamic system
PANIC/GRIEF System

Human sadness system

Guinea pig separation distress circuit

AC, CC, CB, DMT, PAG, VS, BN, dPOA

Cingulate gyrus

Panksepp 2003
Genetic measures
- Candidate genes associated with MDD (i.e., beyond the conventional monoamine focus)
- Candidate genes associated with biological mechanisms and metabolic pathways for antidepressant medications
- Serotonergic mechanisms
- Other mechanisms
- Genome-wide association studies

Molecular measures
- Neurotrophic factors and other growth factors
- Proinflammatory cytokines
- Impaired regulation of the hypothalamic-pituitary-adrenocortical axis

Neuroimaging measures
Abnormalities in anatomically-defined neural systems
- Subcortical neural systems for emotion and reward processing
- Medial prefrontal regions involved in processing and implicit regulation of emotion
- Lateral prefrontal cortical systems involved in cognitive control and voluntary or effortful regulation of emotion

Abnormalities in neurotransmitter-defined neural systems
- Medial prefrontal-limbic network, modulated by serotonin
- Reward network, centred on ventral striatum and medial prefrontal cortices, modulated by dopamine

Newer neuroimaging methodologies to study MDD
- Measurement of brain activity during rest

PANIC-shutdown model of depression
(Panksepp & Watt 2009)

**euthymia**

or

**depressive vulnerability**

↓

**loss:**

separation distress

↓

termination of separation distress:

reunion

sadness

shut down

decathexis

- baseline opioid and oxytocin tone (social contact, good internal objects)
- responsive DA system
- appropriate levels of other global neuromodulators (NE, ACh, 5-HT)

- impaired infrastructure due to history
- impaired infrastructure due to genes
- depressive intrapsychic factors:
  - intrapsychic conflict/defenses around grieving ("the shadow of the object"/relating to negative internal objects)

↑ HPA activation
↑ DA release, NE, ACh
↓ opioids
↑ dynorphin

**Bowlby: protest**

↑ opioids, oxytocin
↓ HPA activation
↑ DA tone

↓ opioids, oxytocin
↓ HPA activation
↓ DA tone
↑ PNS activation

↓

**depression**

- circadian disruption
- immune system - "sickness behavior"
- continued dynorphin activation?
- chronic HPA activation, leading to cognitive and immune problems, hypersensitive amygdala, other…

**Berton and Nestler, 2006**
Questions and discussion?

Tell me about your mother.
Additional slides
Neural interactions characteristics of brain emotional systems:

1) Various sensory stimuli can unconditionally access emotional systems;
2) Emotional systems generate instinctual motor outputs &
3) Modulate sensory inputs.
4) Emotional systems have positive feedback components which can sustain emotional arousal after precipitating events have passed.
5) These systems can be modulated by cognitive inputs, &
6) These systems can modify/channel cognitive activities.

Panksepp 2011 PLoS One