Affective disorders: Neuroanatomy of defensive reactions

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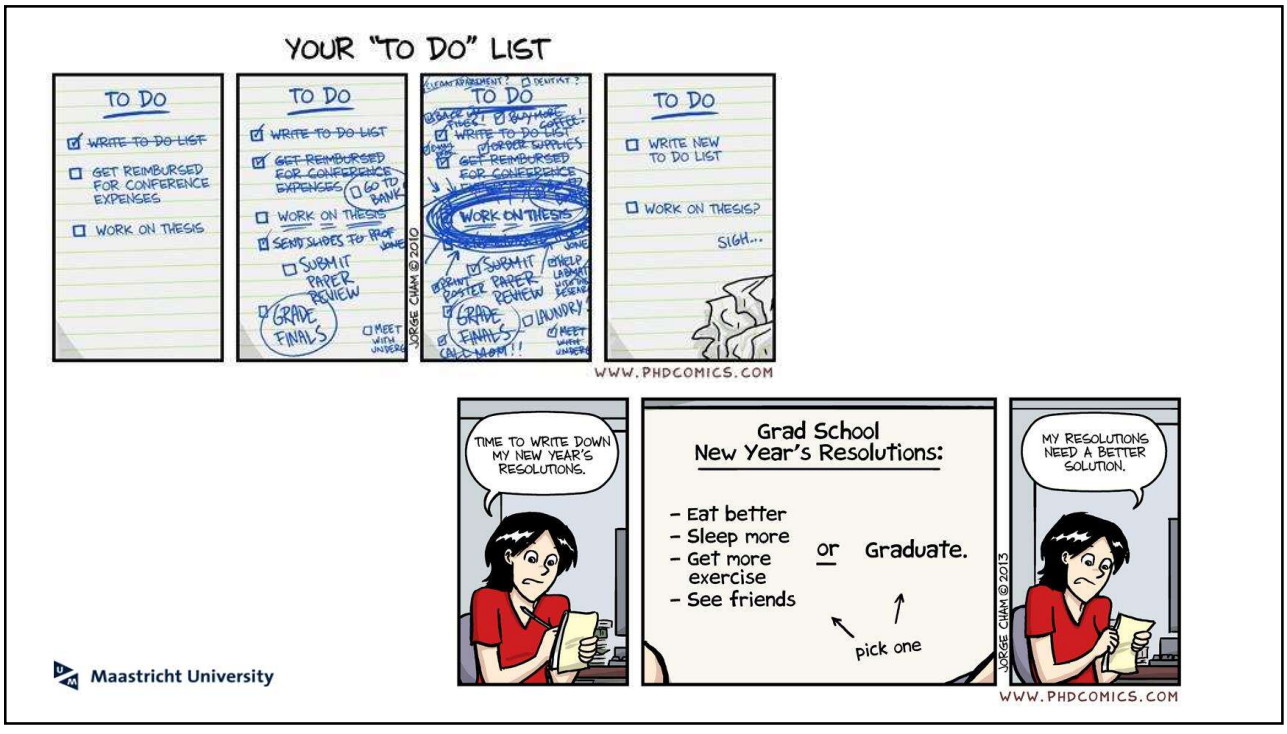

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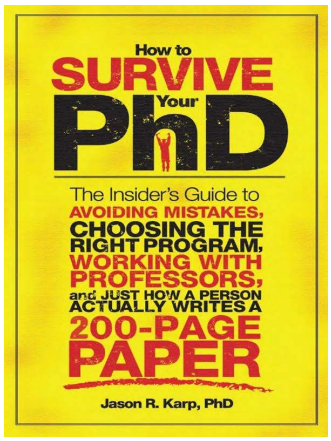

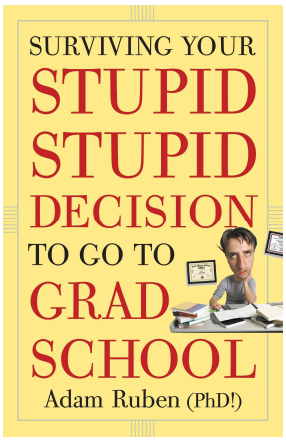

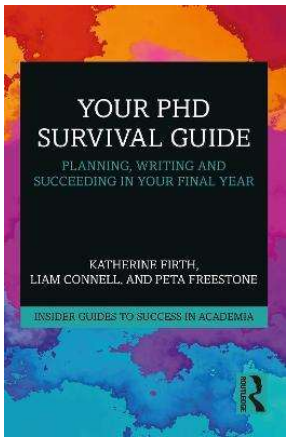

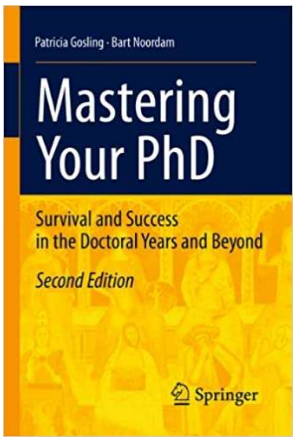

How to survive

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Optimized for Survival

Intrinsic instinct to survive

Seek things we like and need, and avoid harm

Learn what is good/bad → adapt to environment, choose appropriate response to threat

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How do we respond to a threat?

Hungry wolves: 11 sheep killed 03/06/2021

Worried farmers: Wolf kills cow 31/05/2021

2 sheep and lam killed 24/05/2021

Wolf kills deer 08/04/2021

Wolf kills roe deer in residential area 06/04/2021

Wolf kills 4 deer in wild park 26/03/2021

Concerns about future when food resources are limited

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How do we respond to a threat?

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How do we respond to a threat?

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How do we respond to a threat?

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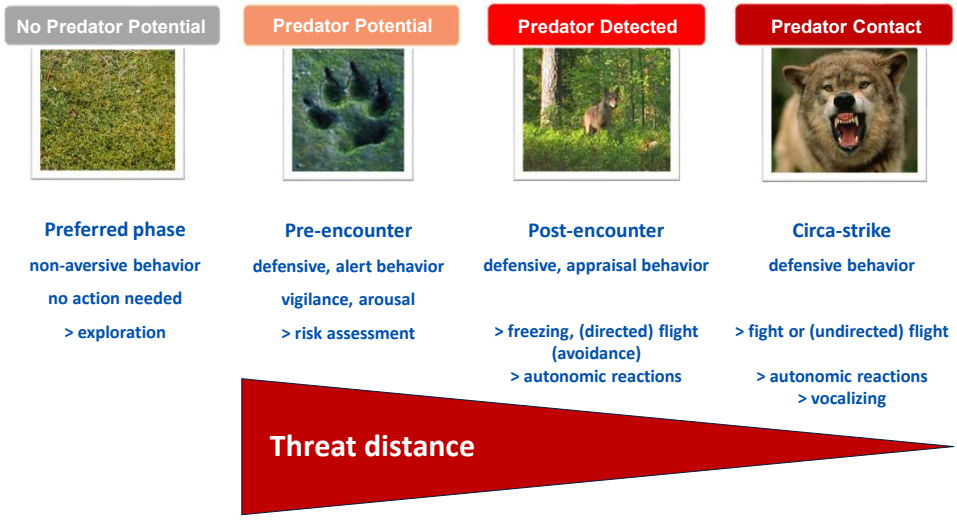
Threat imminence continuum and induced defensive behavior



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Threat imminence continuum
Fanselow and Lester, 1988

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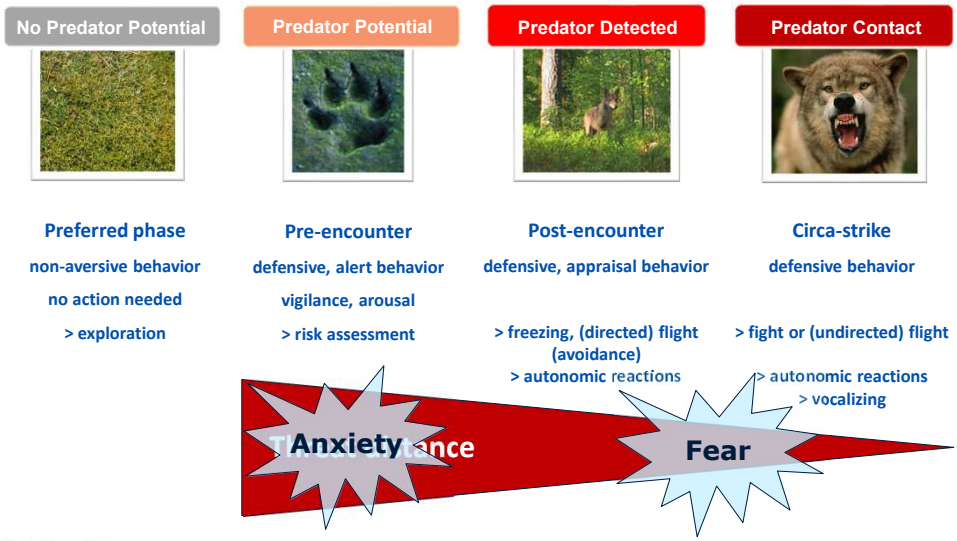
Threat imminence continuum and induced defensive behavior



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Threat induced defensive behavior

Extending the model

External Threat Internal Threat

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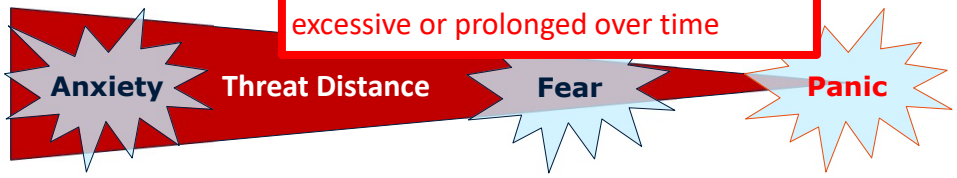
Threat induced defensive behavior

Extending the model

<u>None of these emotions or associated behaviors are pathological per se</u>

> pathological when inappropriate, excessive or prolonged over time



External Threat Internal Threat

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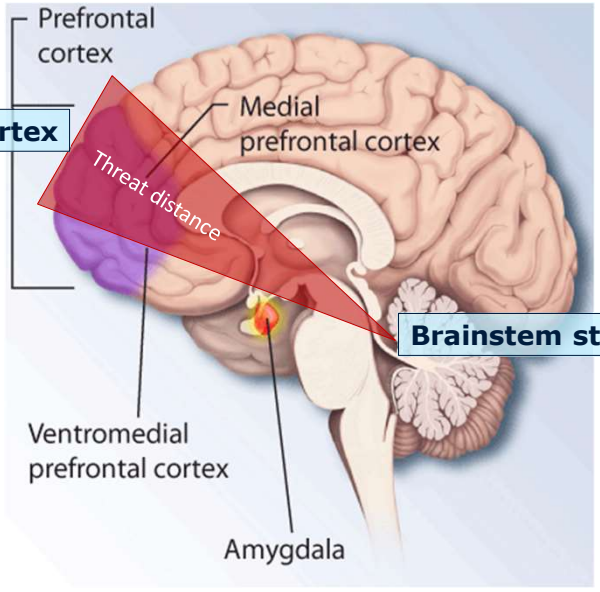
Which brain parts are involved?



Neocortex

Large distance:
Risk assessment;
newer cortical structures

Brainstem structures

Small distance:
Freezing, fight-or-flight;
evolutionarily evolved,
subcortical structures

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Graeff 1994
McNaughton & Corr 2004

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The virtual predator and prey paradigm

How to test in humans?

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Science AAAS Mobbs et al., Science 317, 1079 -1083 (2007)

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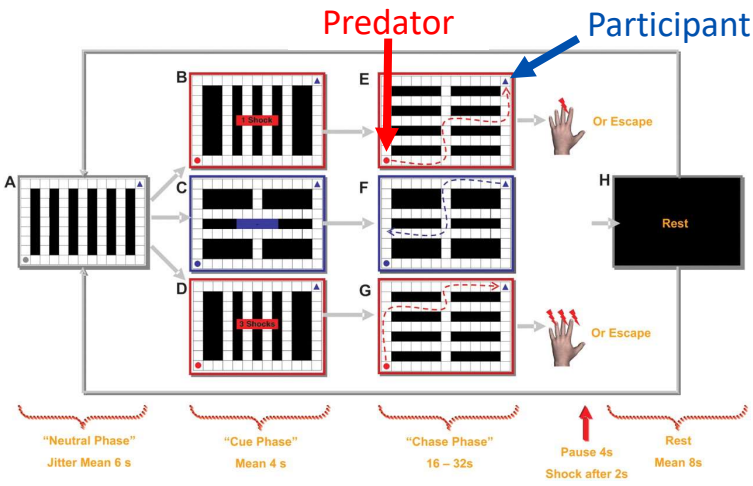
The virtual predator and prey paradigm



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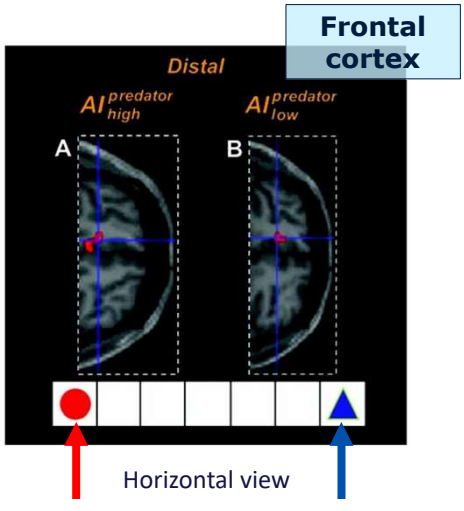
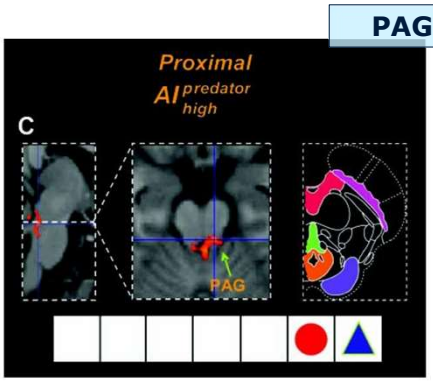
The virtual predator and prey paradigm





Results in line with defensive distance model

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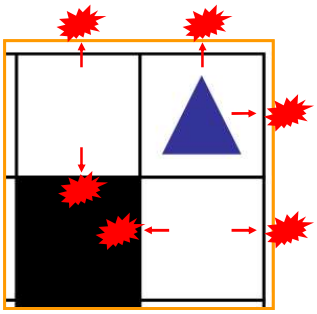
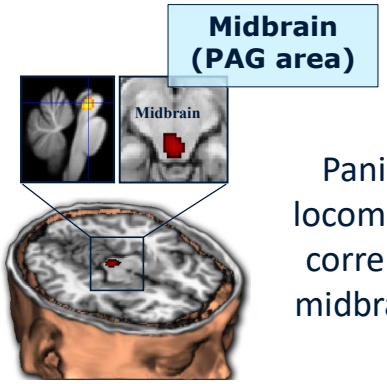
The virtual predator and prey paradigm

Panic-related locomotor errors
(undirected flight behavior)
Bumps into the wall =





Panic-related locomotor errors correlated with midbrain activity

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Mobbs et al., J Neuroscience 29(39): 12236–12243 (2009)

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From virtual predator to "real" predator: (subclinical) fear

Neural activity associated with monitoring the oscillating threat value of a tarantula

Dean Mobbs[a,1], Rongjun Yu[a], James B. Rowe[a,b], Hannah Eich[a], Oriel FeldmanHall[a], and Tim Dalgleish[a]

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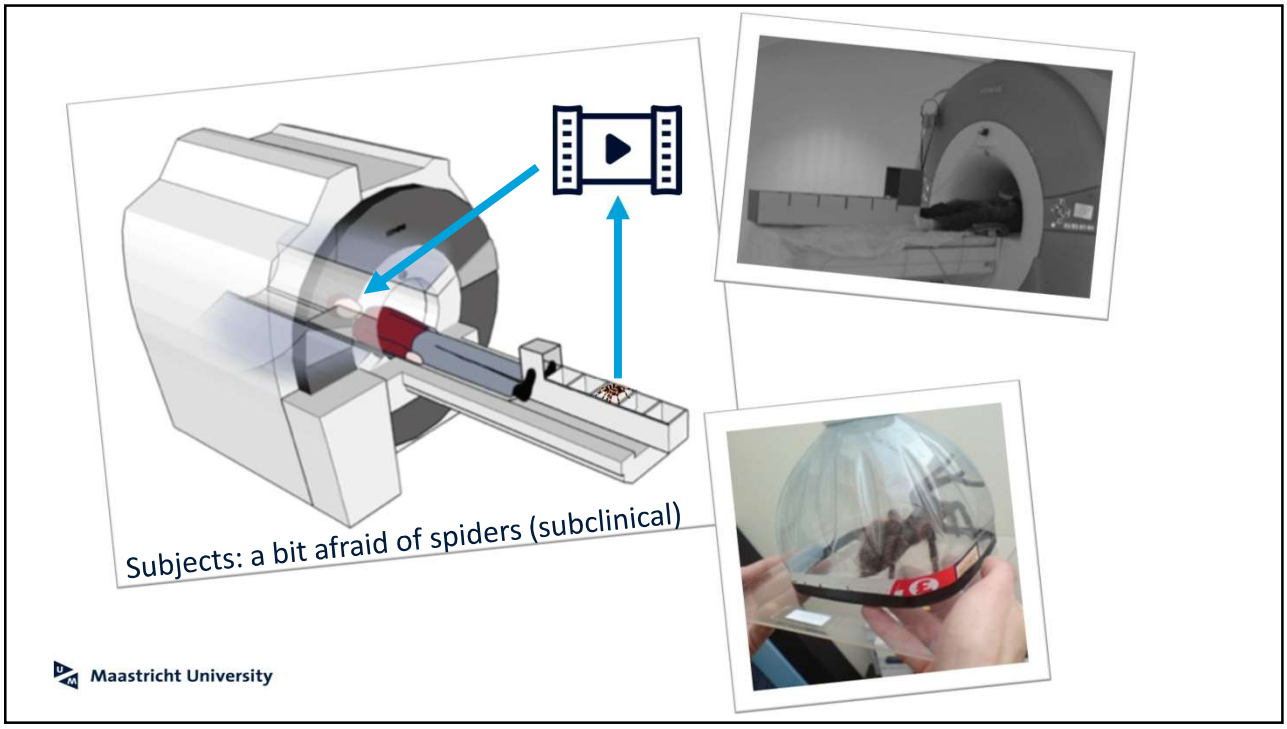
Subjects: a bit afraid of spiders (subclinical)
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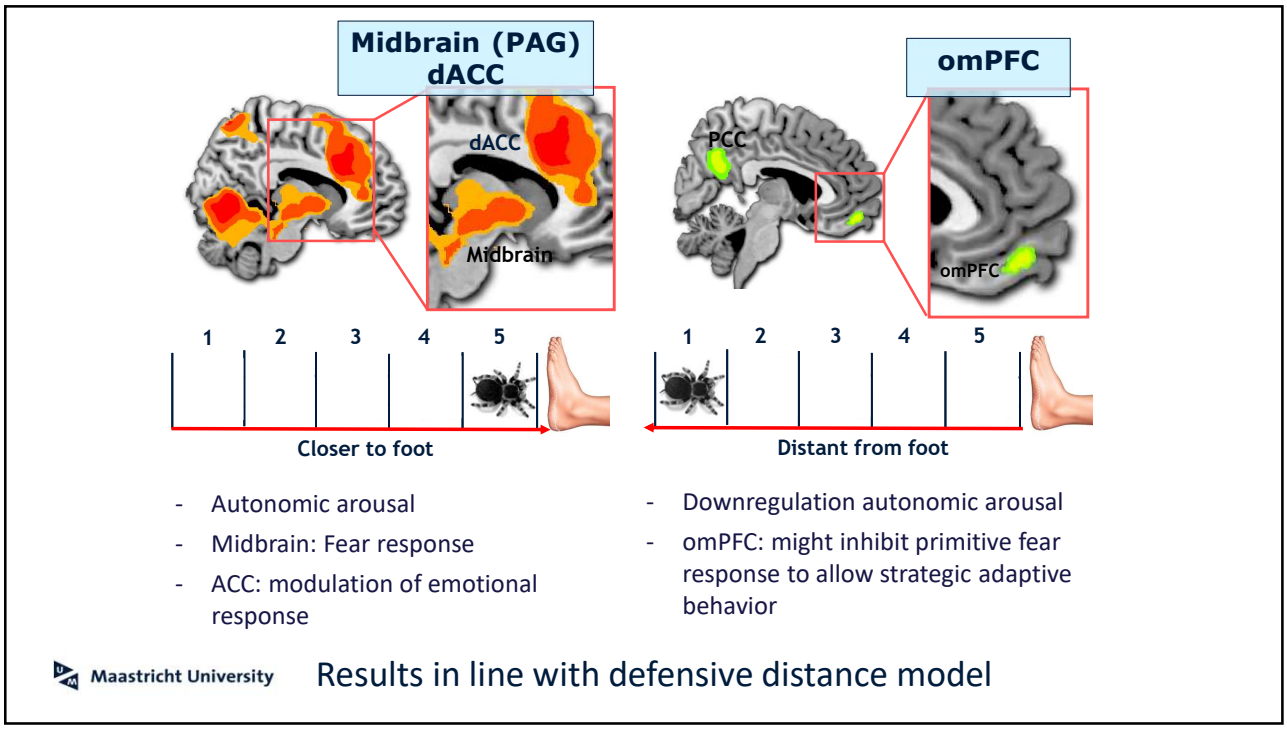
Midbrain (PAG)
dACC
dACC
Midbrain
omPFC
PCC
omPFC
1 2 3 4 5
Closer to foot
1 2 3 4 5
Distant from foot
- Autonomic arousal
- Midbrain: Fear response
- ACC: modulation of emotional response
- Downregulation autonomic arousal
- omPFC: might inhibit primitive fear response to allow strategic adaptive behavior
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Results in line with defensive distance model

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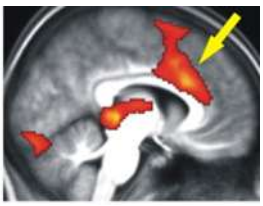
From virtual predator to "real" predator: (clinical) fear

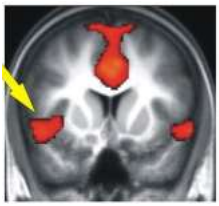
Spider phobia (clinical fear): Symptom provocation studies

>

ACC
- modulation of emotional response
- integration of attention and emotion



Anterior Cingulate Cortex



Amygdala, Insula

Amygdala
- Connected to ACC
- Emotions

Insula
- autonomic arousal

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Goossens et al. Psychiatry Res. 155(2):13-20 (2007)

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From virtual predator to "real" predator: Fear

- Animal model confirmed in humans
- Phobia
  - Example of disorder characterized by an excessive fear response to a stimulus

- In the clinic, do patients always have a disorder consisting of either fear OR anxiety?

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Disorder with either fear OR anxiety?

*"I was walking my dog when I started sweating **out of the blue**. I was unable to breathe. My heart was pounding so hard I thought it might explode out of my chest. My whole body was shaking. I thought I was going to die."*

In the emergency room, no heart or other problems were found.

In the next weeks, Katie experiences more of these episodes; some unexpected, others triggered in similar environments to when she had the first one.

Her day-to-day functioning is significantly impaired; **she avoids work** and walking her dog because she thinks it could trigger another episode.

There is no concrete source of **anxiety** or fear in Katie's life other than **of (future) episodes**. Her psychologist diagnoses her with recurrent panic attacks and panic disorder.

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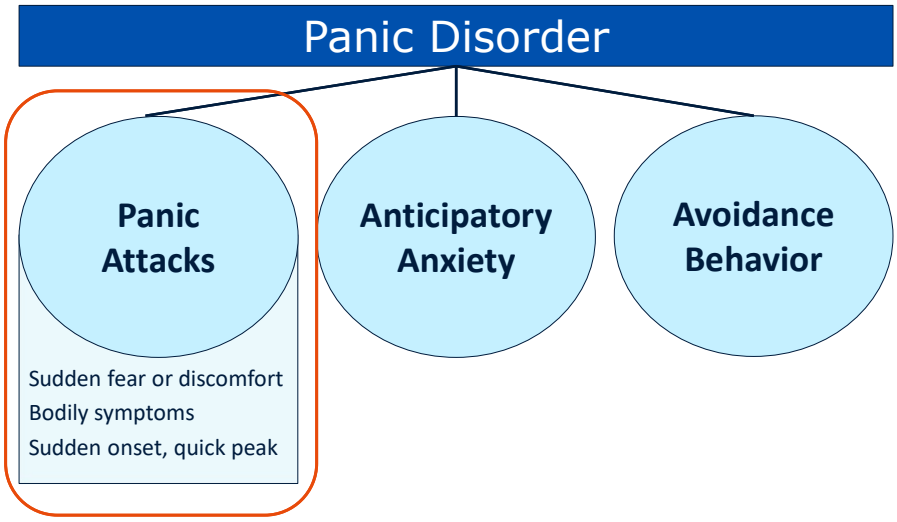
Panic



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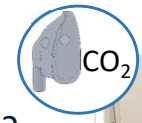
Panic in the lab

- Panic attacks
  - occur spontaneously → challenging to study → provocation in lab



% ?

CO_2 ↓

pH ↓
(potentially life-threatening)

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Panic in the lab

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Panic

Neuroanatomical Hypothesis of Panic Disorder, Revised

Jack M. Gorman, M.D., Justine M. Kent, M.D.,
Gregory M. Sullivan, M.D., and Jeremy D. Coplan, M.D.

Objective: In a 1989 article, the authors provided a hypothesis for the neuroanatomical basis of panic disorder that attempted to explain why both medication and cognitive behavioral psychotherapy are effective treatments. Here they revise that hypothesis to consider developments in the preclinical understanding of the neurobiology of fear and avoidance. **Method:** The authors review recent literature on the phenomenology, neurobiology, and treatment of panic disorder and impressive developments in documenting the neuroanatomy of conditioned fear in animals. **Results:** There appears to be a remarkable similarity between the physiological and behavioral consequences of response to a conditioned fear stimulus and a panic attack. In animals, these responses are mediated by a "fear network" in the brain that is centered in the amygdala and involves its interaction with the hippocampus and medial prefrontal cortex. Projections from the amygdala to hypothalamic and brainstem sites explain many of the observed signs of conditioned fear responses. It is speculated that a similar network is involved in panic disorder. A convergence of evidence suggests that both heritable factors and stressful life events, particularly in early childhood, are responsible for the onset of panic disorder. **Conclusions:** Medications, particularly those that influence the serotonin system, are hypothesized to desensitize the fear network from the level of the amygdala through its projects to the hypothalamus and the brainstem. Effective psychosocial treatments may also reduce contextual fear and cognitive misattributions at the level of the prefrontal cortex and hippocampus. Neuroimaging studies should help clarify whether these hypotheses are correct.

(Am J Psychiatry 2000; 157:493–505)

Animal research: amygdala is center of network involved in fear/panic and response to CO_2

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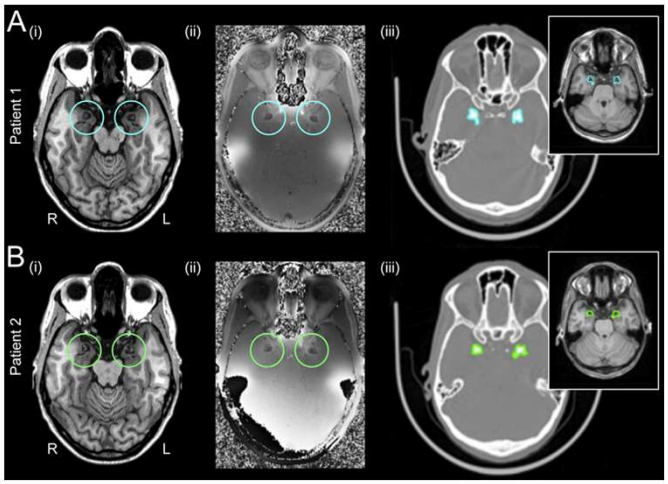
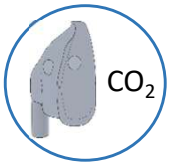
Panic

- Patients with bilateral amygdala damage





Expectation if amygdala is essential and these patients do not have a functional amygdala?

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Feinstein, Nature Neuroscience 16, 270–272 (2013)

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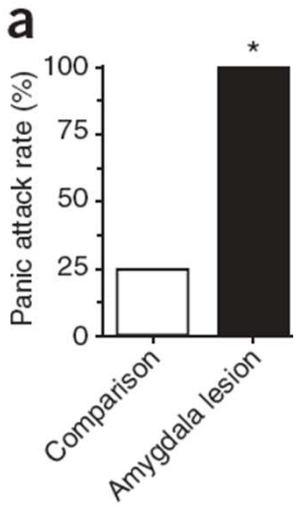
Panic



All patients had a panic attack
(based on symptom questionnaires)

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Feinstein, Nature Neuroscience 16, 270–272 (2013)

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Panic

Fear and panic in humans with bilateral amygdala damage

Justin S Feinstein[1,2,11], Colin Buzza[3,11], Rene Hurlemann[3,4,11], Robin L Follmer[3], Nader S Dahdaleh[5], William H Coryell[3], Michael J Welsh[5–9], Daniel Tranel[1,2,8] & John A Wemmie[3,5,7,8,10]

Decades of research have highlighted the amygdala's influential role in fear. We found that inhalation of 35% CO_2 evoked not only fear, but also panic attacks, in three rare patients with bilateral amygdala damage. These results indicate that the amygdala is not required for fear and panic, and make an important distinction between fear triggered by external threats from the environment versus fear triggered internally by CO_2.

Amygdala is not essential,
which other brain structure is a candidate?

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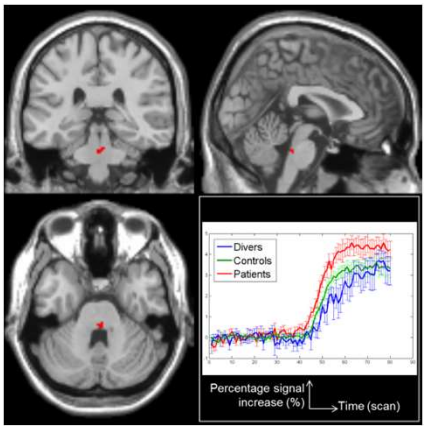
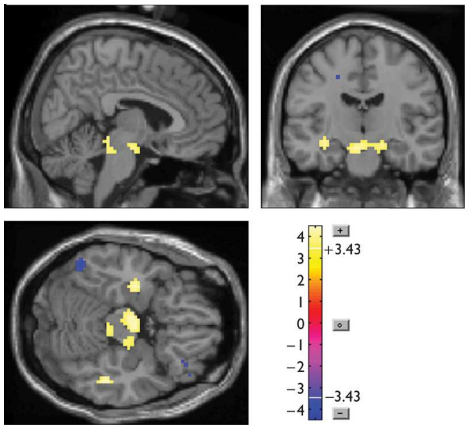
Panic

Elevated brainstem response to CO_2 in panic disorder



Goossens et al. J Psychopharmacol. 28(5):449-56 (2014)

Increased brainstem gray matter density in panic disorder



Protopopescu et al. Neuroreport 17(4):361-3. (2006)

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Panic Disorder

Panic Attacks

Sudden fear or discomfort
Bodily symptoms
Sudden onset, quick peak

Anticipatory Anxiety

Avoidance Behavior

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Anxiety

"When will the next panic attack occur?"

anticipatory cognitive, affective and behavioral processes executed to avoid or reduce the impact of a potential threat

Core feature/distress in anxiety disorders

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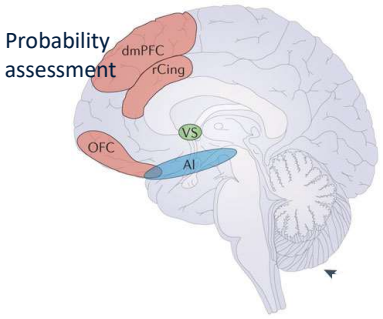
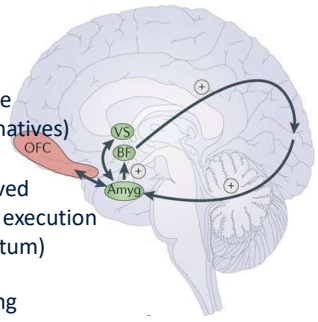
Anxiety

Risk assessment

"If I go for a walk with the dog, will I get a panic attack? Could there be a threat? How dangerous is the threat?"



Anxiety patients:
Bias in expected value calculation, overestimate danger of negative events
→ anticipatory anxiety ↑



Anxiety patients:
Attentional threat detection processes altered
→ perception of harm ↑
Amygdala: also fear/safety learning

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Grupe & Nitschke, Nature Reviews Neuroscience 14, 488–501 (2013)

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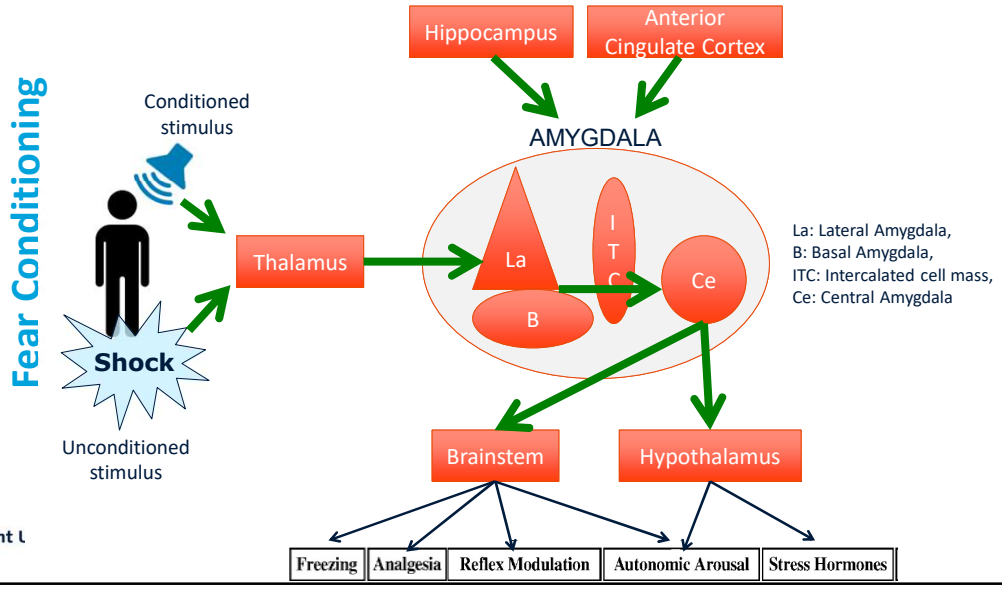
Anxiety - Fear

Fear and Safety learning

Which stimulus/situation is dangerous?



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Panic Disorder

Panic Attacks

Sudden fear or discomfort
Bodily symptoms
Sudden onset, quick peak

Anticipatory Anxiety

Avoidance Behavior

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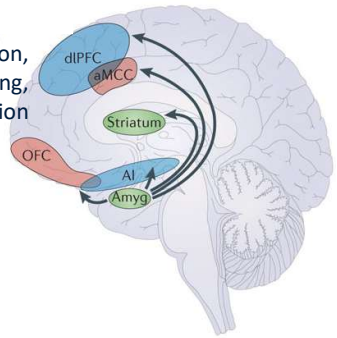
Anxiety - Fear

Avoidance

"If I don't go for a walk with the dog, I won't get a panic attack"

Action selection,
Decision-making,
Execution



Anxiety patients:
Anterior insula (AI) dysfunction
→ Expectancy about impact of potential feared outcome ↑
→ avoidance behavior ↑

Successful treatment of avoidance:
Anterior insula (AI) activity ↓
dlPFC activity ↑

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Grupe & Nitschke, Nature Reviews Neuroscience 14, 488–501 (2013)

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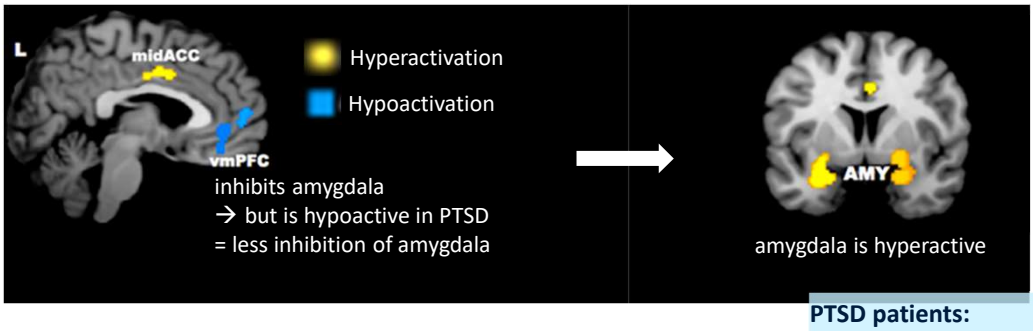
PTSD: vmPFC compromised

- Fear learning studies with negatieve emotional stimuli



PTSD patients:
Enhanced fear conditioning
But also safety cue learning

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Hayes JP, Vanelzakker MB, Shin LM, Front Integr Neurosci (2012)

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Take home message

- Anxiety ≠ fear
  - Linked to distinct brain regions
  - Depending on (perceived) defensive distance to a threat
  - Different behavioral responses
  - Often co-morbid
  - Complex brain networks

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Questions?

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