Neural circuits of fear and anxiety

GS14 1024 – Systems Neuroscience
April 27th, 2021

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Fear and anxiety responses

**Anxiety:** Anticipation of a real or imagined future threat or danger

**Fear:** Emotional response to a real or perceived threat

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*Table 1. Differences between physiological and pathological anxiety*

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Physiological</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Meaningful</td>
<td>Useless</td>
</tr>
<tr>
<td>Duration</td>
<td>Short</td>
<td>Short and long</td>
</tr>
<tr>
<td>Intensity</td>
<td>Strong</td>
<td>Weak/medium/strong</td>
</tr>
<tr>
<td>Cause</td>
<td>Objective threat</td>
<td>Frequently irrational</td>
</tr>
<tr>
<td>Attention</td>
<td>Shortly affected</td>
<td>Prolonged decrease</td>
</tr>
<tr>
<td>Everyday functioning*</td>
<td>Unaffected</td>
<td>Significantly altered</td>
</tr>
<tr>
<td>Somatic manifestation</td>
<td>Rare to none</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

*Social, interpersonal relations at work, within family*
Anxiety disorders

Definition: …“Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)…”

Diagnostic Statistical Manual of Mental Disorders (DSM-V)

Most common type of mental illness (~20% of population)

SUBTYPES OF ANXIETY DISORDERS

- **Generalized anxiety disorder** – anxiety about a number of different things: work, health, money, etc;
- **Separation anxiety disorder** – overly concerned about separating from home, family or friends;
- **Specific Phobia** – fear of animals, natural environment, blood, situational (e.g., airplanes, elevator);
- **Social Phobia** – fear of social interactions, being observed, performing;
- **Panic Disorder** - abrupt surge of intense fear with no obvious trigger with feeling of imminent death;
- **Agoraphobia** - situations of difficult escape (e.g., public transportation, crowded places, open areas, bridge);
- **Post-traumatic stress disorder** – sustained fear after exposure to a shocking, scary or dangerous event.
Subtypes of fear responses

Innate Fear Responses

Conditioned Fear Responses
How to study the neural circuits and mechanisms of fear and anxiety?
Animal models of fear and anxiety

Defensive behaviors

Fear Responses
Animal models of fear and anxiety in rodents

Calhoon and Tye, 2015
Animal model of conditioned fear

Classical Fear Conditioning

Fear memories persist for the lifetime of the animal, which allows us to investigate the neural circuits involved in fear expression.
Auditory fear conditioning in rodents
Freezing responses induced by a shock-paired tone
Auditory fear conditioning in rodents

Ways for the original fear to come back after extinction:
1) Spontaneous Recovery
2) Renewal
3) Reinstatement

Fear memory extinction

Does extinction erase the original fear memory?
Which brain regions are involved in fear memory acquisition?
Fear memory acquisition

Adapted from Do Monte et al. 2016.
The amygdala in fear acquisition

Rodents

Auditory thalamus inputs to LA convey tone information

MGM – medial part of the medial geniculate nucleus
PIN – posterior intralaminar nucleus

Quirk et al, 1997
The amygdala in fear memory

Rodents

Pharmacological inactivation of the lateral amygdala blocks fear conditioning

Willensky et al, 1999

Photostimulation of LA replaces an aversive stimulus

The amygdala in fear memory

Rodents

The lateral thalamus integrates CS-US information

The amygdala in fear memory

Humans

Patient S.M.
(Urbach-Wiethe disease)

Deficits in recognizing fear in facial expressions

Fearful

Happy

Adolphs et al., 1994
The amygdala in fear memory

**Humans**

PTSD patients show increased amygdala activity

Cognitive therapy reverts amygdala hyperactivity

Hayes et al, 2012

Roy et al, 2014
Which brain regions regulate fear memory retrieval?
mPFC modulates fear retrieval

mPFC

Amygdala

(Auditory Thalamus) (Somatosensory Thalamus)

PAG (freezing)

Hypothalamus (autonomic)

Reticular formation (startle)
Prelimbic (PL) cortex is critical for fear retrieval

Inactivation of PL (at 24 h)

Sierra-Mercado et al. 2011, NPP.

Electrical stimulation of PL (at 24 h)

Vidal-Gonzalez et al. 2006.
mPFC modulates fear extinction

Vertes, 2004, Synapse

Do Monte et al 2015.

Photoinhibition of IL

Photoactivation of IL

Fear Extinction

% Freezing

Trial Blocks

Day 1
Day 2
Day 3

Cond
Extinction
Retrieval

Cond
Extinction
Retrieval

mPFC

ACd
PL
IL
IL-amygdala projections and fear extinction

Rodents

Bukalo et al 2015.
The prefrontal cortex in fear regulation

Humans

More than ¼ of the cerebral cortex

Anterior midcingulate cortex, dorsomedial prefrontal cortex, perigenual anterior cingulate cortex, rostromedial prefrontal cortex, medial orbitofrontal cortex, subgenual anterior cingulate cortex

Goal-directed behavior
Social behavior
Attention
Working memory
Behavioral flexibility
Decision-making
Emotional regulation
The homolog of the prefrontal cortex in rodents

Anterior cingulate cortex = cingulate cortex (area 24)
dmPFC/area = PL (area 32)
vmPFC = IL (area 25)

The prefrontal cortex in fear regulation

Reduced vmPFC activity in PTSD

Humans

Hayes et al, 2012
How does the brain differentiate safety from fearful environments?
Hippocampus and contextual information

Hippocampus

Amygdala

mPFC

Hypothalamus

Reticular formation

(Auditory Thalamus)

(Somatosensory Thalamus)

PAG (freezing)

Hypothalamus (autonomic)

Reticular formation (startle)
Hippocampus and contextual fear

Rodents

SH – Sham
FX – Fornix/hippocampal formation
DH - Dorsal hippocampus
EC - Entorhinal cortex

Electrolytic lesion

Hippocampus and contextual fear

Optogenetic stimulation of a hippocampal engram activates fear memory recall

Xu Liu*, Steve Ramirez*, Petti T. Pang, Corey B. Puryear, Arvind Govindarajan, Karl Deisseroth & Susumu Tonegawa

Rodents

a. Fear Cond, cFosTA + ChR2, Dox-off two days before FC
b. Same as a., but no footshock
c. Same as a., but eYFP

Liu et al, 2012
Activity in vHipp→IL projections causes fear relapse

Photoactivation of vHipp induces feed-forward inhibition of IL

Chemogenetic manipulation

Marek et al. 2018.
Hippocampus size in PTSD patients

- Hippocampal MRI in twins

Reduced hippocampal volume is a risk factor for PTSD

Gilbertson et al, 2002
Do the same neural circuits regulate fear across time?
Do the same circuits regulate fear across time?

Do Monte et al. 2015.
Tone-responses of PVT neurons increase with time

Single-unit recording

pre-cond  →  2 h  →  24 h after conditioning

PVT

From bregma: -2.5 mm

-2.8 mm

-3.1 mm

Group Data

Tone responses of PVT neurons increase with time.

Do Monte et al. 2015.
Which PVT pathways are involved in late retrieval?

Paraventricular Thalamus (PVT)


For a review see: Do Monte et al. 2016.
Silencing of PL circuits with time

(Both timepoints tested in the same rat)

Do Monte et al. 2015.
Shifting of retrieval circuits with time

(Both timepoints tested in the same rat)

Do Monte et al. 2015.
Reorganization of retrieval circuits across time

Early Retrieval

Late Retrieval

Highly relevant to understand fear-related disorders in humans where the symptoms take months to manifest
How to study innate fear responses?
Animal models of innate fear

Visual innate fear

CRUISING PREDATOR

APPROACHING PREDATOR

Visual loom

FREEZE

FLIGHT

Olfactory innate fear

Innate fear response

PREDATOR ODOR
Looming-induced escape response
Looming-induced freezing response
Visual innate fear induced by looming stimuli

- Retinal ganglion cells (RGC)
- Superior colliculus (SC)
- Lateral posterior nucleus of the thalamus (PL)
- Basolateral amygdala (BLA)
- Parabigeminal nucleus (PBGN)
- Central nucleus of the amygdala (CeA)

Freezing response

Escape response

Ren and Tao, 2020 Review.
Olfactory innate fear induced by predator odor
How is predator odor identified?

**Kairomones** – semiochemicals that mediate interspecific interactions.

Neural circuits activated by cat odor exposure

Predator odor

Accessory Olfactory bulb

Amygdala

MeApv

Hypothalamus

VMHdm

AHN

Midbrain

PAGdl

Freezing response

Escape response

Questions?