Stress, the Evolution of Mood and Clinical Depression

For UC Berkeley IB 139, Fall 2022

Julio Ozores, M.D.

Four Days, Six Questions

- Day One: *Why do animals have moods?*

- Day Two: *How did animals evolve depressed mood as an adaptive response to social stressors?*

- Day Three: *Why and how does mood regulation go awry in the human depressive mood disorders?*

- Day Four: *How is disordered depressed mood treated? Why is there an increasing prevalence of depression in "Gen Z"? What to do about it?*

Four Talks: From the foundation to the penthouse of "a phylogenetic building"

○ Day Three and Day Four:
  ◉ The Penthouse
  Human normal and disordered low mood (clinical depression)

○ Day Two:
  ◉ Higher Floors The Social Risk Hypothesis,
  ◉ Lower Floors The Social Competition Hypothesis
  The evolution of *normal* low mood

Up from phylogenetic depths

○ Day One:
  ◉ "The Foundation of Mood":
  Mood as a primitive regulator of animal behavior

THE STRESS RESPONSE IS
NON-SPECIFIC

Stress is "the non-specific response
of the body to any demand".
Hans Selye, 1929

injury

worry

isolation

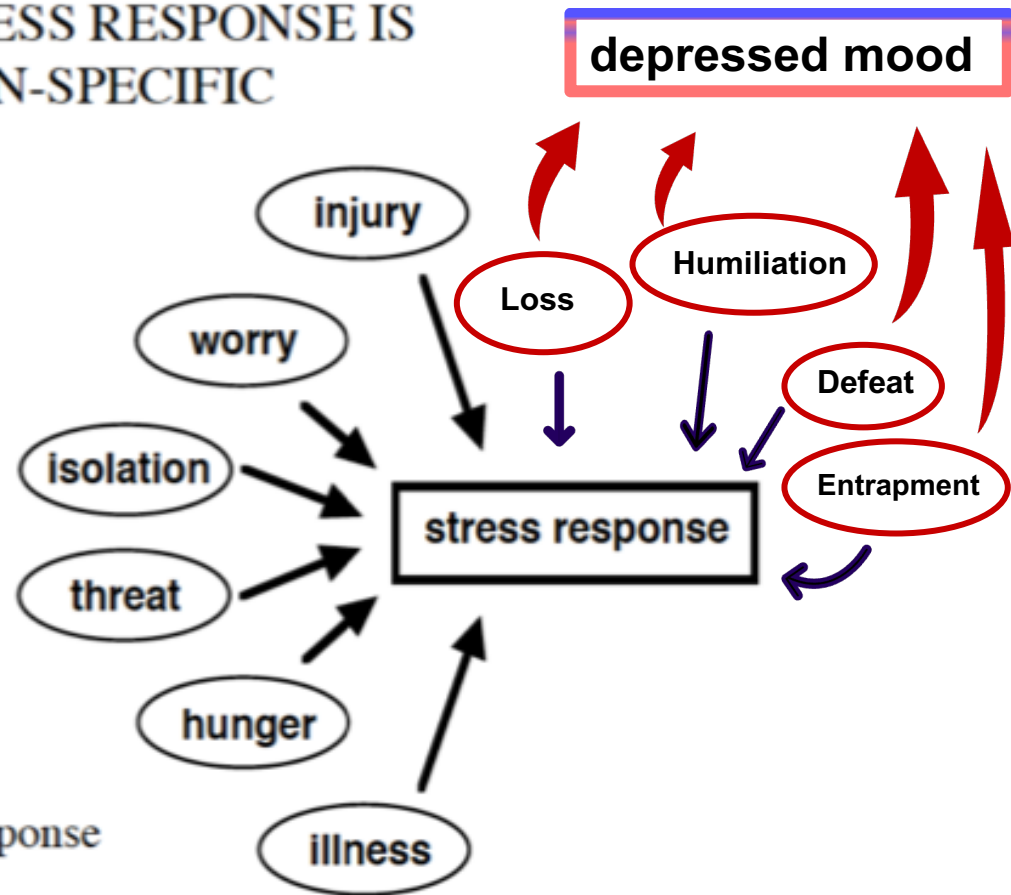threat

hunger

illness
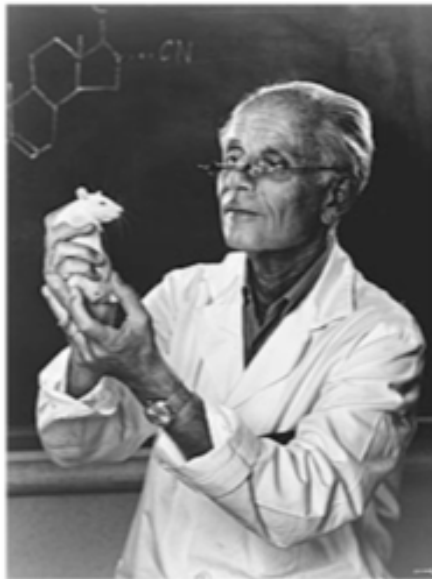
stress response

...some psychological stressors have special effects on mood.

THE STRESS RESPONSE IS NON-SPECIFIC

depressed mood

injury
worry
isolation
threat
hunger
illness

Loss
Humiliation
Defeat
Entrapment
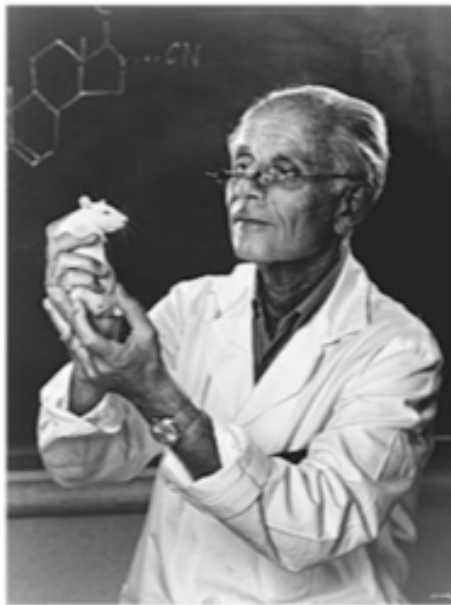
stress response

Stress is "the non-specific response of the body to any demand".
Hans Selye, 1929

Using evolution to make sense of things…

"Everything is the way it is because it got that way that way" D'Arcy Thompson

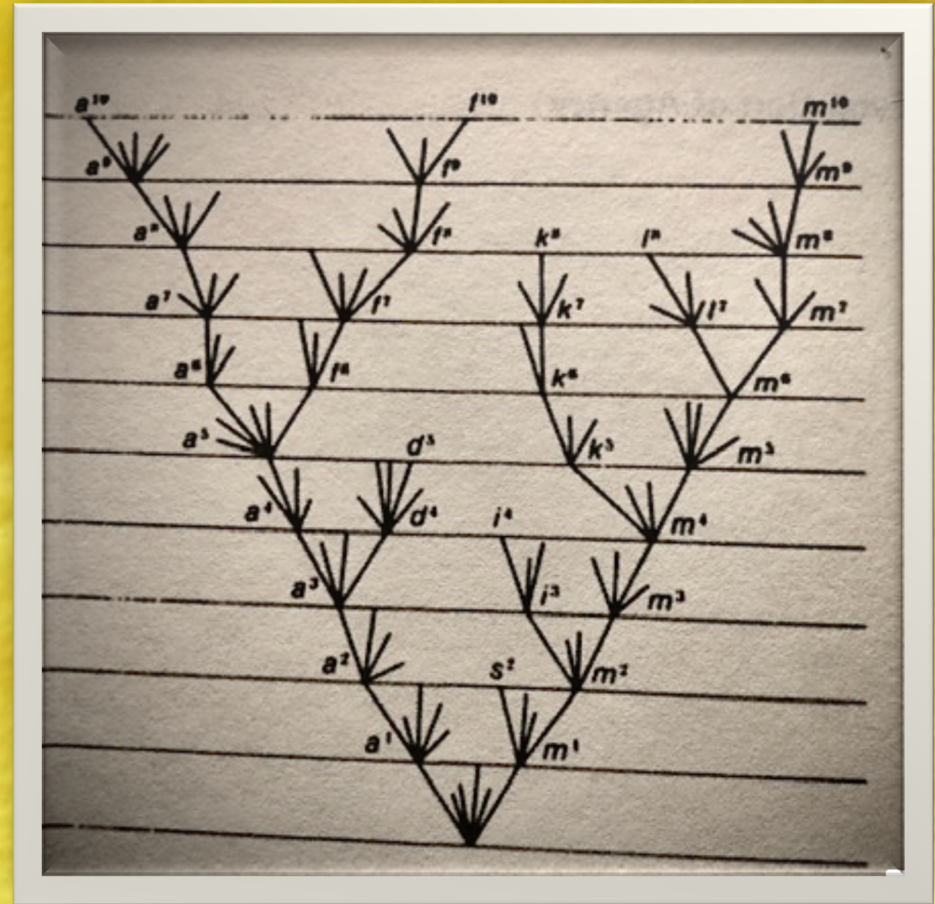## So why *is* depressed mood the way it is?

Phylogeny

*Or...things being the way they are because of **common ancestry**.*

"Similarity is older than difference" Gregory Bateson

Adaptation

Things being the way they are because thru natural selection, what works sticks around.

"Biology is not just like engineering; it is engineering." Daniel Dennett

Using evolution to make sense of things...

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Imagining phylogenetic time-depth:
Human mood is like a fancy penthouse apartment

The mood apartment is built on layers of evolved mechanistic structure that we share with recent evolutionary relatives..

...down to a rough, simple **foundation of mood** that we share with many (most?) animals.

The Penthouse: Human mood and its disorders- especially depression.

Higher Floors: The Social Risk Hypothesis

Lower Foors: The Social Competition Hypothesis

How can we tell animal mood *across species* ?

The Foundation: Mood as a primitive regulator of animal behavior, *in general*

How can you tell animal mood?
In monkeys, easy - *just look*.

In lab rodents, by noticing social and appetitive behavior over time.
(For example, after experimental stressors, such as Social Defeat)

For animals very dissimilar to us, we _can_ assess mood via "_cognitive bias_".

- Because "_Similarity is older than difference_", if we find similarities amongst very different species, it suggests they are of **_great phylogenetic depth_** ("The Foundation")
- The construct of "**cognitive bias**" _has_ been detected in many species, even in invertebrates. It allows a <u>scientific definition</u> of "**mood".**
- **Cognitive biases** are tendencies to interpret _ambiguous situations_ optimistically vs. pessimistically[i]
  - _Imagine being invited to an iffy party..._ and deciding whether to go when you are feeling down, vs. feeling up.
- **Cognitive biases** allow assessing not not only the effects of "bad stress", but also the effects of "_the opposite of stress_".

Sample of studies measuring **cognitive bias** in birds, rats, pigs, and... *honeybees*

Larger, enriched cages are associated with 'optimistic' response biases in captive European starlings (*Sturnus vulgaris*)

Stephanie M. Matheson, Lucy Asher, Melissa Bateson ⊠

⊞ Show more
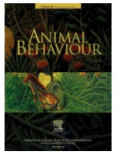
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Environmental enrichment induces optimistic cognitive bias in rats

Nichola M. Brydges [a] ⊠, Matthew Leach [b, 1], Katie Nicol [a], Rebecca Wright [a], Melissa Bateson [b, 1]

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Environmental enrichment induces optimistic cognitive biases in pigs

Catherine Douglas [a] ⊠, Melissa Bateson [b] ⊠, Clare Walsh [a] ⊠, Anaïs Bédué [c] ⊠, Sandra A. Edwards [a] ⊠

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Report

Agitated Honeybees Exhibit Pessimistic Cognitive Biases

Melissa Bateson,[1] Suzanne Desire,[1] Sarah E. Gartside,[1] and Geraldine A. Wright[1,*]
[1]Centre for Behaviour and Evolution, Institute of Neuroscience, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK

Summary

Whether animals experience human-like emotions is controversial and of immense societal concern [1–3]. Because animals cannot provide subjective reports of how they feel, emotional state can only be inferred using physiological, cognitive, and behavioral measures [4–8]. In humans, negative feelings are reliably correlated with pessimistic cognitive biases, defined as the increased expectation of bad a manipulation of state, the subjects' judgment is probed by testing their classification of novel stimuli with sensory properties intermediate between the two trained stimuli. A pessimistic cognitive bias is manifested in an increased tendency of subjects to classify stimuli as likely to predict punishment (or a reward of less value). We were able to use the same approach to test for cognitive biases in honeybees because bees are capable of associative learning and can base judgments about novel stimuli on previous experiences [24–27]. Using an olfactory learning protocol for conditioned proboscis extension, we trained honeybees to extend their mouthparts to a two-component odor mixture (CS+) predicting a reward (e.g., 1.00 or 2.00 M sucrose) and to withhold their mouthparts from another mixture (CS−) predicting either punishment or a less valuable reward (e.g., 0.01 M quinine solution or 0.01 M sucrose; Figure 1). The experiment comprised three conditions differing

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Results and Discussion

Identifying the best objective measures of negative affect (i.e., emotion) in animals is currently the focus of intense debate a manipulation of state, the subjects' judgment is probed by testing their classification of novel stimuli with sensory properties intermediate between the two trained stimuli. A pessimistic cognitive bias is manifested in an increased tendency of subjects to classify stimuli as likely to predict punishment (or a reward of less value). We were able to use the same approach to test for cognitive biases in honeybees because bees are capable of associative learning and can base judgments about novel stimuli on previous experiences [24–27]. Using an olfactory learning protocol for conditioned proboscis extension, we trained honeybees to extend their mouthparts to a two-component odor mixture (CS+) predicting a reward (e.g., 1.00 or 2.00 M sucrose) and to withhold their mouthparts from another mixture (CS−) predicting either punishment or a less valuable reward (e.g., 0.01 M quinine solution or 0.3 M sucrose; Figure 1). The experiment comprised three conditions differing in the pairs of rewards and punishers used, to allow us to determine to what extent any differences in behavior were explained by the salience of the unconditioned stimuli (USs) used.

Immediately after training, half of the honeybees were subjected to vigorous shaking for 60 s to simulate the state produced by a predatory attack on a concealed colony. Physical agitation is likely to be a good predictor of imminent attack in honeybees because brood predators and honey thieves such as the honey badger (*Mellivora capensis*) have been observed to use their accomplished digging skills to break into beehives [28]. To confirm that our shaking manipulation produced a physiological change, we used a different group of bees to measure changes in biogenic monoamine levels previously shown to be affected by shaking, spinning, or agitating [29, 30]. We found that 60 s of shaking significantly reduced constitutive levels of octopamine, dopamine, and serotonin in honeybee hemolymph at a time point following shaking that corresponded to when the cognitive tests reported below were performed (Figure 2).

We observed that shaken bees exhibited pessimistic judgment biases. Within 5 min of the shaking manipulation, all of the trained bees began a sequence of unreinforced test trials with five odor stimuli presented in a randomly chosen order

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Pessimistic bees video

Stressed bees were more likely to classify *ambiguous stimuli* as predicting punishment: A *depressive cognitive bias*
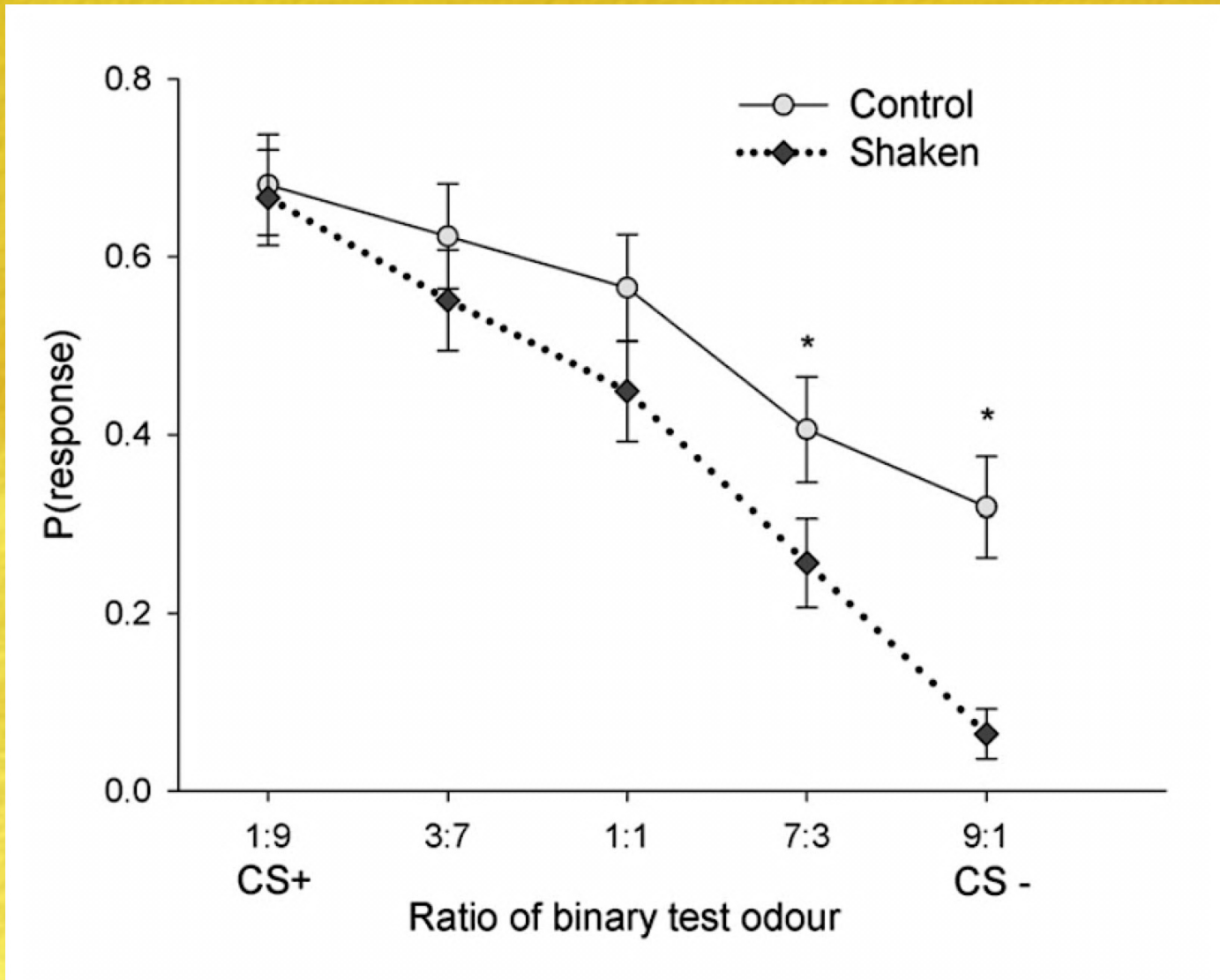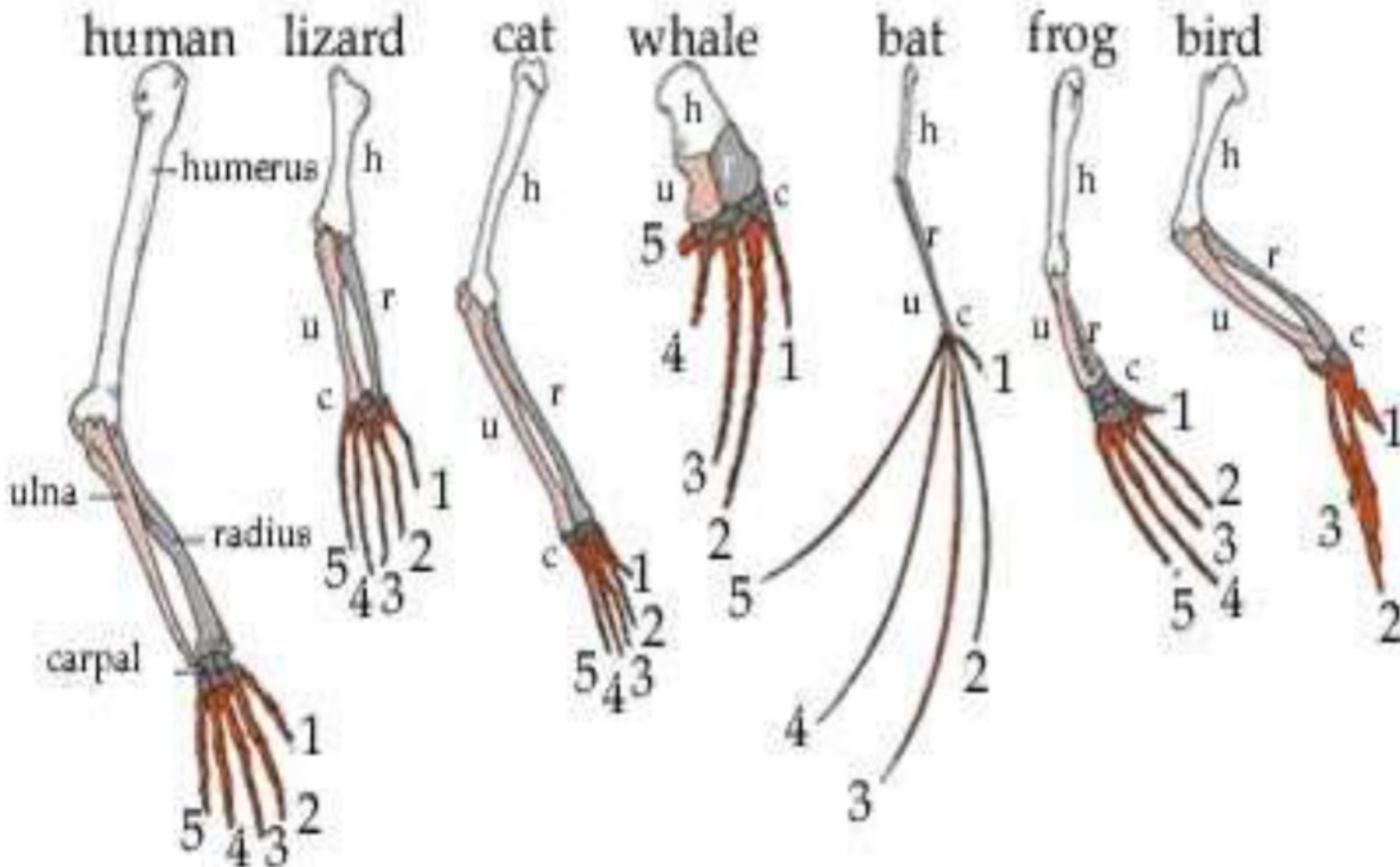

Figure 3. Shaken Honeybees Exhibit a Pessimistic Cognitive Bias

Are bug moods homologous with human moods?
Well, what is homology?
Classically, it was all about morphology

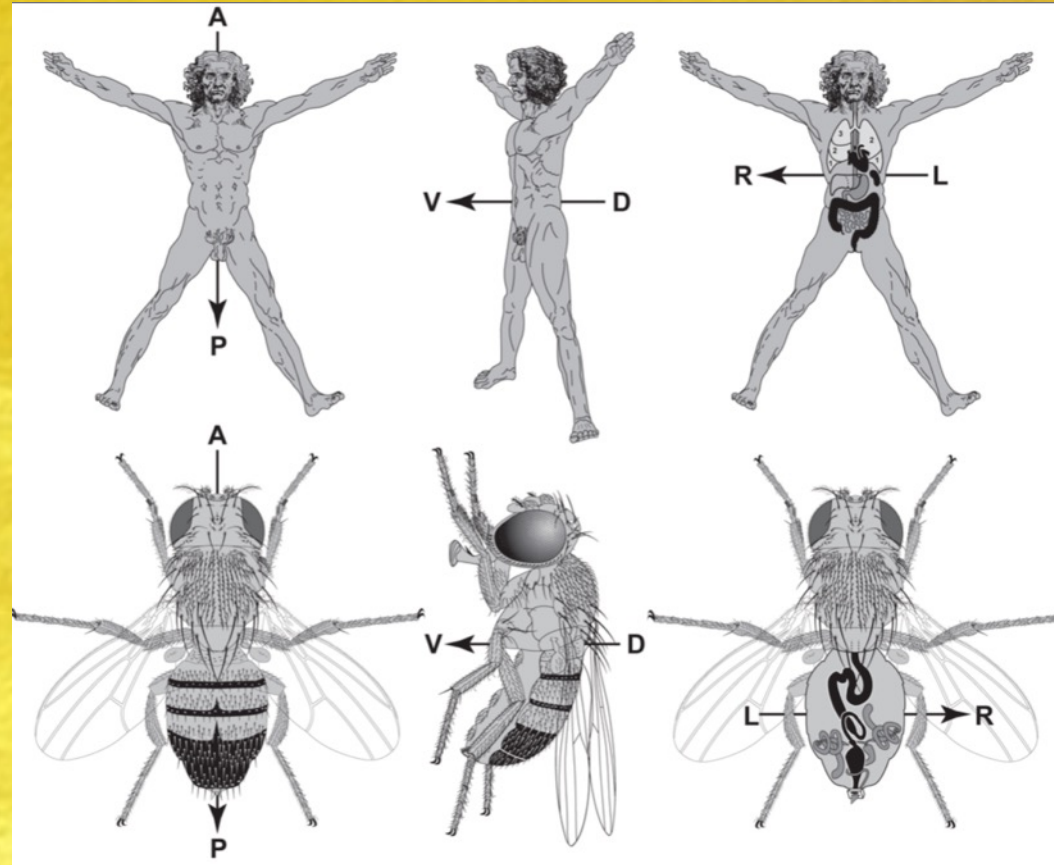# …but the concept of homology expanded to *behavioral* homology

behavioral homology includes us...

The concept of homology expanded to "*deep* homology" after the discovery of Hox genes.

- Some genes active in embryological development for are similar across phyla that have evolved separately for a long, long time...

- "Within the animal kingdom, Hox genes are present across the *bilateria*... This implies that Hox genes arose over 550 million years ago."

- You are very different from a fly, but you too are a *bilaterian*.

Expanding the concept of homology:
Is there a *deep* <u>*behavioral*</u> homology also?

- Physiological similarities also suggest **"something like" deep homology of emotion/mood**
  - ⊙ **"The early bilaterian brain also used transmitters to regulate arousal (serotonin) and reward learning (dopamine)."** [1]
  - ⊙ There may be a "..conserved role for serotonergic neurotransmission...mediating social behavior in octopus" [2]
- Behavioral findings relating stressors and "opposite of stressors" to "cognitive biases" exist for <u>vertebrates</u> and <u>invertebrates</u>
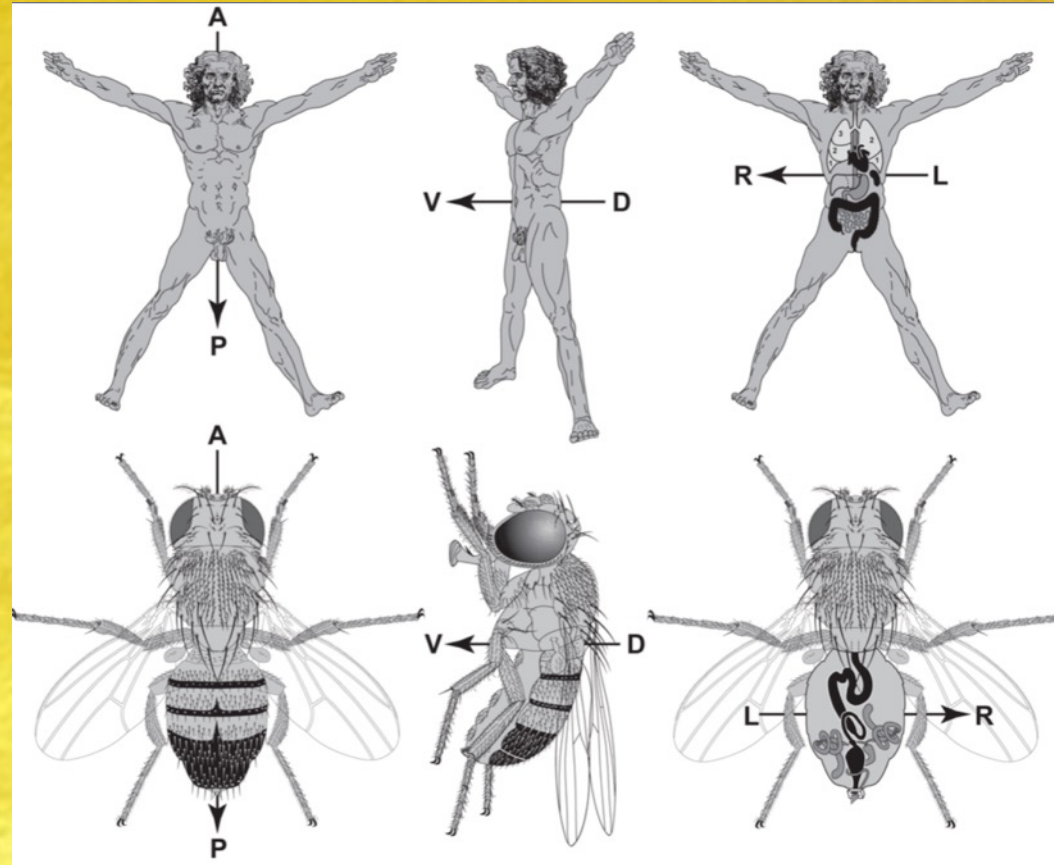
But again... why are we talking about *bug moods* ?

- They suggest that mood-like phenomena "highly conserved":

("Similarity is older than difference.")

- ...and possibly, *homologous* with <u>our</u> "mood machinery".

  - Note the same or similar monoamines: 5-HT (serotonin) and OA (octopamine - the norepinephrine of invertebrates)
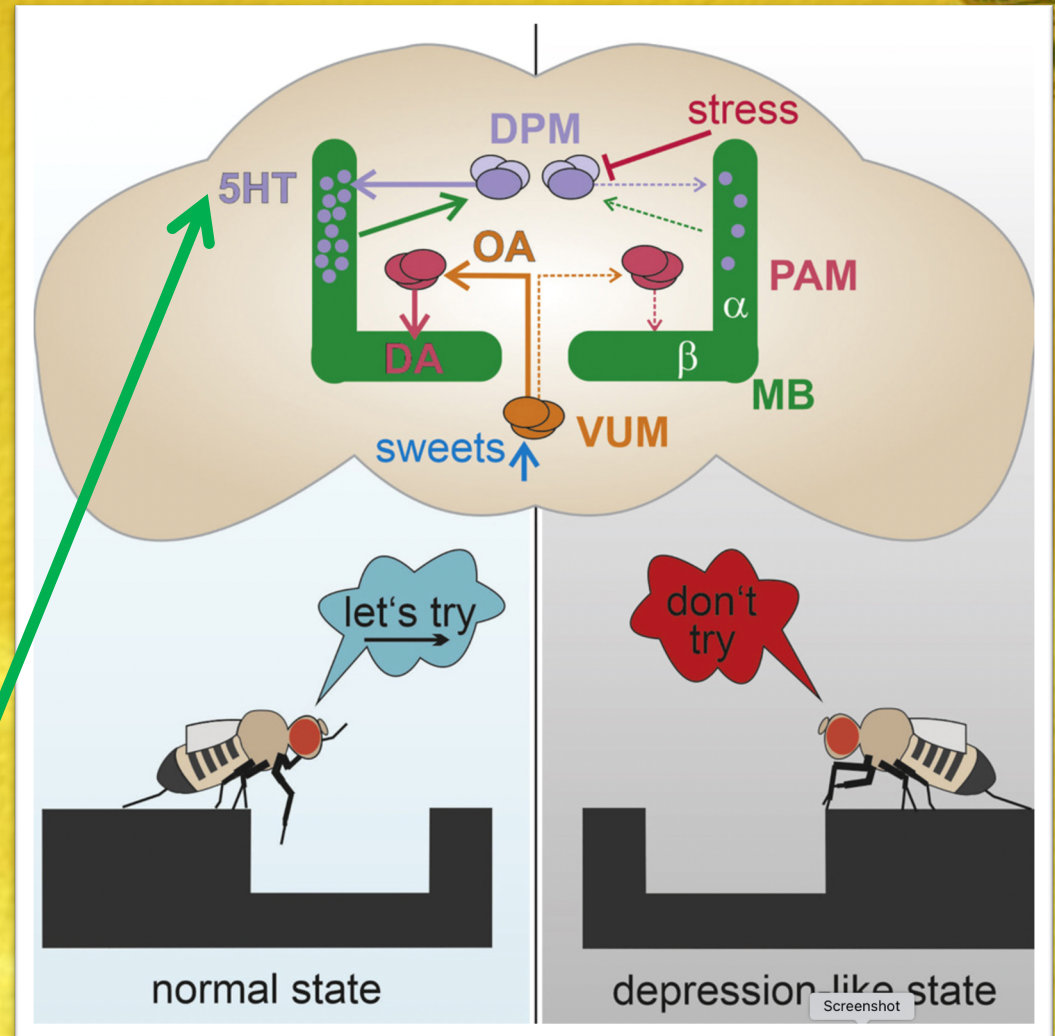
Graphical abstract from ***Octopamine mediates sugar relief from a chronic-stress-induced depression-like state in Drosophila***

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Where Affective Neuroscience meets   Behavioral Ecology meets *Engineering Robotics*

Stress, Evolution and Mood at "The Foundation"   ➔➔➔➔

The Evolutionary Origins of Mood and Its Disorders

Review

Daniel Nettle and Melissa Bateson

The term 'mood' in its scientific usage refers to relatively enduring affective states that arise when negative or positive experience in one context or time period alters the individual's threshold for responding to potentially negative or positive events in subsequent contexts or time periods. The capacity for mood appears to be phylogenetically widespread and the mechanisms underlying it are highly conserved in diverse animals, suggesting it has an important adaptive function. In this review, we discuss how moods can be classified across species, and what the selective advantages of the capacity for mood are. Core moods can be localised within a two-dimensional continuous space, where one axis represents sensitivity to punishment or threat, and the other, sensitivity to reward. Depressed mood and anxious mood represent two different quadrants of this space. The adaptive function of mood is to integrate information about the recent state of the environment and current physical condition of the organism to fine-tune its decisions about the allocation of behavioural effort. Many empirical observations from both humans and non-human animals are consistent with this model. We discuss the implications of this adaptive approach to mood systems for mood disorders in humans.

moods are, how they should be classified, and what the adaptive function of mood systems may be. The framework provides us with a clear definition of mood that can be applied across taxa, and we show that much of what we know empirically about mood phenomena both in humans and other species fits naturally into it. We also briefly discuss what light the adaptive perspective on mood *systems* sheds on the origins and distribution of mood *disorders* in humans.

The framework presented here integrates ideas from a number of sources, notably work on emotions as the activity of survival circuits related to reward and punishment [2–4], the dimensional classification of emotions [5–8], signal detection approaches to emotions [9–11], and the human and animal cognitive bias literatures [8,12,13]. It suggests potential relevance to mood phenomena of ideas from behavioural ecology concerning the adaptive tracking of changing environments [14–16], and the sensitivity of adaptive decisions to the individual's current physical condition [17]. These may be promising areas for future work.

Emotions: The Signal Detection Approach

Mood belongs to the class of affective, or emotion-related, phenomena. Emotions are suites of cognitive, motivational and physiological changes that are triggered by appraisal of specific classes of environmental situations [4,18]. Fear, for example, is a suite of responses including increased vigilance, attentional bias to potential sources of danger,

The Evolutionary Origins of Mood and Its Disorders

*(Yipes! Highly **theoretical** Behavioral Ecology!)*

Why love this paper that is of **no** *apparent* use for neuroscience that studies mechanisms? Nor apparently useful for practical psychiatry?

Because it's a "first principles" inquiry that *could* clarify some complexities in neuroscience, and the conceptual mess that is psychiatry...

- **Emotions** are "*...cognitive, motivational and physiological changes triggered by the **appraisal** of environmental situations",* changes that **allocate and marshal** the individual's cognitive and behavioral resources towards the most *immediately* important, *fitness-relevant* priorities given the <u>current</u> state of the world."

- Think of emotions working like ***detectors***: <u>Input</u> ➔<u>Output</u>
  - ⊙ <u>Input</u> : Event in the state-of-the-world ➔ <u>Output</u> : *Cognitive, physiological and motivational changes* that are adaptive for *coping* with - *or taking advantage* of - whatever triggered the <u>input</u> .

- Emotions ***detect and respond*** (later we'll contrast this with what **moods** do).

- (Remember we are at "The Foundation", so "emotions" here are only *basic emotions*).

- Organisms are constantly pelted with <u>noisy</u> information, whose *interpretation* is always **uncertain** – only probabilistically associated with "what's-really-out-there". Examples:
  - ⊙ Rustling noise in the forest... A patch of red, way across the valley...your friend ignores you passing by... an appealing stranger smiles...your S.O. takes *forever* to text back...
- But <u>decisions</u> whether to respond <u>must</u> be made, regardless of uncertainty! The signal-within-the-noise <u>could</u> be crucial for fitness or survival.

- *Thus organisms must "decide" how much information to gather before "firing the detector" (mobilizing a response).*

Four conditions of signal detection <u>decisions</u> and how <u>thresholds</u> affect responses: Two correct, two incorrect (errors of omission, errors of comission)

	X is the case	X is <u>not</u> the case
Responds as if X were the case	**Hit !** ✔ (true positive) *Lowering t h r e s h o l d*	**False alarm...** (false positive) *increases # of these*
Responds as if X were <u>not</u> the case	*Raising t h r e s h o l d* **Miss...** (false negative)	*increases # of these* **Correctly abstaining from responding** ✔ (true negative)

What is a detector's **optimal** threshold ("trigger happiness)?
An intuitive story: Imagine a smoke detector…

Beep! Beep! Beep!

	X is the case	X is <u>not</u> the case
Responds as if X were the case	**Hit !** ✔ **(true positive)** *Lowering threshold increases # of these*	**False alarm...** **(false positive)**
Responds as if X were <u>not</u> the case	*Raising threshold increases # of these* **Miss...** **(false negative)**	**Correctly abstaining from responding** ✔ **(true negative)**

Box 1

An illustrative model of mood effects.

How much information should a detector whose function is to detect a dangerous situation of class X require before outputting that X has occurred? Signal detection theory gives the optimal threshold as:

$$\lambda > \frac{(1-p)}{p} \cdot \frac{(w_{TN} + w_{FP})}{(w_{TP} + w_{FN})} \tag{1}$$

Here, λ is the likelihood ratio of the currently received information being generated when X does obtain compared to when it does not, p is the probability for the current environment that X does obtain, and the ws are the long-term expected fitness payoffs of the four possible outcomes of detection, the true positive (TP), the true negative (TN), the false positive (FP), and the false negative (FN). From (1), we see that as X becomes more prevalent in the environment (p is higher), the optimal threshold gets lower, and if the false negative is very costly compared to the false positive, the threshold should also be low (the 'smoke detector principle' [11,32]).

If the environment was dangerous today, how does this affect the optimal threshold for detecting threats tomorrow? Assume a world where the prevalence of threats has a long-term mean μ, and today's threat level, p_t, is partly predicted by the prevalence of threats yesterday p_{t-1}. We can thus write the expected deviation of p_t from μ as $\beta(p_{t-1} - \mu)$, where β is the temporal autoregression coefficient of the environment. Also, it could be the case that more threats yesterday, by depleting an individual's physical condition, makes undetected threats today more difficult to cope with, whilst few threats yesterday leads to an improvement in physical condition meaning undetected threats today are easier to cope with. We capture this by changing w_{FN} for today by an amount proportional to yesterday's threat prevalence ($\delta(p_{t-1} - \mu)$, where δ is a scaling factor). The optimal threshold for detecting a threat today is thus:

$$\lambda_t > \frac{(1 - \mu - \beta(p_{t-1} - \mu))}{(\mu + \beta(p_{t-1} - \mu))} \cdot \frac{(w_{TN} + w_{FP})}{(w_{TP} + (1 + \delta(p_{t-1} - \mu))w_{FN})} \tag{2}$$

Under these assumptions, then, events yesterday affect the optimal threat-detection threshold for today in two ways: via the autoregression coefficient of the environment (the more autocorrelated the environment, the more a bad yesterday should lower the optimal threat-detection threshold for today, and a good yesterday raise it) but also by the degree to which events yesterday affect the individual's capacity to cope with undetected threats today (the stronger the spillover effect δ, the more a bad yesterday should lower the optimal threshold today, and a good yesterday raise it). We can see how these forces interact by plotting the optimal threat-detection threshold for today against the prevalence of threats in the environment yesterday for representative values of the parameters of the model (Figure 2). Very similar models could be constructed for reward-approach rather than threat-avoidance, where positive experiences or an improvement in physical condition yesterday would affect the optimal threshold for responding to potential cues of reward today.

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From **emotions** as detectors to **moods**:
The engineering (*adaptationist*) challenge

Suppose that...

Stressors (punishments) tend to *clump together* as "bad times" and...

Rewards ("the *opposite* of stress") *clump together* as "good times".

→

Engineering question:

How would you set thresholds to trigger **emotions** (that only **detect-and-respond** moment–to-moment), so that the new thresholds usefully **predict and prepare**, now that you know that Stressors and Rewards *clump together*?

Mood as *adjustment of detection thresholds:* Preparing behavior for the future

- Appraising <u>repeated</u> stimuli as punishments triggers negative emotions - **and** sets a **lower threshold** for **detection** (and acting upon) future punishment.

  *Thus, a series of punishments lead to **anxious mood** that <u>persists</u> despite no immediate punishment.* (Anxious mood, i.e. vigilant attention-bias to threats, hyper-arousal etc.)

- Appraising <u>repeated</u> stimuli as rewards triggers positive emotions- **and** sets a **lower threshold** for **detecting** (and "going for") future reward

  *Thus a series of rewards lead to **elevated mood** that <u>persists</u> despite no immediate rewards.* (Elevated mood, i.e quick to initiate reward-approach, optimistic cognitive bias, etc)

- (A link to "learned helplessness": ***Repeated <u>futility</u>** of effort may compute as unexpected <u>absence</u> of Reward – ie as Punishment.*)

Classifying moods

- Notice, we have **two independent variables**:
  - *Threshold to detect/respond* to Punishment
  - *Threshold to detect/respond* to Reward

- Two independent variables cry out for plotting on x and y axes – so let's do so...

A 2D framework for classifying moods

High

Not anxious, but depressed

Not anxious, and not depressed (elevated)

High

Threshold for responding to possible *Reward*

Threshold for responding to possible **Punishment**

Anxious and depressed

Not depressed (elevated), but anxious
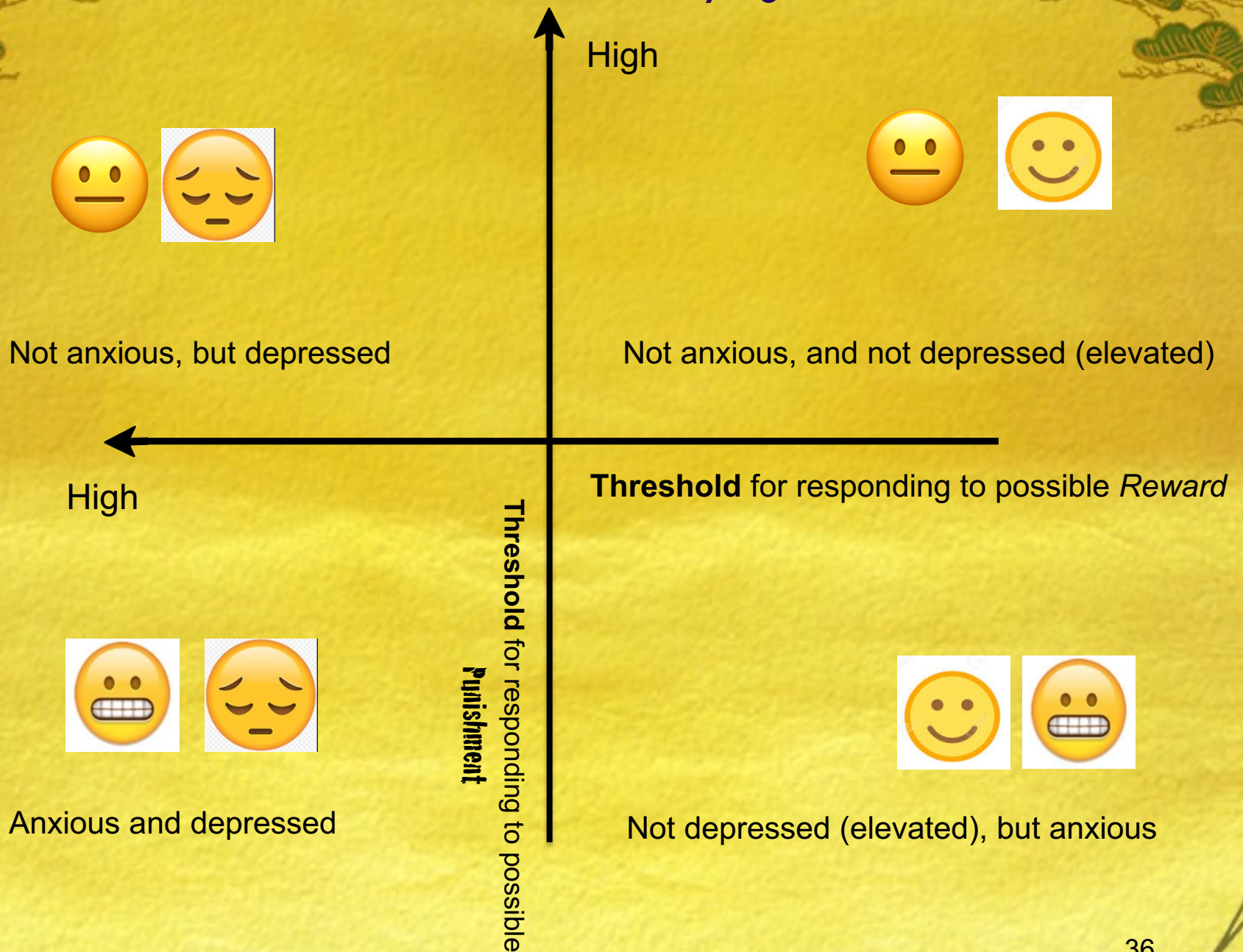
The line x=y captures subjective valence – disliking to liking

High

Feeling good →

High

Threshold for responding to possible *Reward*

Threshold for responding to possible **Punishment**
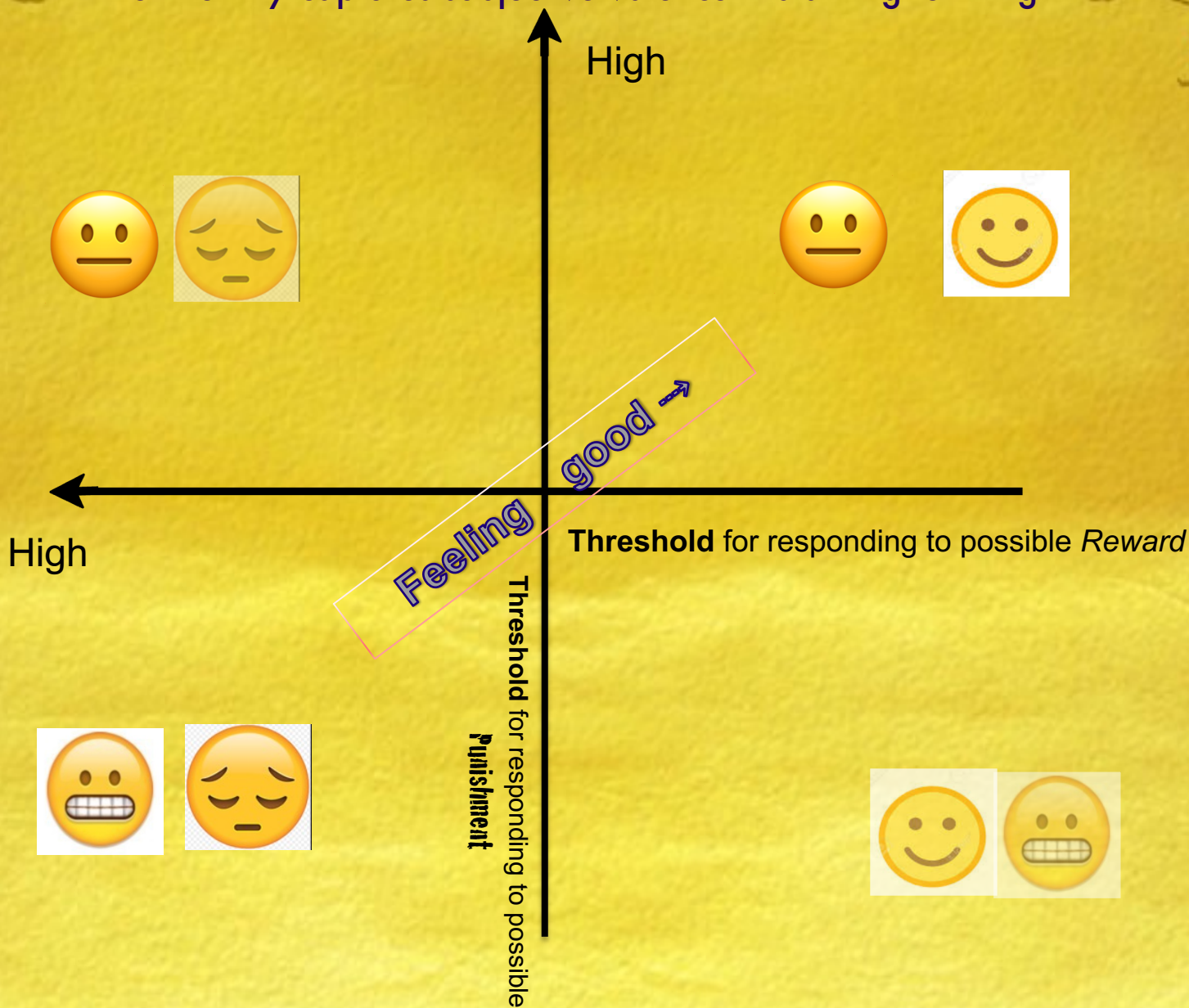
A definition of "mood" that applies from bugs to humans

- **"Moods** are relatively <u>enduring</u> states that arise when negative or positive experience in one *context or time period* <u>adjusts the individual's</u> *threshold for responding to* potentially negative or positive events *in subsequent contexts or time periods*."
  - ⊙ (Notice, *consciousness not needed*! Think of *blindsight*...)
- Unlike emotions, **moods** are detached from any one *immediate* triggering stimulus –their *proximate* cause appears to be *an integrative function* of the organism's emotional experiences *over time*.
- *Moods* "spill over" emotional states beyond current events or context. *Moods make a bet that "here and now " will apply to "then and there".*

  Emotions **detect and respond;** *moods* **integrate to prepare.**

- But, we still haven't answered the **central adaptationist question**: What's the point of "integrating"? Of "spilling over"?

Rewards and Punishments "clumping together", or The autocorrelation of the world

- So... mood induced by stimuli *biases* judgment about later, "unrelated" stimuli. *Why would this make sense?* Why not evaluate each situation as it comes, at immediate face value? We must figure out why this BIASED JUDGMENT could promote ADAPTIVE behavior.

- Because of the basic structure of the universe! Punishments *clump together* as "bad times" and rewards *clump together* as "good times", because

  The world is generally <u>autocorrelated</u>...

  (i.e, today's world **predicts** tomorrow's)

  (An idea so dumb, it's deep...)

- Thus our emotion system should exploit this information and set detection thresholds accordingly – to **optimally allocate effort.**

  *Having emotions but no moods would be **like flying blind**.*

Notice: So far, we've talked about the probability of rewards and punishments "out in the world". What about what kind of shape the organism is in?

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The **physical condition** of the organism is *also autocorrelated*
(Lame today, likely lame tomorrow…)

- **Physical condition** is not relevant to the <u>probability</u> of rewards and punishmenst, <u>but</u> it does affect the <u>value</u> (costs vs. profits) of signal detection decisions. For example:
  - Costly false negatives in the domain of <u>predation</u> if you are **lame** (hobbled escape...)
  - Costly false positives in the domain of <u>foraging</u> when **poorly nourished** (wasted effort...)

- Notice, *physical infirmity* means that individuals are <u>both</u> less able to cope with threats, <u>and</u> less able to risk wasted energy failing at reward capture.
  - *A psychological prediction: **Being weak, lame, or sick** should make **both** anxious and depressed moods more likely.*

- So, the *autocorrelation* of the *organism's condition* makes carrying over the impact reward and punishment adaptive (makes a further case for adjusting detection thresholds).

Now, "the organism's condition" might mean more than just "health of the body"…

- Highly social organisms don't just have a "physical condition", they also have a **social** **condition** that also *autocorrelates* from today to tomorrow.

    (Low status today, likely low status tomorrow.)

- (We'll see how the **social condition** of the organism plays *the key role indeed* in determining mood, when we study the two "middle of the high-rise" hypotheses).

Extra credit (unofficial 😉 …) for Office Hours discussion!

Help Dr. Ozores reconcile this theory ("The Foundation of Mood") with "upper floor theories" of the evolution of mood that we'll discuss next time: How can animal models of "stress - causes-depression" use what seem like "punishments" to elicit depression, instead of anxiety? (To get you started: Maybe stressors like tail suspension may "compute as" lameness/bad physical condition/helplessness? Social defeat, more than punishment, may compute as futility of effort and low status? For humans, "bad news" or losses are not "punishment" but predictors of "bad times / low chance of goal-attainment rewards" coming? (For example, getting a bad grade...)

"The Foundation of Mood" Summary

- Why do we call it "The Foundation"? Because no more basic factors governing animal behavior are conceivable than reward and punishment, the condition of the organism, and the **autocorrelations** of the world and the condition of the *self*.

- **Emotions <u>detect and respond</u>** to "good and bad", to rewards and punishments here and now. **Moods <u>integrate</u>** information about such *frequency* of rewards and punishments "out in the environment", and the *condition of the organism*, fine-tuning **how to allocate effort** by setting detection thresholds.

Takeaways:

Emotions detect and respond.

Moods integrate to predict and prepare.

Moods track the propitiousness of situations.

Moods "represent the momentum of the world".