ZNZ Advanced Course in Neuroscience
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Limbic System II

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Limbic system – outline

1. Introduction
   - history
   - definition

2. Theories of hippocampal Function – rodent tests
   - declarative memory
   - episodic memory
   - cognitive map
   - relational memory

3. The hippocampus beyond memory
   - exploratory behavior and anxiety
   - species typical behaviors
   - home cage behavior

4. Emotions
   - general properties
   - rodent models: fear and anxiety

5. Anatomy of the Amygdala
   - components
   - extended amygdala

6. Amygdala and fear conditioning
   - behavioral model
   - brain circuits

7. Amygdala and anxiety
   - behavioral model
   - brain circuits
Emotions

Innate or acquired response

stimulus

Innate or acquired response

Conscious sensation “feeling”

Cortical processing

Subcortical processing

Motor and autonomic control systems

Peripheral

Behavioral response

Autonomic and endocrine response

Amygdala

Hypothalamus

Brainstem

Humans 1 2 3

Rodents 2 3 1?
Fear and anxiety in rodents

Fear
- defensive emotional response to specific and immediate threatening stimulus;
  rodent models: fear conditioning, fear of predator odor.

Contextual fear: contextual fear conditioning

Generalized fear: context / cue discrimination

Anxiety
- sustained state of heightened apprehension in the absence of immediate threat;
  rodent models: elevated O- and plus-maze, open field, light-dark transition test, Vogel-test

Behavior:
- avoidance, flight
- risk assessment
- freezing
- vocalization
- feeding suppression
- drinking suppression
- analgesia
- reflex potentiation

Autonomic arousal:
- blood pressure increase
- heart rate increase
- respiration increase
- hyperthermia

Endocrine responses:
- HPA axis activation
Amygdaloid complex - components

- **AA***: anterior amygdaloid area
- **ACo***: anterior cortical nc
- **PLCo***: posterolateral cortical nc
- **PMCo***: posteromedial cortical nc
- **APir***: amygdalopiriform transition area
- **AHi***: amygdalohippocampal transition area
- **LOT***: nc of lateral olfactory tract
- **BAOT***: bed nc of accessory olfactory tract
- **CeL***: central nc, lateral
- **CeM***: central nc, medial
- **mgr**
- **IMG***: intramedullary gray
- **Me***: medial nc
- **CEXA***: central division of extended amygdala
- **MEXA***: medial division of extended amygdala
- **Spring cortic-like nuclei**: olfactory amygdala, vomeronasal amygdala

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Extended amygdala

 amygdaloid complex                  bed nucleus of stria terminalis                  substantia innominata

 CEXA  central division of extended amygdala
       
       CeL  central nc, lateral
           CeM  central nc, medial

 MEXA  medial division of extended amygdala
       
       Me  medial nc

 BSTL  lateral bed nc of stria terminalis
       
 SLEAC  central sublenticular extended amygdala
 IPAC  interstitial nucleus of posterior limb of anterior commissure

 BSTS  supracapsular bed nc of stria terminalis
       
 SLEAM  medial sublenticular extended amygdala
       
 BSTM  medial bed nc of stria terminalis

 BSTIA  intraamygdaloid bed nc of stria terminalis

 dorsal route  ventral route
Classical (Pavlovian) conditioning

**Training**
- **CS** (Conditioned Stimulus): neutral
- **US** (Unconditioned Stimulus): appetitive or aversive
- **UR** (Unconditioned Response)

**Testing**
- **CS** (Conditioned Stimulus): associated with US
- **CR** (Conditioned Response)
Pavlovian (cued) fear conditioning

training

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<th>CS</th>
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<td>baseline</td>
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<td>1-3 training cycles</td>
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measured response
- defensive behavior (freezing, vocalization, flight)
- reflex potentiation (startle)
- hypoalgesia
- autonomic arousal (blood pressure, heart rate)
- HPA axis stimulation

test

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<td>CS test</td>
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Cued and contextual fear conditioning

**training**

- Baseline
- 1-3 training cycles
- Co-termination of CS and US

**tests**

- Test chamber
- Baseline
- CS test
- Training chamber
- Context test

Variant: context discrimination
Trace fear conditioning

**training**
- training chamber
- CS US
  - baseline
  - 5+ training cycles
- trace interval between CS and US

**tests**
- test chamber
  - CS US
  - baseline
  - CS test
- training chamber
  - CS US
  - context test
Extinction of conditioned fear

**Training**
- CS
- US
- Baseline
- 1-3 training cycles

**Extinction**
- Test chamber
- Baseline
- Repeated CS
- Reappearance of CR after extinction:
  - Recovery (with time)
  - Reinstatement (US exposure)
  - Renewal (new context)
Amygdala: cytoarchitecture and flow of information

- La, BM/BL share cortex-like cytoarchitecture with 80% excitatory principal neurons
- Ce has striatum-like cytoarchitecture with 95% medium spiny-like projection neurons
- Ce (inhibitory!) and BST (mostly excitatory) are the principal output structures
- overall information flow is from laterobasal complex (La, BM/BL) to extended amygdala
- CS-US associations formed and stored in La, lesion disrupts acquisition and retrieval

Amygdala harbors strong inhibitory GABAergic network.
CS-on and CS-off cells as a fear gate in the CeL

- CS-on cells in the CeL acquire positive response to CS with learning
- CS-off cells in the CeL acquire negative response to CS with learning
- Cell-type specific plasticity in the CeL to CeM pathway may gate fear expression
- Conditioned fear responses are driven by activity of CeM output neurons

Ciocchi S et al. Nature 468:277, 2010
Amygdala: sensory and cortical inputs

- quick and dirty pre-thalamic (especially nociceptive) and thalamic sensory input
- slower and more precise input from sensory cortex to basal and extended amygdala
- multimodal and contextual input from hippocampus
- bidirectional modulation by medial prefrontal cortex (IL, PL)
- extinction signal mediated by IL prefrontal cortex via intercalated cells
Amygdala: output and control by thalamus

- Brainstem output controls behavioral responses (mainly PAG)
- Output to medial hypothalamus (PVN) controls hormonal response
- Output to lateral hypothalamus controls autonomic and behavioral responses
- PVT required for acquisition and long-term retrieval of fear memories
- Convergence of US and US prediction signals in PAG permits calculation of prediction error
Rodent tests of anxiety-related responses

- openfield exploration
- elevated O-maze
- light/dark transition
- emergence test
- object exploration

- forced exploration
- free exploration with safe zone

- exploration zone
- home zone
Bidirectional control of anxiety through the BST

- optogenetic stimulation (1) of GABAergic interneurons in the BST increases PM open arm time and decreases respiration rate
- optogenetic stimulation (2) of basolateral input to BST decreases PM open arm time and increases respiration rate

Bidirectional control of anxiety by the amygdala

- optogenetic stimulation (1) or inhibition (2) of basolateral input to CeL decreases or increases anxiety, respectively
- optogenetic stimulation (3) of basolateral output increases anxiety