Emotion I:
General concepts, fear and anxiety

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Outline

Emotion I (first part)

• Studying brain substrates of emotions in animals and humans – general considerations and concepts
• Fear and anxiety and relevant brain substrates

Emotion II (second part)

• Reward, pleasure, and desire, and relevant brain substrates
• Overlap between brain substrates of positive and negative emotions
• Recapitulation
“You always complain that I don’t know how to show my emotions, so I made these signs.”
Emotions are states elicited by rewarding or aversive stimuli (S+ or S-) and their omission (−) or termination (!).

These states comprise thoughts (‘‘feelings‘‘) and physiological/behavioural responses to emotional (i.e., rewarding or aversive) stimuli.

Physiological/behavioural responses to emotional stimuli can unambiguously be measured in humans and nonhuman animals.
Evolutionary considerations

Physiological/behavioural responses to aversive and positive stimuli have fundamental survival value and, therefore, have been relatively preserved throughout evolution and are often very similar in different animals incl. humans.

After Swanson (2005) J Comp Neurol 493:122

The principal organization of the brain is very similar among all mammalian species.

After Swanson (2005) J Comp Neurol 493:122
Rat as a model system

ADVANTAGES

Easy to breed and keep

Well-established behavioural tests

Brain large enough to apply selective manipulations to distinct brain structures and brain anatomy very well characterized

DISADVANTAGE

Genetic manipulations difficult (alternative: mouse)
The emotional brain – an overview and short list of classic milestones

**Hippocampus, amygdala, and hypothalamus:**
- Papez theory of emotion (1937)
- Klüver and Bucy’s description of temporal lobe lesion effects in monkeys (1939)
- MacLean’s limbic system theory (1949)

**Prefrontal cortex:**
- Case of Phineas Gage described by Harlow (1868)
- Nauta (1971): Frontal lobes and interoception

**Meso-corticolimbic dopamine system:**
- Olds and Milner (1954): Brain-stimulation induced reward
- Wise et al. (1978): Neuroleptic-induced anhedonia
How could ANXIETY and FEAR be characterised without reference to subjective feelings?

a) A state caused by presence of a positive reinforcer.

b) A state caused by presence of aversive stimulus.

c) A state caused by absence of positive reinforcer.

d) A state caused by omission or termination of aversive stimulus.
Much animal research on brain substrates of emotion over the last 30 years has focused on fear and anxiety (Caroline and Robert Blanchard, Jeffrey Gray, Michael Davis, Michael Fanselow, Joseph LeDoux, and colleagues).

Fear and anxiety comprise protective/defensive responses normally elicited by aversive stimuli.
Fear and anxiety 2

Fear rather refers to phasic escape or avoidance responses to distinct aversive stimuli. Anxiety rather refers to a tonic response to diffuse aversive situations and is associated with conflict and uncertainty (compare Davis et al., 2010, *Neuropsychopharmacology* 35: 105–135).

There are many different types of fear and anxiety responses, and the brain substrates of these different responses may differ.

Fear- and anxiety-related disorders in humans include generalized anxiety disorder, obsessive compulsive disorder (OCD), panic disorder, phobias, and post-traumatic stress disorder (PTSD).
Conditioned fear and the amygdala

Classical fear conditioning

**Conditioning**
- Tone
- Shock

**Test**
- Tone
- "FREEZING"

Functional-anatomical model of conditioned fear: central role for the amygdala

**A**
- CONDITIONED STIMULUS (CS) (tone or light)
- UNCONDITIONED STIMULUS (US) (footshock)

**B**
- THREATENING STIMULI
- Natural Threat Cond Stimulus
- FEAR RESPONSES
  - defensive behavior
  - autonomic arousal
  - hypalgesia
  - reflex potentiation
  - stress hormones


The slippery slope of fear

Joseph E. LeDoux

Center for Neural Science, New York University, 6 Washington Place, New York, NY 10003, USA

‘Fear’ is used scientifically in two ways, which causes confusion: it refers to conscious feelings and to behavioral and physiological responses. Restricting the use of ‘fear’ to denote feelings and using ‘threat-induced defensive reactions’ for the responses would help avoid misunderstandings about the brain mechanisms involved.
Functional anatomical model of conditioned fear (aka threat-induced defensive reactions): a central role for the amygdala

Requirement of lateral and central amygdala in conditioned fear

Lesions of different amygdala nuclei before fear conditioning

Lesion effects on conditioned freezing

Different CE outputs mediate different conditioned fear responses

Different CE outputs mediate different conditioned fear responses

Lesions of lateral hypothalamus and caudal central gray before fear conditioning

Lesion effects on conditioned fear responses
Fear-conditioning-related plasticity in LA neurons

Fear-conditioning-related plasticity in LA neurons

LA neurons come to fire in response to a tone when the tone is paired with a foot shock.

And the human amygdala?

Amygdala damage impairs conditioned fear

Bechara et al. (1995) *Science* 269:1115

Amygdala fMRI signals in a conditioned fear paradigm

LaBar et al. (1998) *Neuron* 20:937
IMPORTANT NOTES:

The role of the amygdala in conditioned fear has been very well characterised, nevertheless:

- Other brain structures (e.g., hippocampus, prefrontal cortex) may also make important contributions to fear and anxiety, and the substrates of conditioned fear may differ from those of other fear/anxiety-related behaviours.

- Amygdala is involved in other emotional and behavioural processes as well.
Hippocampus in fear and anxiety

Ventral hippocampus and conditioned freezing

Richmond et al. (1999) *Behav Neurosci* 113:1189

Ventral hippocampus and innate/unconditioned anxiety responses

Elevated plus maze

Hippocampal lesions increase the time rats spent in the open arms of the elevated plus maze. What does this finding indicate?

a) Hippocampal lesions cause anxiety.

b) Hippocampal lesions reduce anxiety.

c) Hippocampus does not play a role in anxiety.
Hippocampus in fear and anxiety

Ventral hippocampus and conditioned freezing

Richmond et al. (1999) Behav Neurosci 113:1189

Ventral hippocampus and innate/unconditioned anxiety responses

Elevated plus maze

Brightly lit test chamber

### Hippocampus and anxiety disorders

#### Similarity between effects of hippocampal lesions and anxiolytics

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= Tested with Buspirone


#### Decreased hippocampal benzodiazepine receptor binding in panic disorder

Area of decreased [I-123] iomazenil binding in panic disorder patients relative to controls in the left hippocampus

Bremner et al. (2000) *Biol Psychiatry* 47:96
Emotion I: General concepts, fear and anxiety – Selected Reading

**Textbook chapter:**

**Book:**

**Review articles:**

**General**


**Fear and anxiety:**


Emotion I: General concepts, fear and anxiety
– Some questions for revision

• Is it necessary to refer to subjective feelings if we want to study brain substrates of emotions?

• What advantages and disadvantages does it have to study neural mechanisms of emotion without reference to subjective feelings?

• How can we study brain substrates relevant to fear/anxiety in rat models?

• How can we confirm that similar brain substrates are also important for human fear/anxiety?