



Computational modeling of interoceptive dysfunction across psychiatric disorders

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How well do you understand the concept of interoception?

- A. Not very well
- B. A little
- C. Moderately
- D. Quite well



LIBR

Laureate Institute for Brain Research



No conflicts of interest to disclose

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and The William K. Warren Foundation

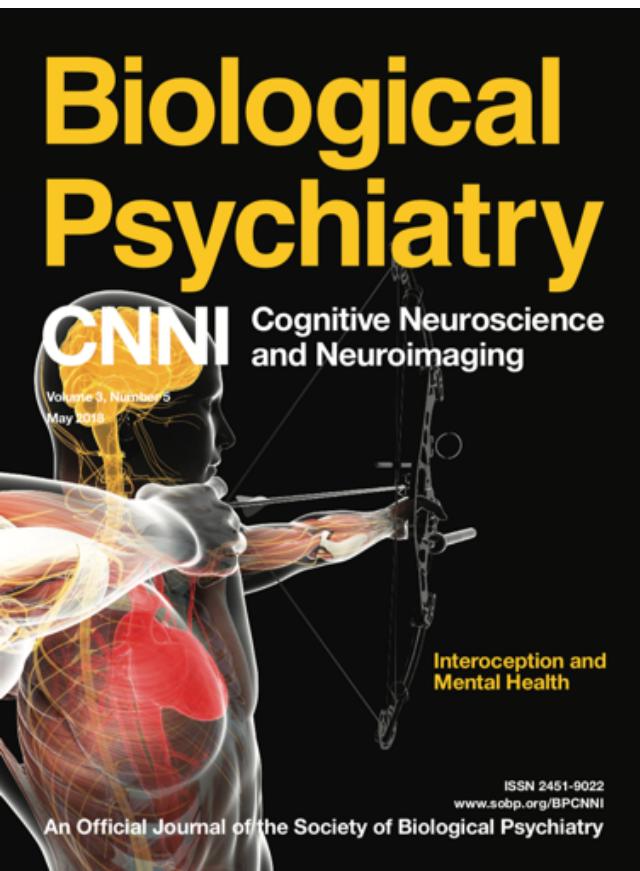
The Laureate Institute for Brain Research (LIBR) is a
nonprofit clinical neuroscience research institute focused
on discovering novel therapies and tools for helping
individuals with mental illness.



Review

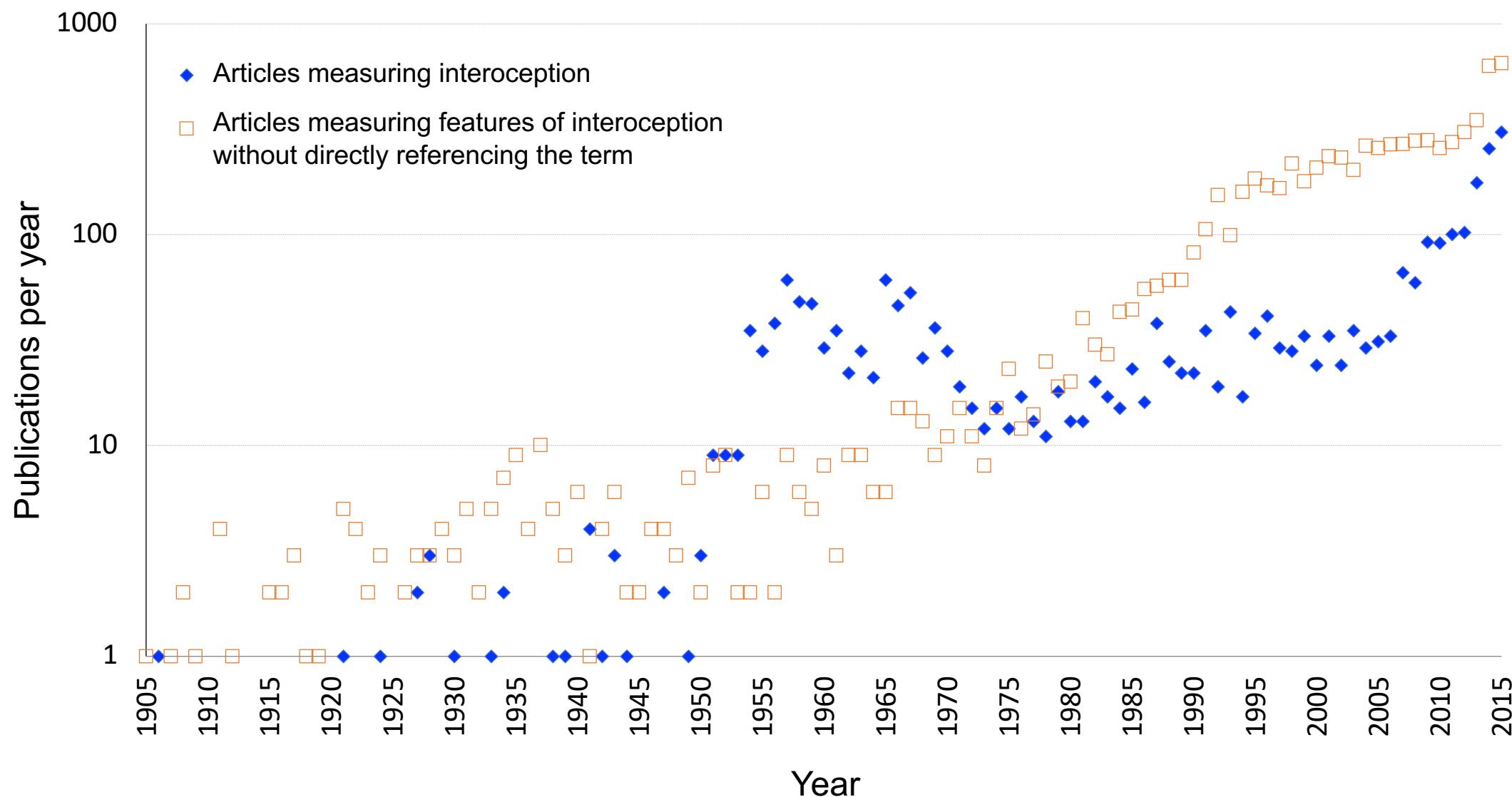
Interoception and Mental Health: A Roadmap

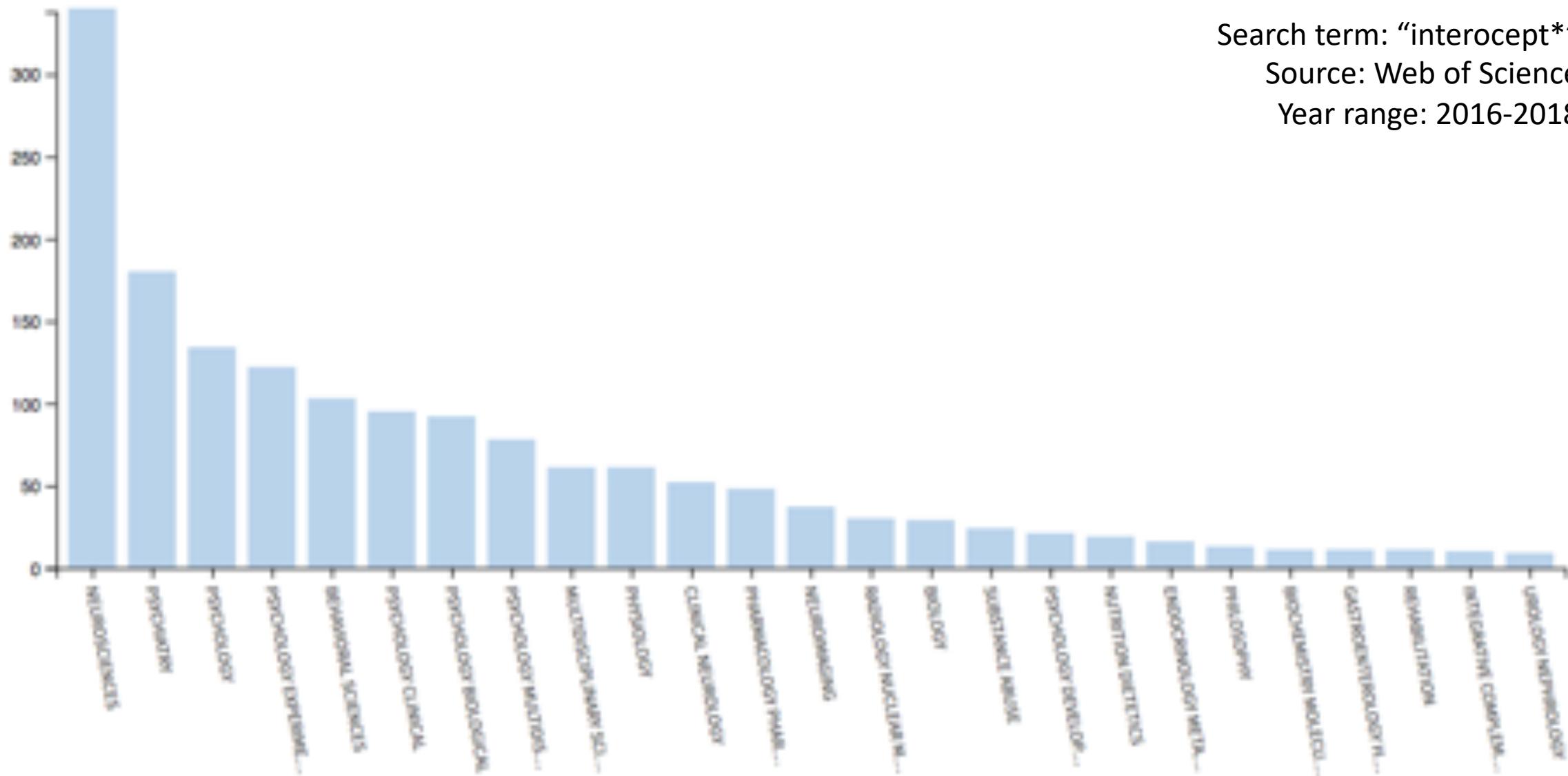
Sahib S. Khalsa, Ralph Adolphs, Oliver G. Cameron, Hugo D. Critchley, Paul W. Davenport, Justin S. Feinstein, Jamie D. Feusner, Sarah N. Garfinkel, Richard D. Lane, Wolf E. Mehling, Alicia E. Meuret, Charles B. Nemeroff, Stephen Oppenheimer, Frederike H. Petzschner, Olga Pollatos, Jamie L. Rhudy, Lawrence P. Schramm, W. Kyle Simmons, Murray B. Stein, Klaas E. Stephan, Omer Van den Bergh, Ilse Van Diest, Andreas von Leupoldt, Martin P. Paulus, and the Interoception Summit 2016 participants



Interoception refers to the process by which the nervous system senses, interprets, and integrates signals originating from within the body, providing a moment-by-moment mapping of the body's internal landscape across conscious and unconscious levels.

It forms the basis for regulation of internal body signals, participating in a '**brain-body feedback loop**'





Search term: “intercept*”
Source: Web of Science
Year range: 2016-2018

Interoception is critical for ensuring homeostasis

Table 1. Physiological Processes Often Ascribed to Interoception

Nonpainful

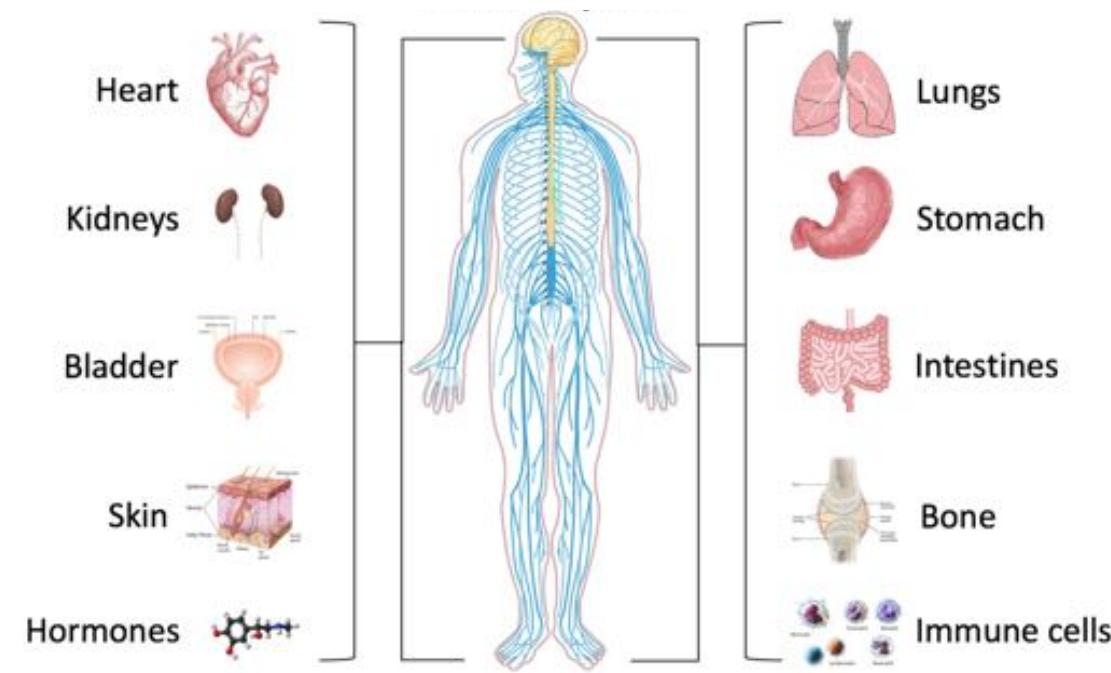
Cardiovascular, respiratory, gastrointestinal (esophageal, gastric, intestinal, colorectal), bladder, hunger, thirst, blood/serum (pH, osmolality, glucose), temperature, vasomotor flush, air hunger, muscle tension, shudder, itch, tickle, genital sensation, sensual touch, fatigue

Painful

Visceral: kidney stone, pleuritic, angina, pericardial, bowel ischemia, pelvic, sickle crisis

Somatic: abscess/boil, bruising, myalgia, inflammation (systemic/laceration), headache

Skeletal: fractured/bruised bone, stress fracture, inflammatory/mechanical joint pain



<https://en.wikipedia.org/wiki/Interoception>



Cardiovascular

Respiratory

Urinary

Temperature

Hunger

Palpitation

Gastrointestinal

(esophageal,
gastric, intestinal, colorectal)

Itch

pH

Vasomotor flush

Thirst

Dyspnea

Kidney pain

Fatigue

Pleasurable touch

Glucose

Interoceptive dysfunction in psychiatric disorders

Psychiatric Disorder	Symptoms	Signs	Sample Studies
Panic Disorder	Palpitations, chest pain, dyspnea, choking, nausea, dizziness, flushing, depersonalization/derealization	Elevated heart rate and/or blood pressure, exaggerated escape, startle, and flinching	(5,140,141)
Depression	Increased or decreased appetite, fatigue, lethargy	Weight gain, weight loss, psychomotor slowing	(142,143)
Eating Disorders	Hunger insensitivity, food anxiety, gastrointestinal complaints	Severe food restriction, severe weight loss, binging, purging, compulsive exercise	(72,95)
Somatic Symptom Disorders	Multiple current physical and nociceptive symptoms	Medical observations do not correspond with symptom report	(144,145)
Substance Use Disorders	Physical symptoms associated with craving, intoxication, and/or withdrawal (drug specific)	Elevated/decreased: heart rate, respiratory rate, and/or blood pressure, pupil dilation/constriction, others (drug specific)	(101,146,147)
Posttraumatic Stress Disorder	Autonomic hypervigilance, depersonalization/derealization	Exaggerated startle, flinching, and/or escape responses, elevated heart rate and/or blood pressure	(148)
Generalized Anxiety Disorder	Muscle tension, headaches, fatigue, gastrointestinal complaints, pain	Trembling, twitching, shaking, sweating, nausea, exaggerated startle	(149,150)
Depersonalization/Derealization Disorder	Detachment from one's body, head fullness, tingling, lightheadedness	Physiological hyporeactivity to emotional stimuli	(151,152)
Autism Spectrum Disorders	Skin hypersensitivity	Selective clothing preferences	(107,153,154)

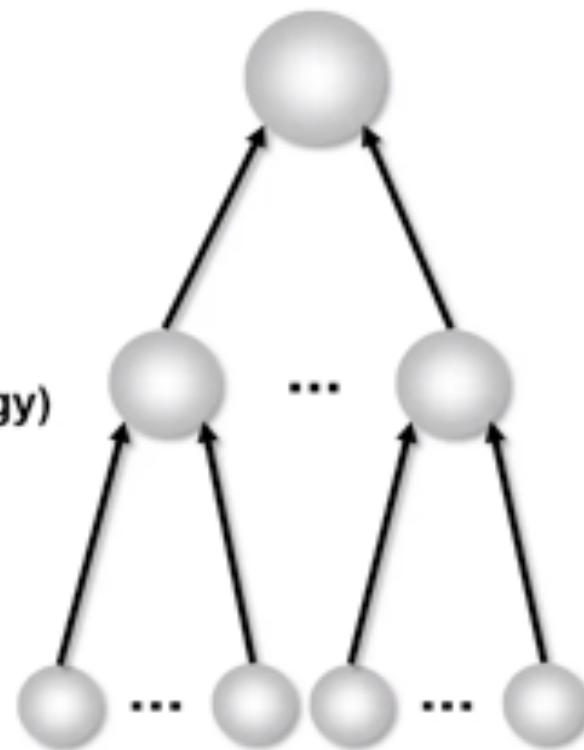
Interoceptive dysfunction in psychiatric disorders

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Autism Spectrum Disorders	Skin hypersensitivity		

SYMPTOM

MECHANISMS
(pathophysiology)

CAUSES
(aetiology)



Stephan: *Translational Neuromodeling & Computational Psychiatry, in prep.*

Can you feel your heartbeat right now
(without taking your pulse)?

A. Yes

B. No

How well can you feel your heartbeat?

40%

Ferguson & Katkin 1996

30%

Schneider et al 1998

17%

Wiens et al 2000

25%

Mesas & Chica 2003

34%

Average

47%

Mesas & Chica 2003

39%

Khalsa et al 2009

Meditation

33%

Katkin et al 2001

44%

Khalsa et al 2009

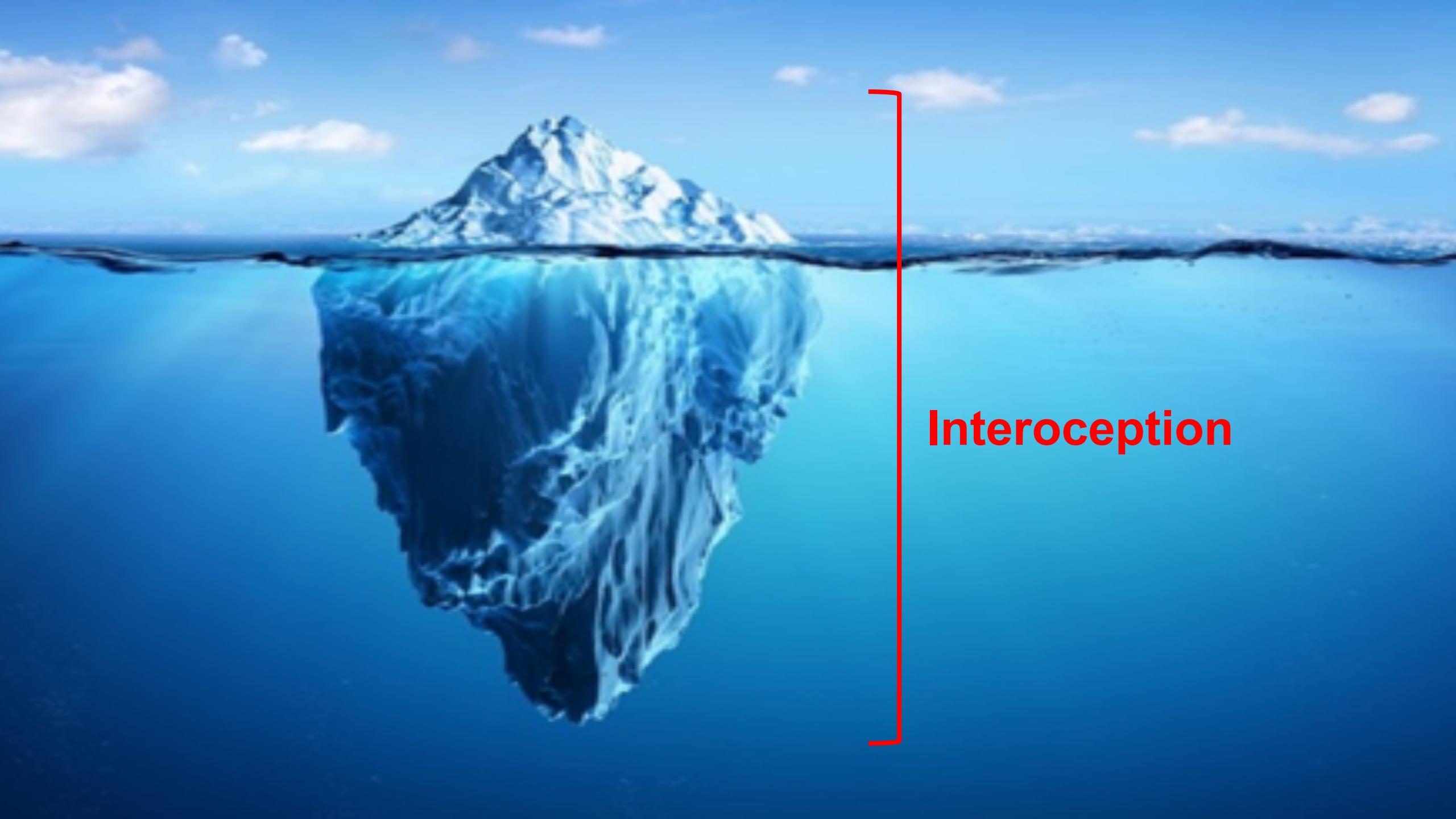
Meditation

35%

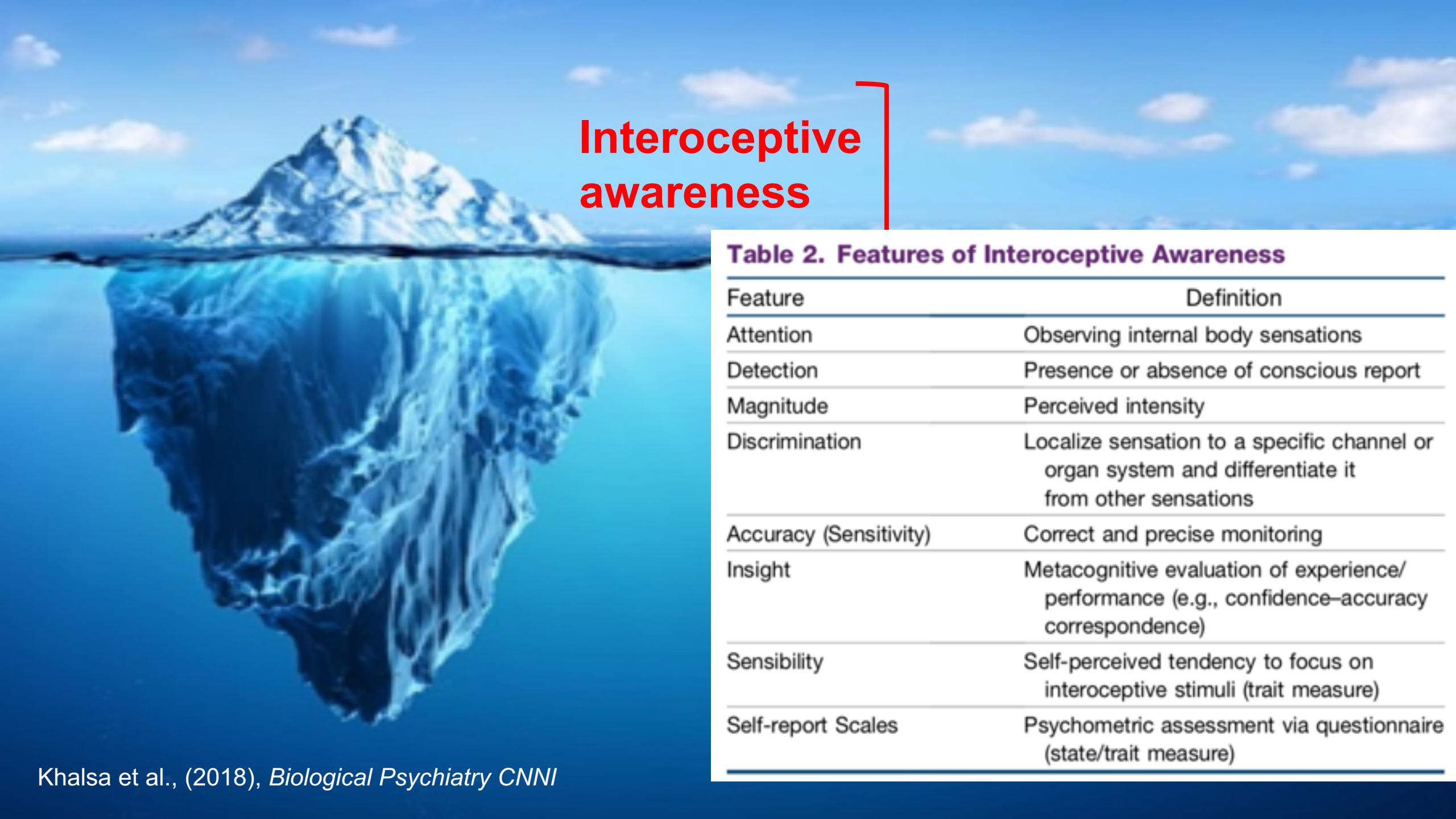
Heart transplant

Barsky et al 1998

See Khalsa & Lapidus (2016)
Front Psychiatry for a review



Introception

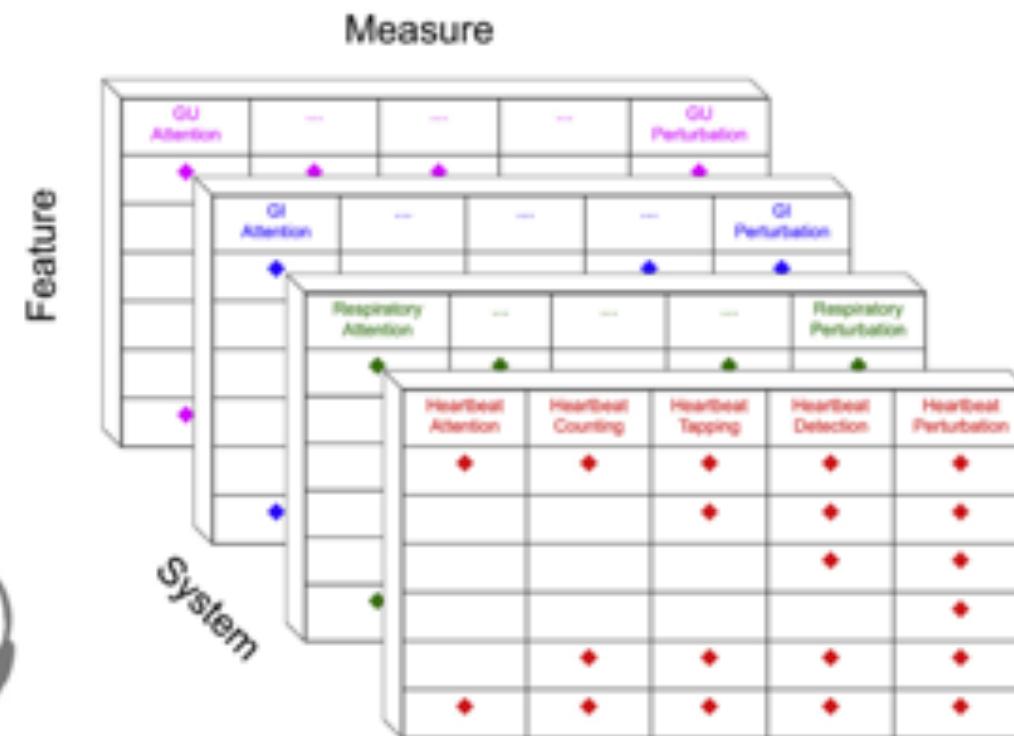
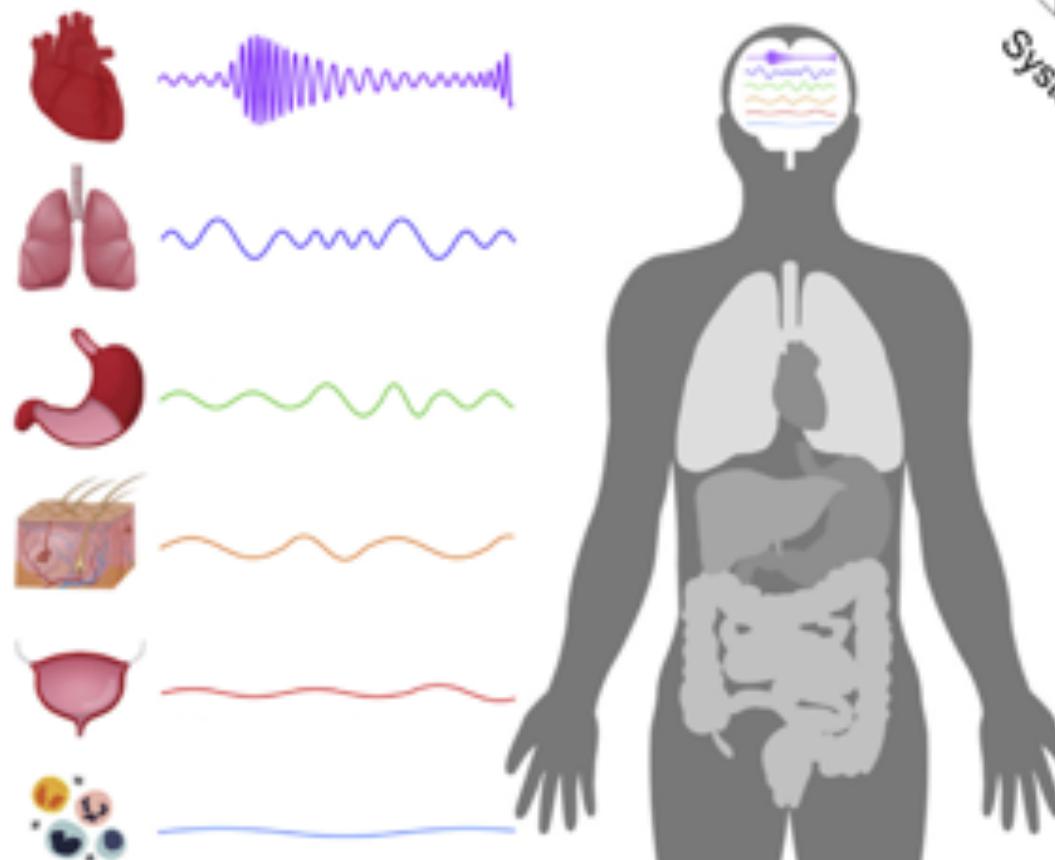


Interoceptive awareness

Table 2. Features of Interoceptive Awareness

Feature	Definition
Attention	Observing internal body sensations
Detection	Presence or absence of conscious report
Magnitude	Perceived intensity
Discrimination	Localize sensation to a specific channel or organ system and differentiate it from other sensations
Accuracy (Sensitivity)	Correct and precise monitoring
Insight	Metacognitive evaluation of experience/ performance (e.g., confidence–accuracy correspondence)
Sensibility	Self-perceived tendency to focus on interoceptive stimuli (trait measure)
Self-report Scales	Psychometric assessment via questionnaire (state/trait measure)

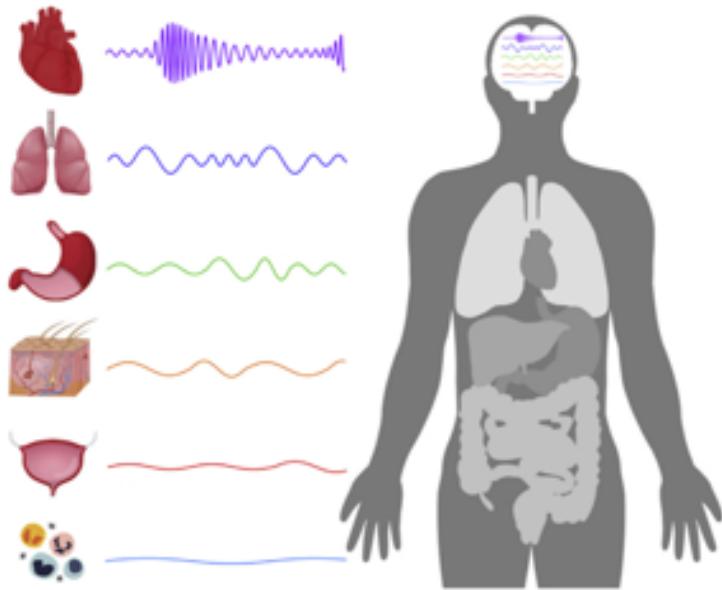
Feature	Heartbeat Attention	Heartbeat Counting	Heartbeat Tapping	Heartbeat Detection	Heartbeat Perturbation
Attention	♦	♦	♦	♦	♦
Detection		♦	♦	♦	♦
Discrimination			♦	♦	♦
Intensity				♦	♦
Accuracy		♦	♦	♦	♦
Self report	♦	♦	♦	♦	♦



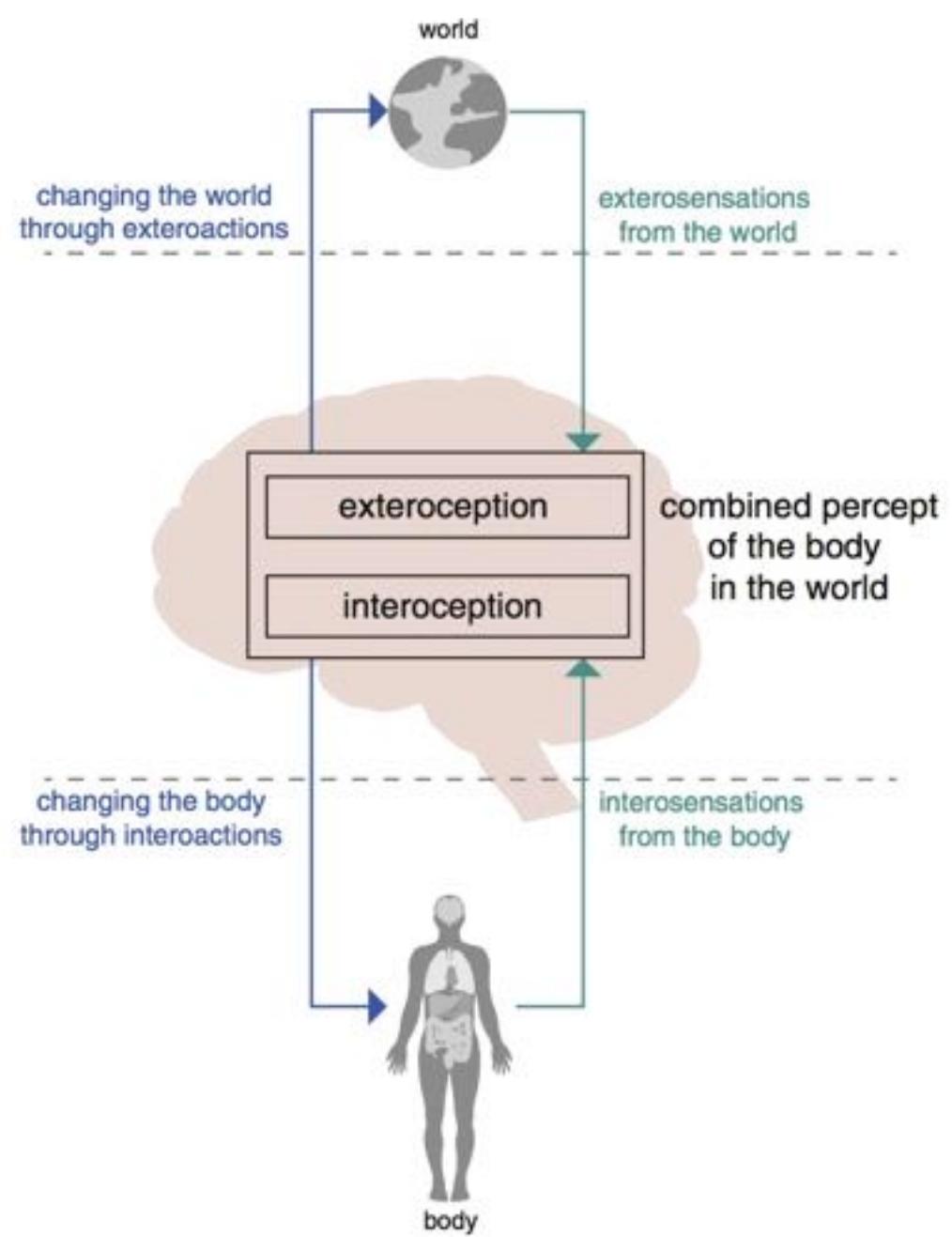
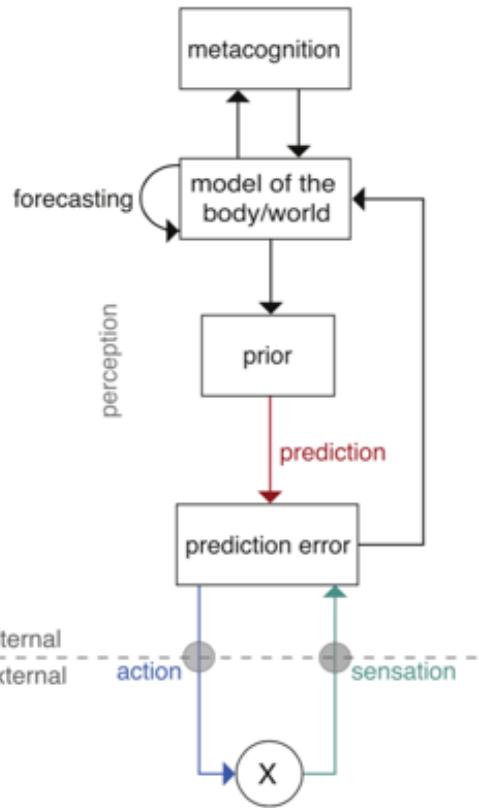
Amplitude modulation

Frequency modulation

Amplitude and frequency modulation



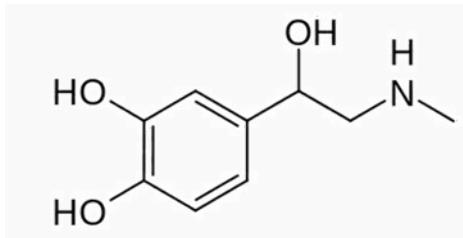
Khalsa et al., (2018)
Biological Psychiatry CNNI



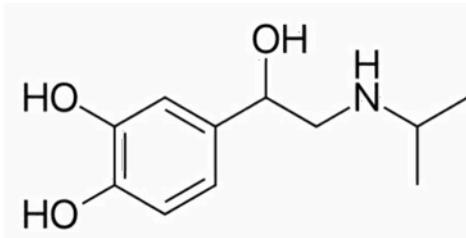
Petzschner et al (2017) *Biological Psychiatry*

One approach to studying signaling pathways involved in interoception

Approach: examine the brain's response to peripheral stress

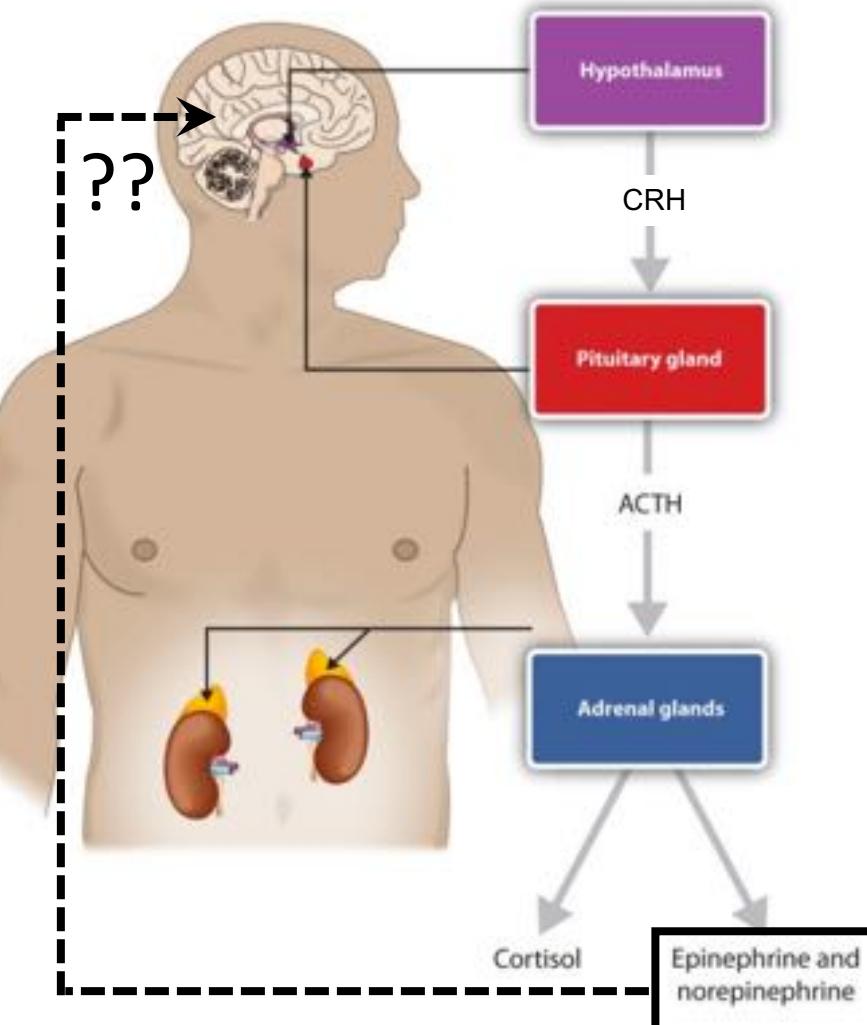
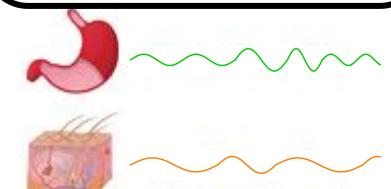
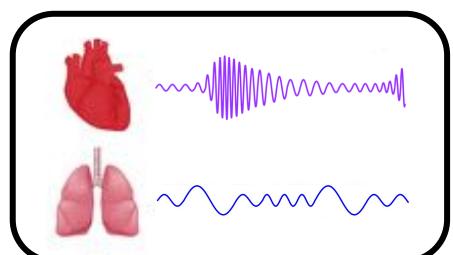


Epinephrine
(Adrenaline)

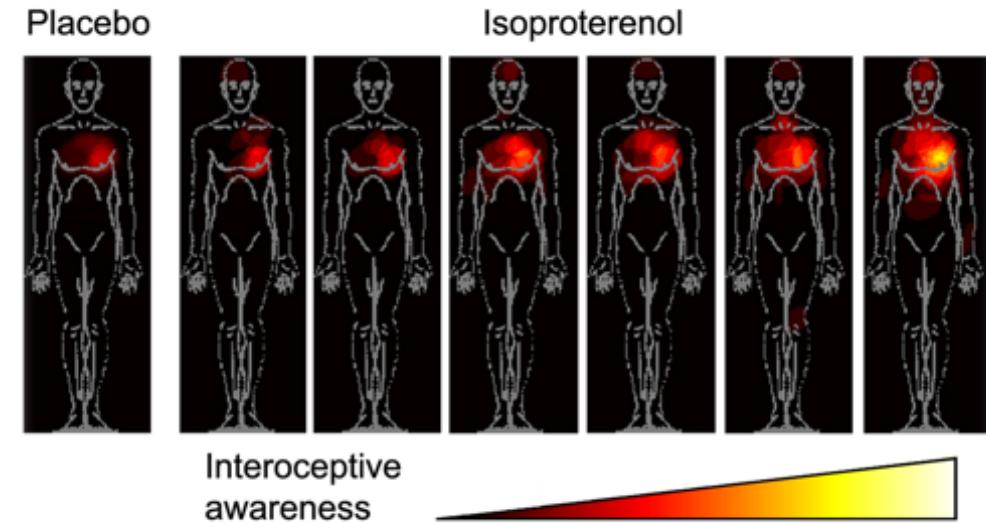
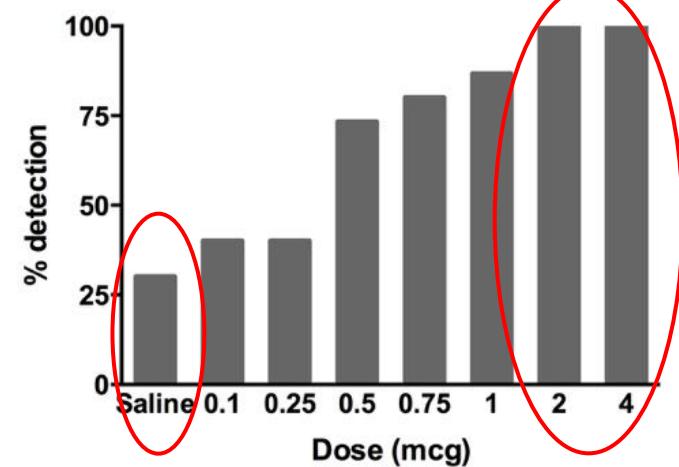
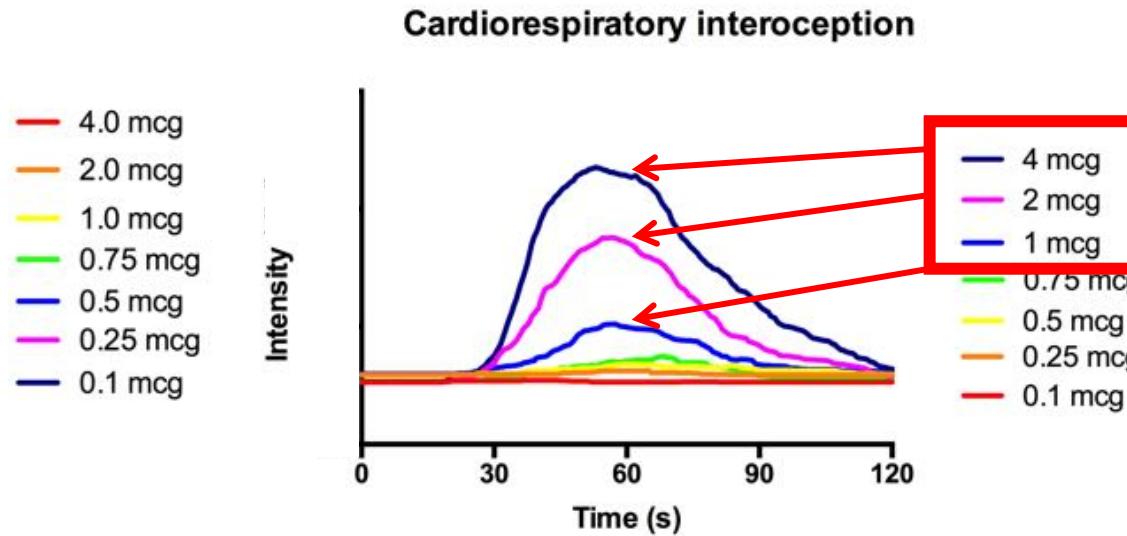
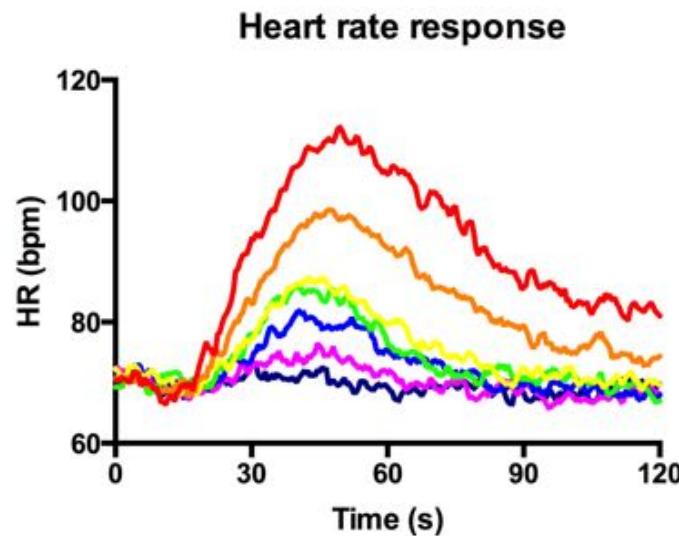


Isoproterenol

Isoproterenol stimulates beta-adrenergic receptors in the heart and lungs



Isoproterenol increases sympathetic arousal and the conscious experience of cardiorespiratory sensations

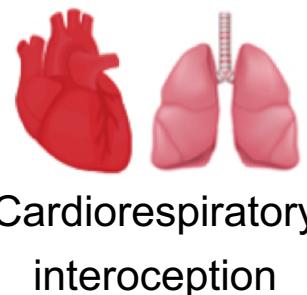


The Insular Cortex Dynamically Maps Changes in Cardiorespiratory Interoception

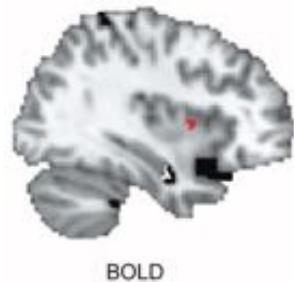
Neuropsychopharmacology (2018) 43, 426–434

Mahlega S Hassanpour¹, W Kyle Simmons^{1,2}, Justin S Feinstein^{1,2}, Qingfei Luo¹, Rachel C Lapidus³, Jerzy Bodurka^{1,4}, Martin P Paulus¹ and Sahib S Khalsa^{2,1,2}

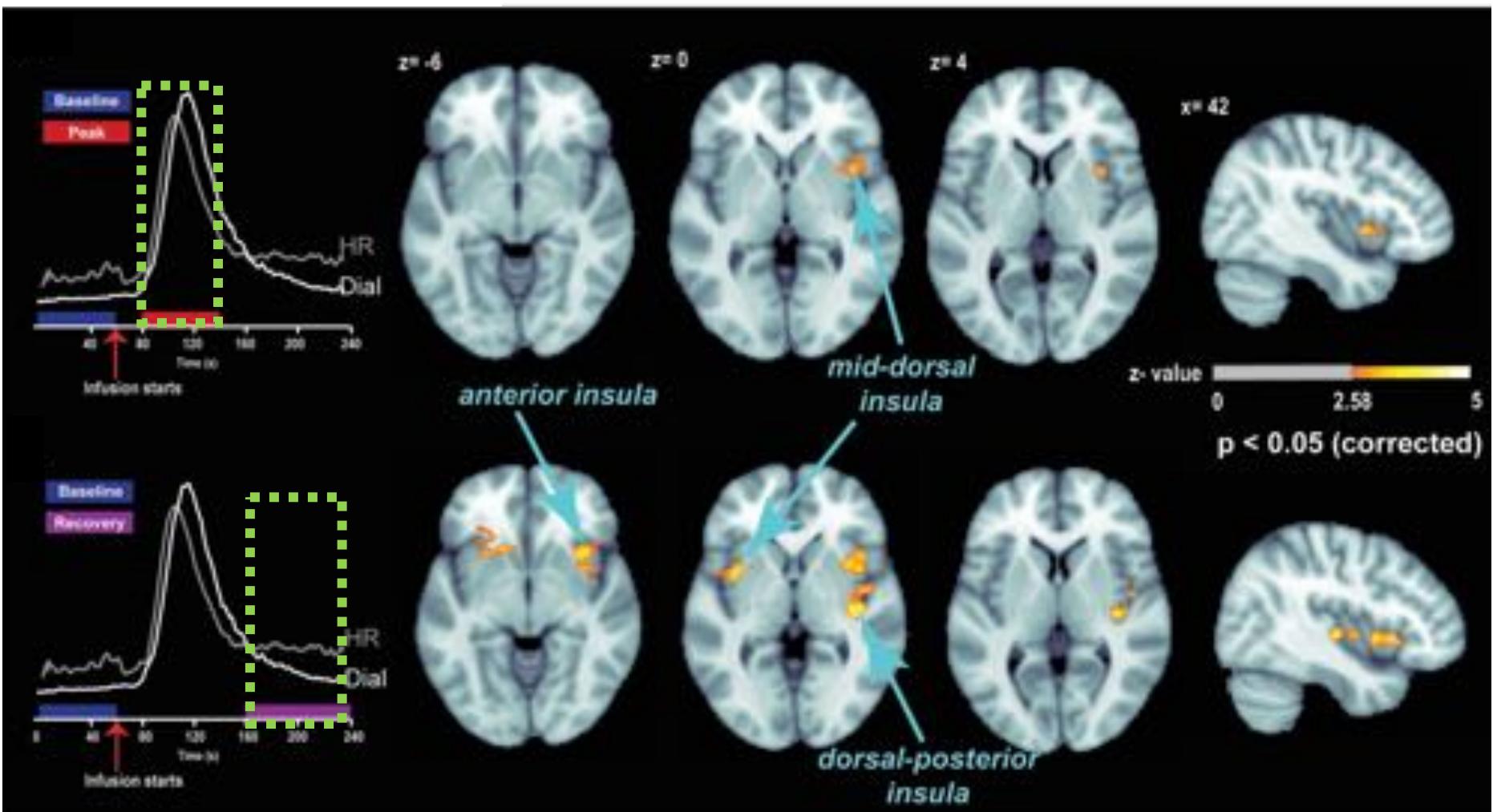
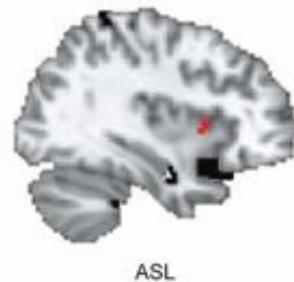
¹ Laureate Institute for Brain Research, Tulsa, OK, USA; ² Oxley College of Health Sciences, University of Tulsa, Tulsa, OK, USA; ³ Department of Psychology, University of Tulsa, Tulsa, OK, USA; ⁴ Stephenson School of Biomedical Engineering, University of Oklahoma, Norman, OK, USA



First study



Replication

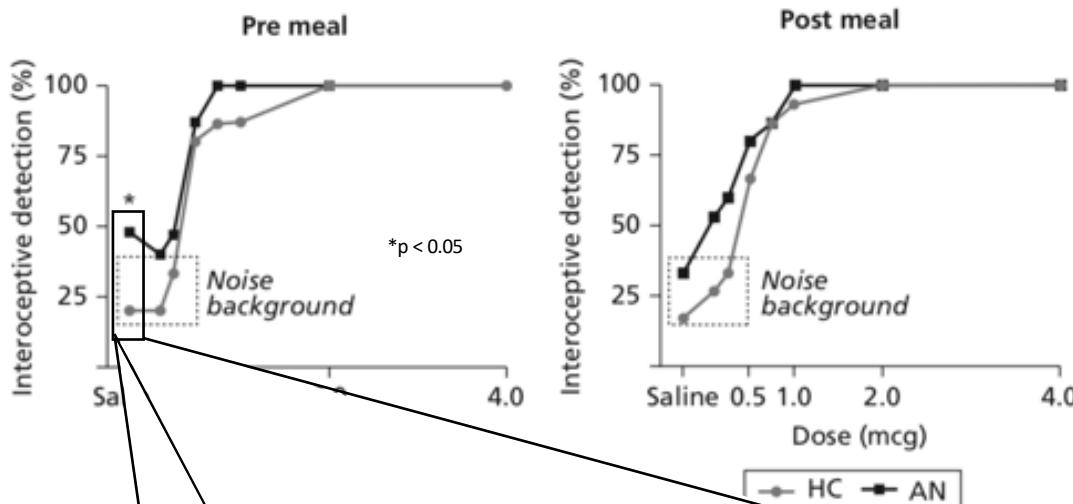


Erroneous interoceptive mapping in anorexia nervosa (AN)

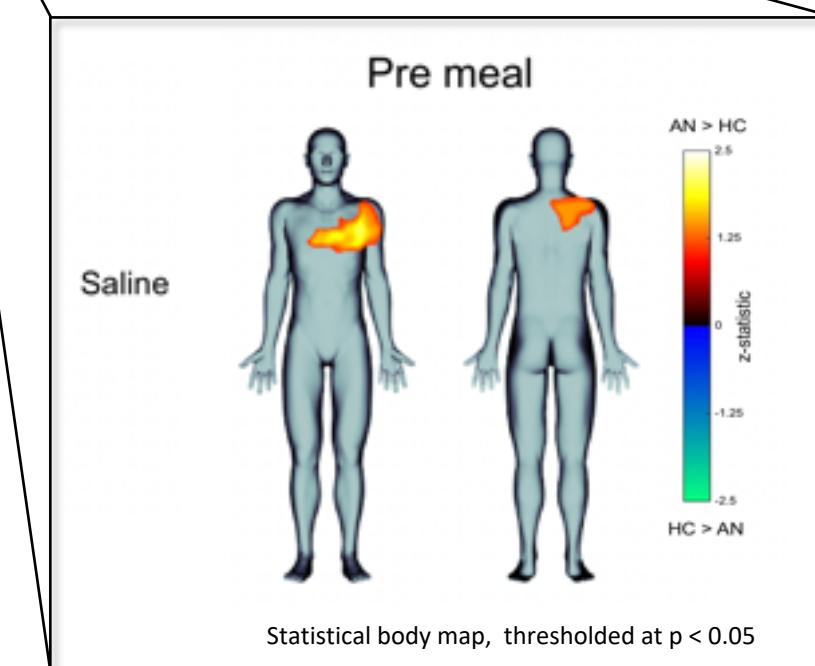
Individuals with AN reported greater false perceptions of the cardiorespiratory sensations during the pre meal time period

The false perceptions were associated with a greater localization of heartbeat sensations to the chest – in the absence of any stimulation!

These “*visceral illusions*” suggest that AN is associated with an abnormal representation of the heartbeat, particularly before anxiety-provoking meals



Khalsa et al. (2015)
Int. J. Eating Disorders

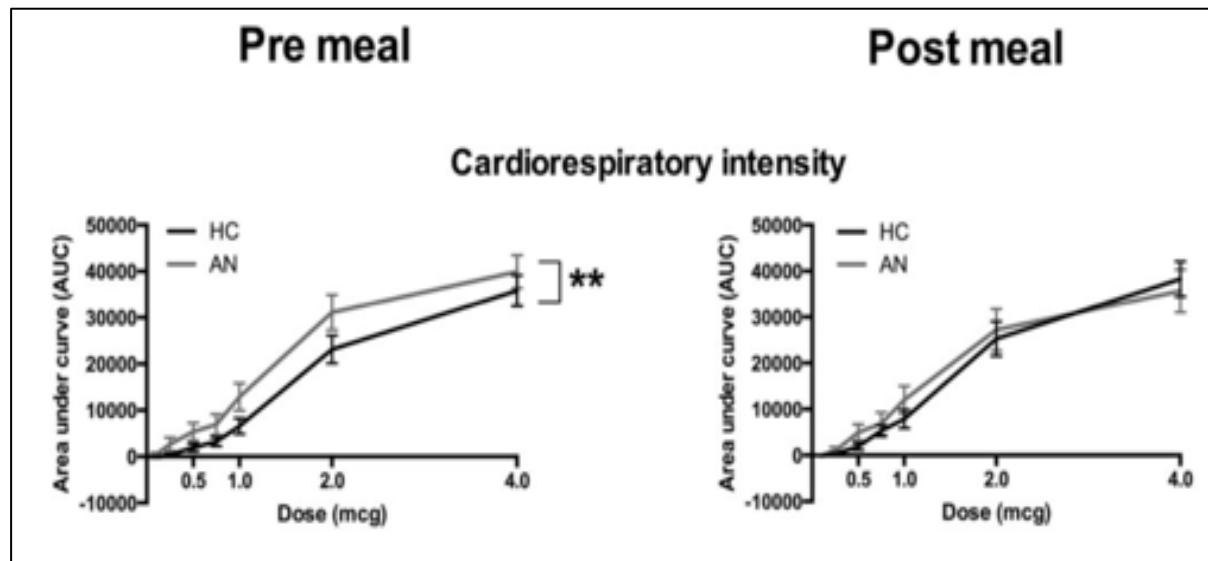


Khalsa et al. (2018)
Front Psychiatry

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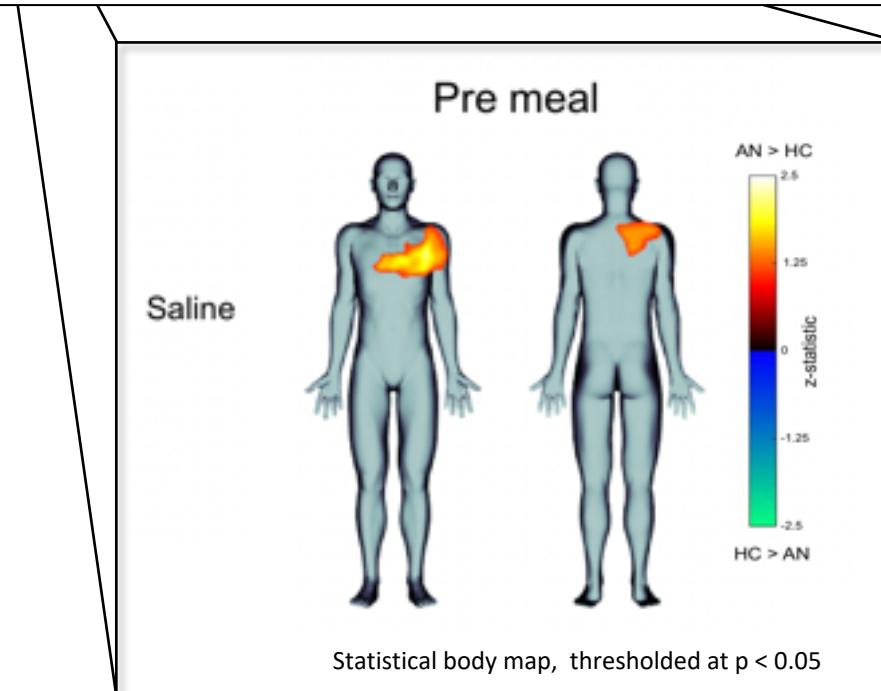
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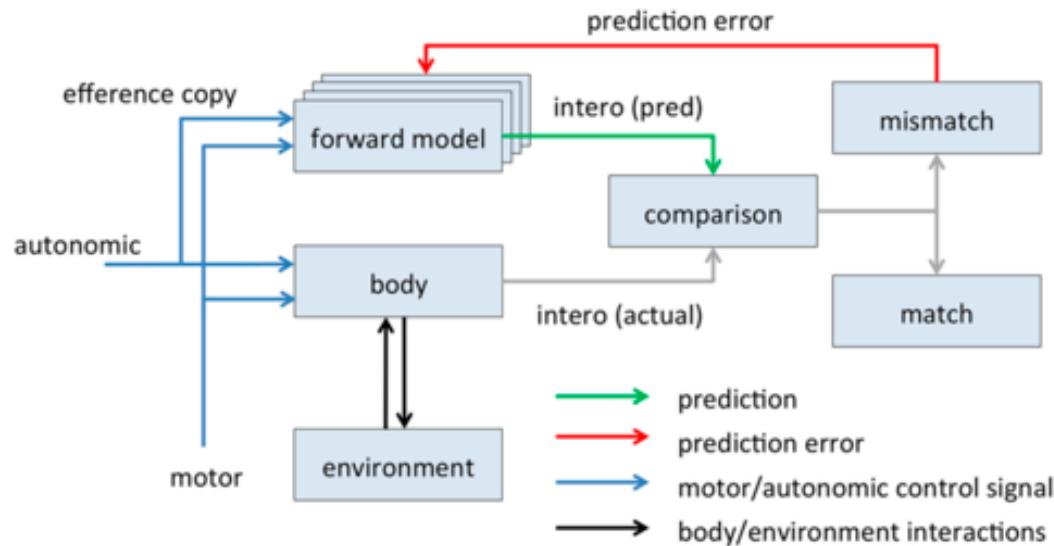


Khalsa et al. (2015)
Front. J. Eating Disorders

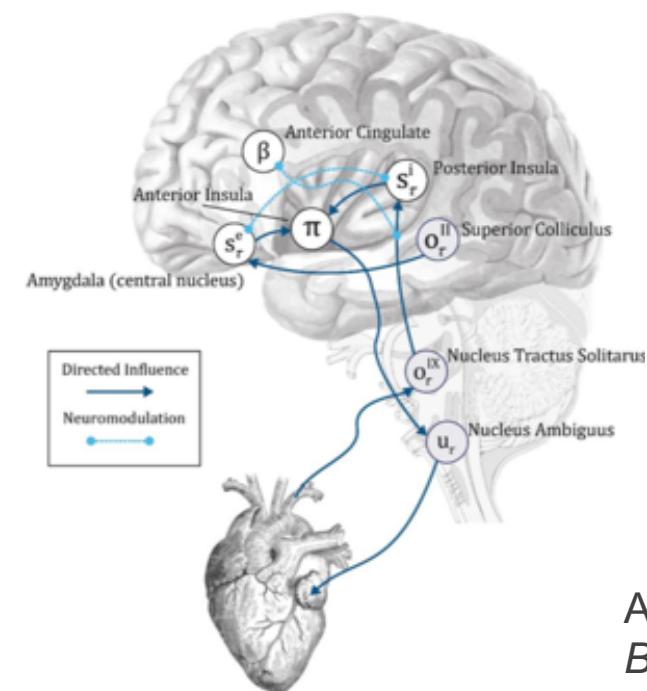
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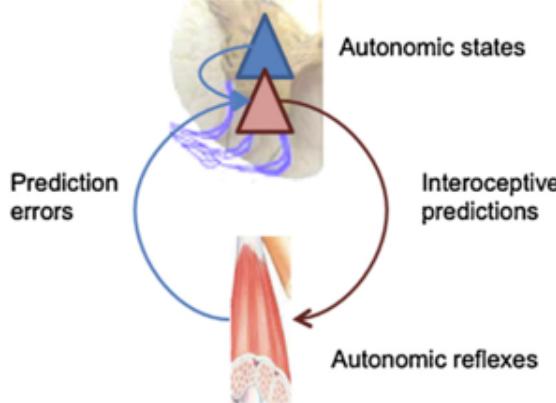
Khalsa et al. (2018)
Front Psychiatry



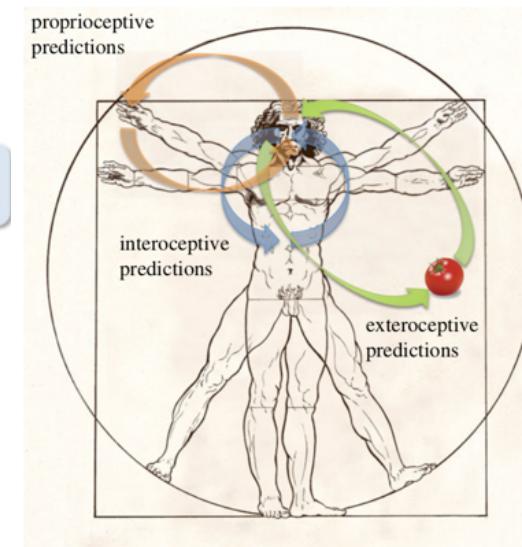
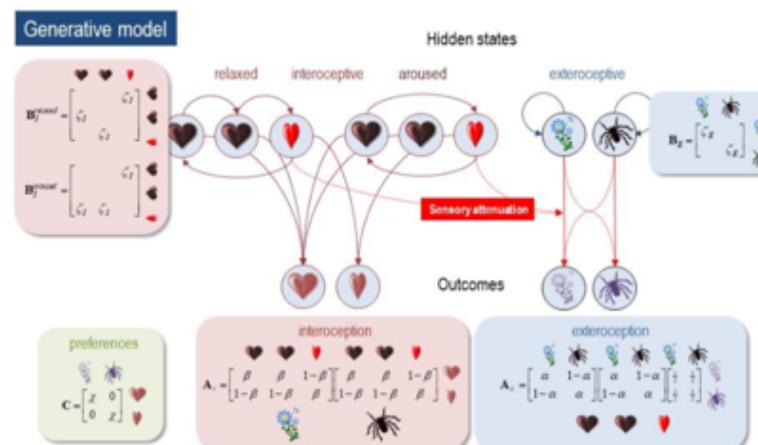
Seth, Suzuki & Critchley (2011), *Front Psychology*



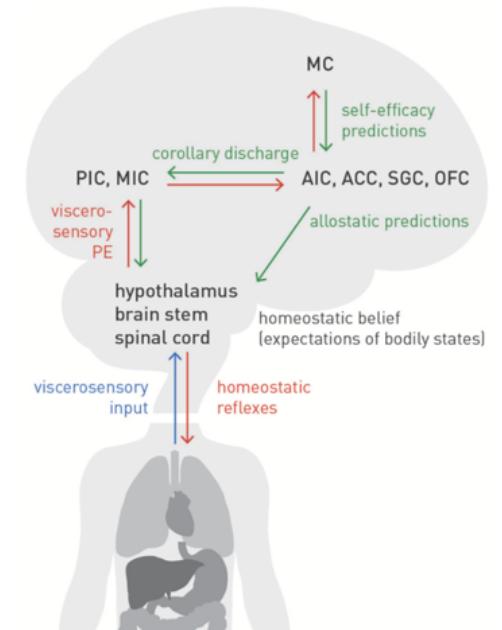
Allen, Levy, Parr, Friston (2019)
BioRxiv



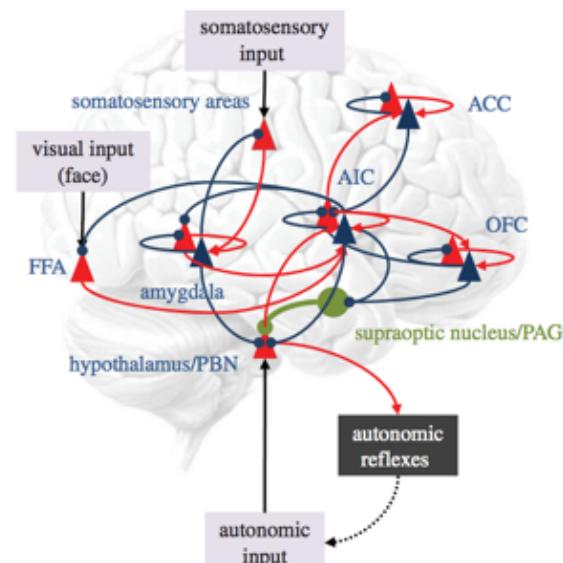
Pezzulo, Rigoli & Friston
(2015), *Prog Neurobio*

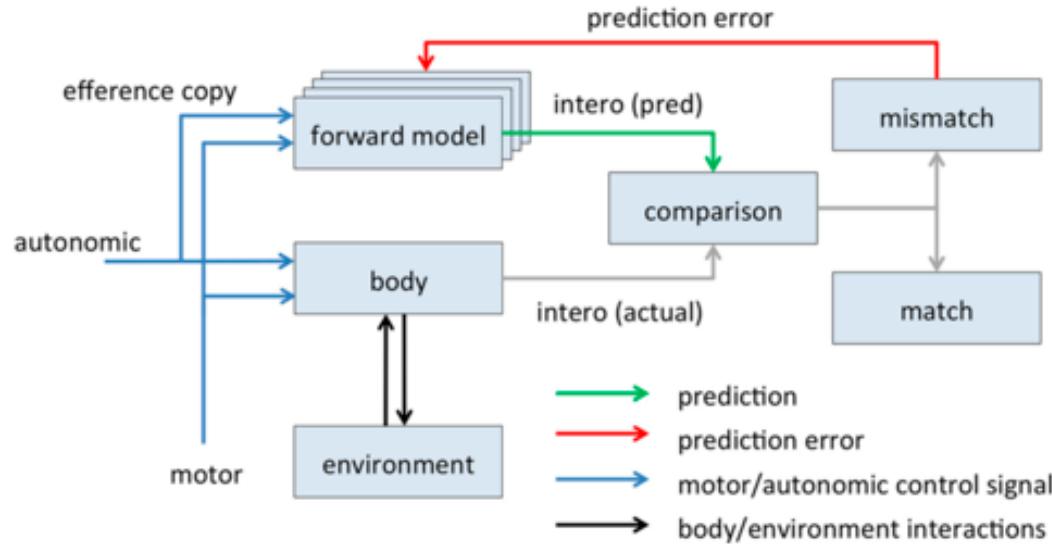


Seth & Friston (2016)
Phil Trans R Soc B

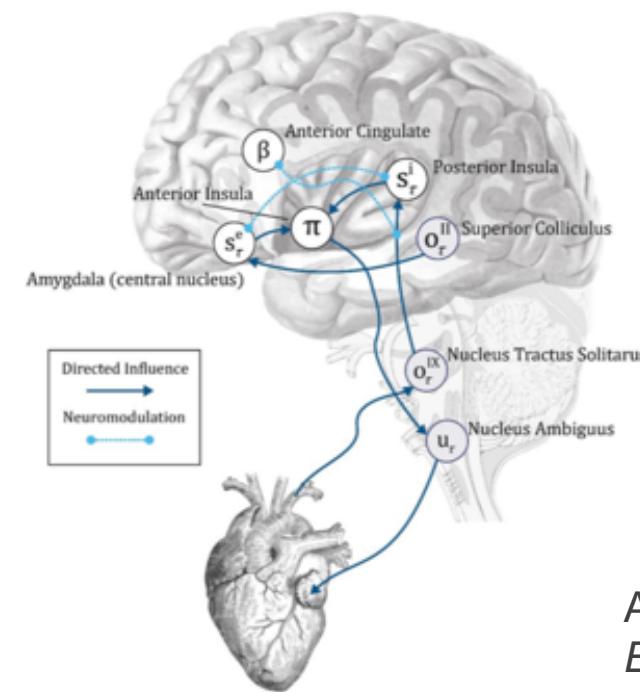


Stephan et al. (2016), *Front Hum Nsci*

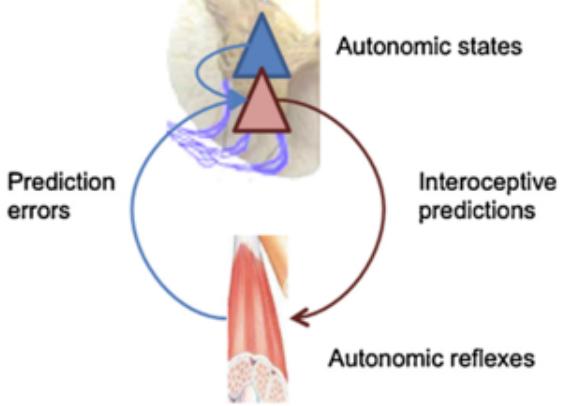




Seth, Suzuki & Critchley (2011), *Front Psychology*



Allen, Levy, Parr, Friston (2019)
BioRxiv



Pezzulo, Rigoli & Friston (2015), *Prog Neurobio*

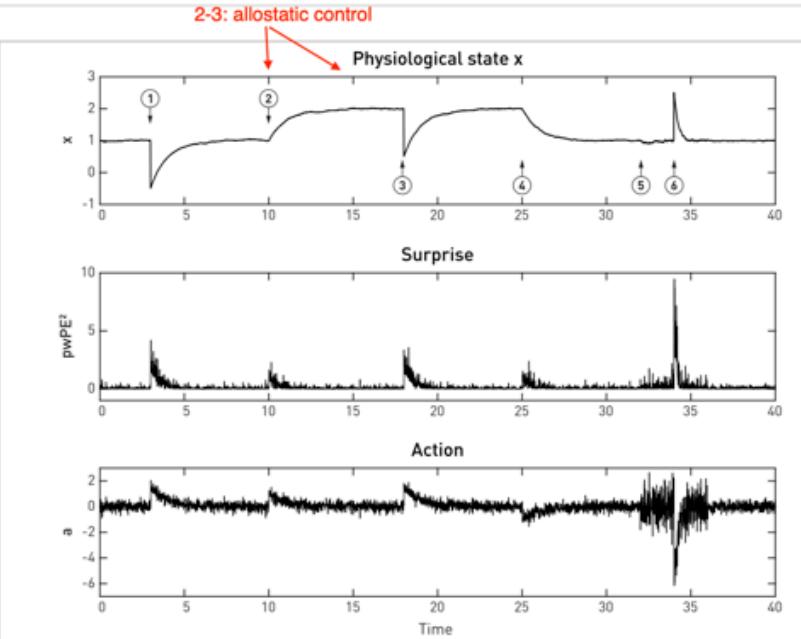
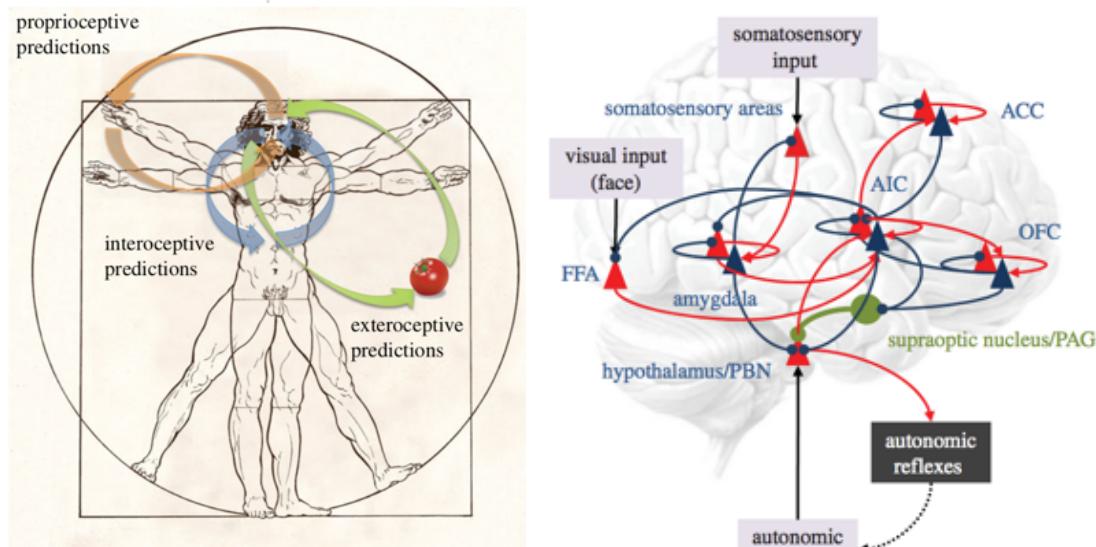


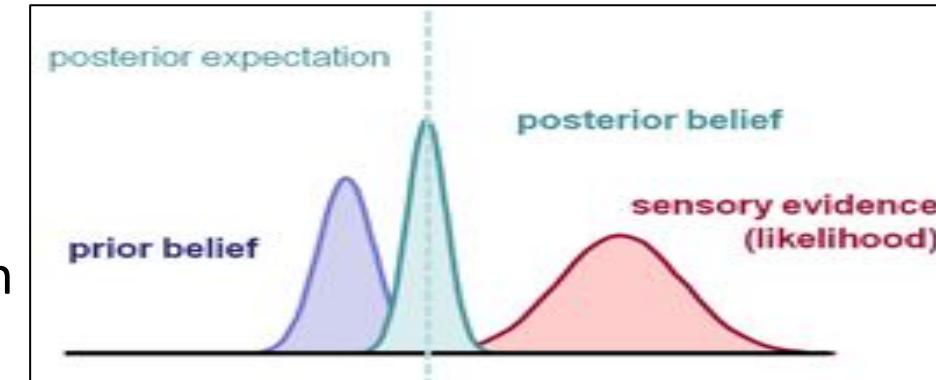
FIGURE 6 | A simulated example of allostatic regulation of homeostatic control, based on Equations (8)–(12). The upper panel shows the temporal evolution of a fictitious physiological state x (Equation 11) which is affected by environmental perturbations Θ , Θ , Θ , all with a magnitude of 1.5. The middle and lower panels display an approximation to interoceptive surprise—i.e., squared precision-weighted prediction error (pwPE^2)—and the associated action signal (Equation 10), respectively. Following the timeline from left to right, the homeostatic setpoint or belief is initially specified with a prior mean and



Seth & Friston (2016)
Phil Trans R Soc B

Computational dysfunction

- Main idea - an **inability** of the brain to **update its model of the body** in the face of interoceptive prediction errors
- Dysfunctional **precision-weighting**
 - Poor control of the relative influence of prior expectations and afferent bodily signals in perception
- In other words, the brain may **treat afferent bodily signals as though they are not reliable** indicators of bodily states
 - leading perception to be insufficiently constrained by true visceral states
 - Perception is then primarily determined by (in many cases inaccurate/maladaptive) prior expectations.
- However, it's unclear whether **prior expectations** are **over-weighted** or **afferent signals** are **under-weighted**
 - Role of attention-mediated **learning** is also unclear



Annual Review of Clinical Psychology (2019)

An Active Inference Approach to Interoceptive Psychopathology

Martin P. Paulus,¹ Justin S. Feinstein,^{1,2}
and Sahib S. Khalsa^{1,2}

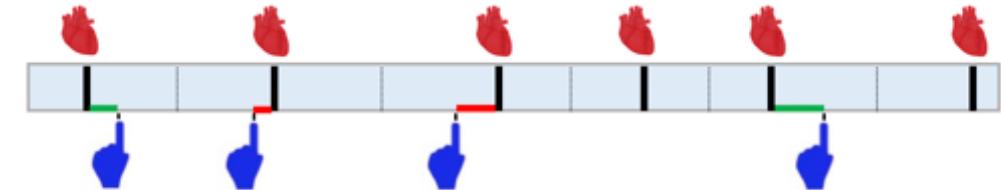
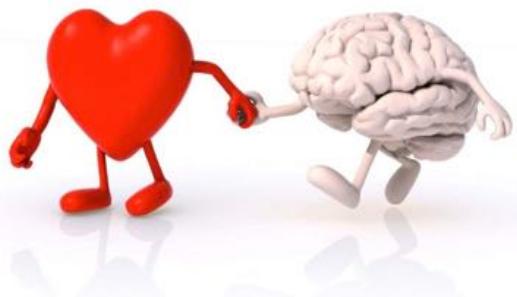
Abstract

Interoception refers to the process by which the nervous system senses and integrates signals originating from within the body, providing a momentary mapping of the body's internal landscape and its relationship to the outside world. Active inference is based on the premise that afferent sensory input to the brain is constantly shaped and modified by prior expectations. In this review we propose that interoceptive psychopathology results from two primary interoceptive dysfunctions: First, individuals have abnormally strong expectations of the situations that elicit bodily change (i.e., hyperprecise priors), and second, they have great difficulty adjusting these expectations when the environment changes (i.e., context rigidity). Here we discuss how these dysfunctions potentially manifest in mental illness and how interventions aimed at altering interoceptive processing can help the brain create a more realistic model of its internal state.

A computational Bayesian model reveals a failure to adapt interoceptive precision estimates across depression, anxiety, eating, and substance use disorders

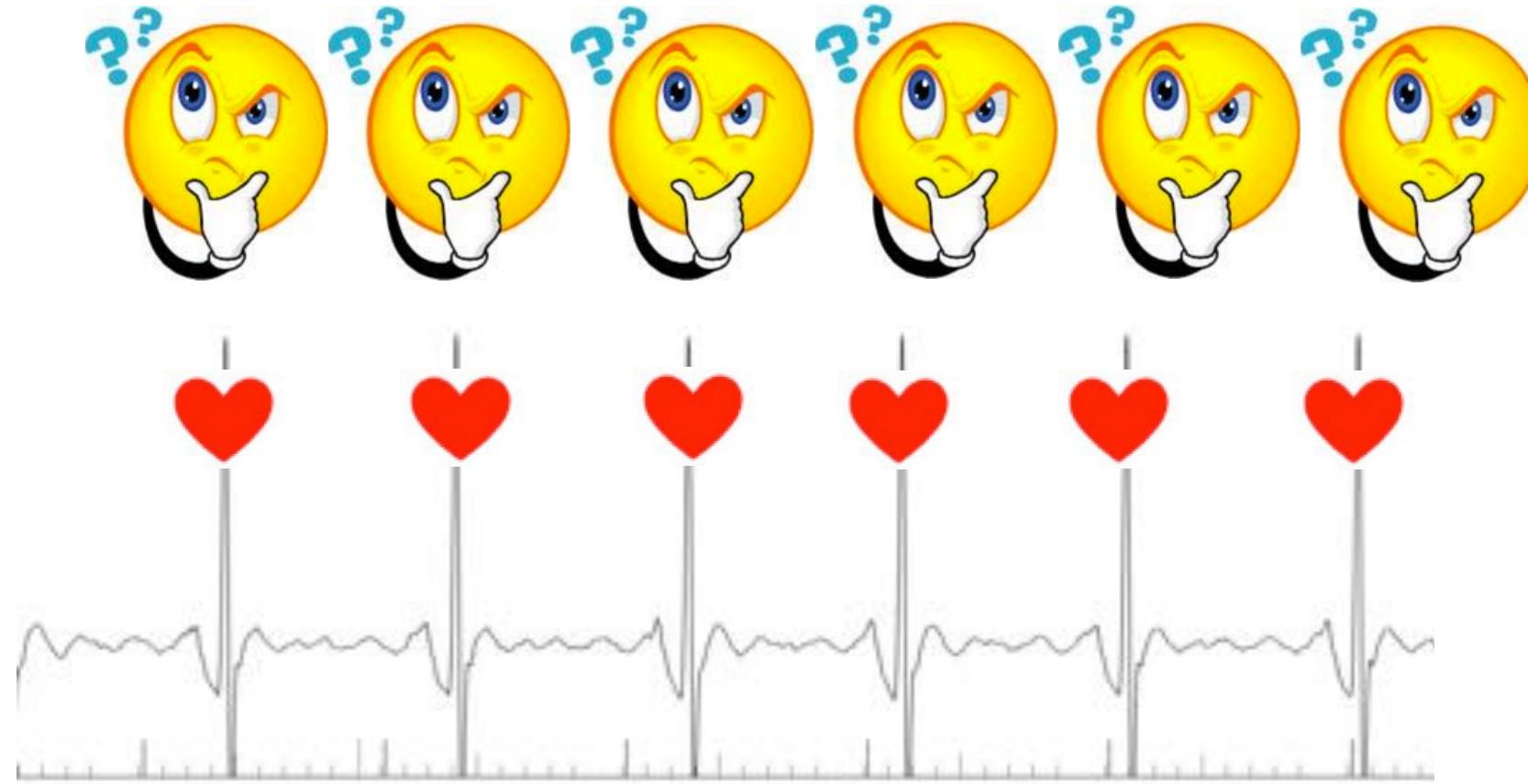
Ryan Smith, Rayus Kuplicki, Justin Feinstein, Katherine Forthman, Martin P. Paulus, Tulsa 1000 investigators, and

Sahib S. Khalsa



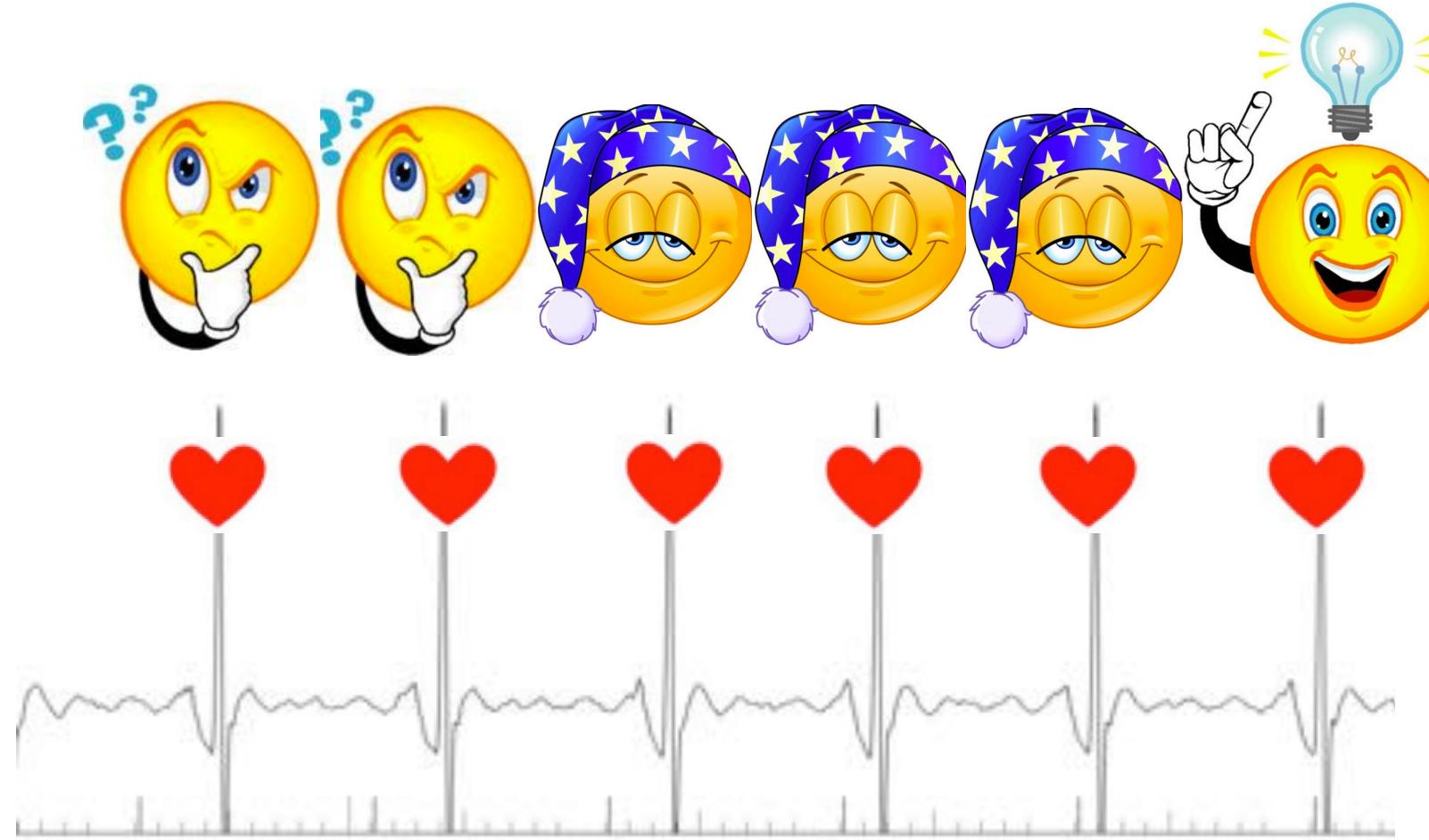
Smith et al, 2020, MedRxiv

Heartbeat counting task: assumption



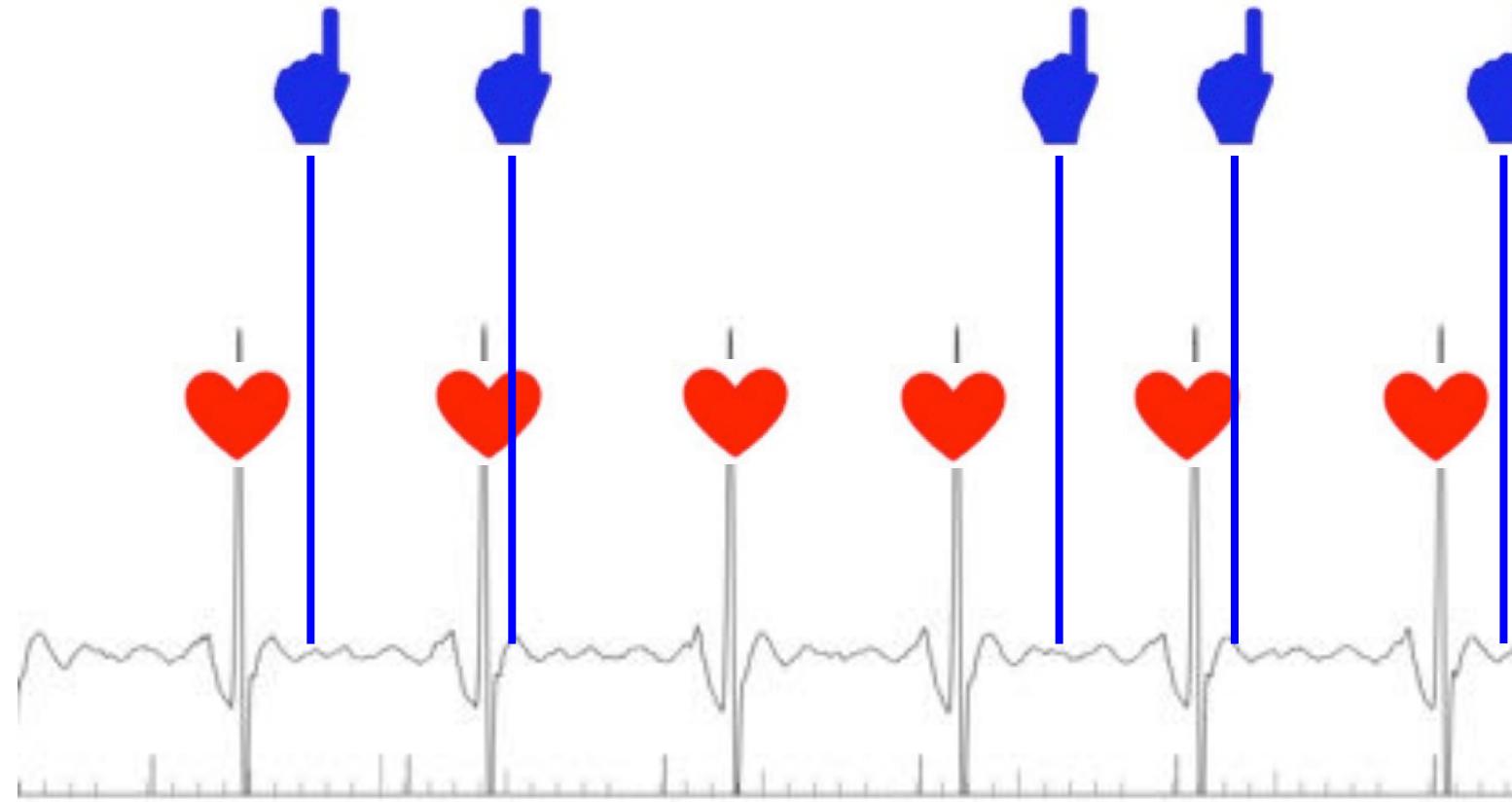
Cue “Start”	Attend to stimulus	Response: <i>“Five”</i>
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Heartbeat counting task: reality?



Cue “Start”	Attend to stimulus	Response: <i>“Five”</i>
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Heartbeat tapping captures real time behavior



Cue “Start”	Attend to stimulus	Response: Five taps
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Heartbeat tapping task

- Three conditions:

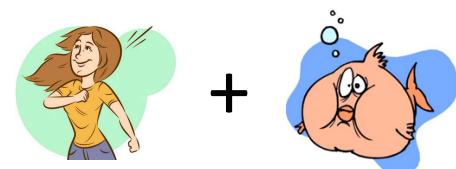
- ‘Best guess’



- ‘No guessing’



- ‘No guessing’ during inspiratory breath hold – **respiratory perturbation** (to increase afferent signal strength)



- Tone tapping – exteroceptive control



- Participants instructed to press a keyboard button in synchrony with their heartbeat
- Each condition 1 minute in duration

Self-report measures

- Directly **after** completing **each task condition**, individuals were asked the following using a visual analogue scale:
 - “**How accurate was your performance?**”
 - “**How difficult was the previous task?**”
 - “**How intensely did you feel your heartbeat?**”
- Each scale had anchors of “**not at all**” and “**extremely**” on the two ends. Numerical scores could range from **0 to 100**.

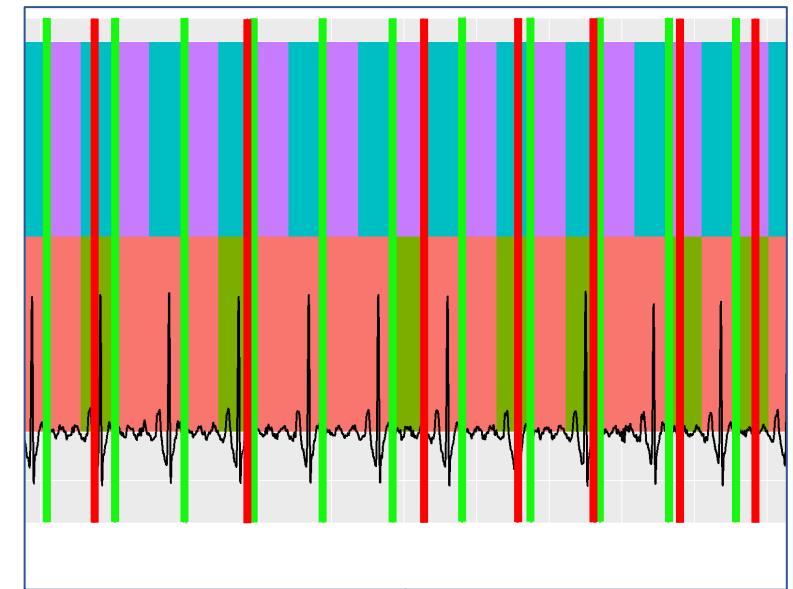
Computational modelling

- Our primary aims were to
 - 1) **demonstrate the sensitivity** of a novel Bayesian **computational approach** for measuring the precision weighting of interoceptive signals and prior expectations
 - 2) test the hypothesis that patient groups show **lower interoceptive precision** weightings than HCs, **more precise prior expectations** than HCs, or **both**
 - 3) explore whether prior expectations and/or interoceptive precision is **abnormal in general or selectively** within resting or interoceptive perturbation conditions.

Participants: Mean (and standard deviation) for clinical and demographic variables.

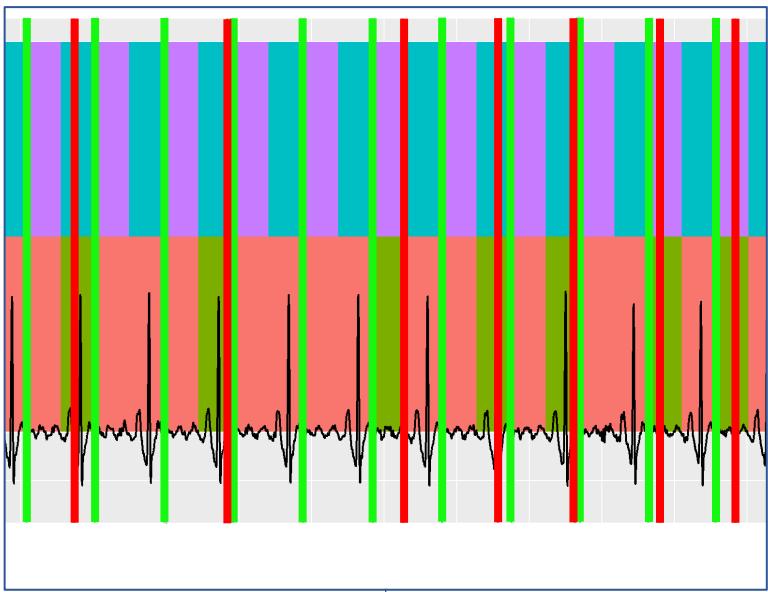
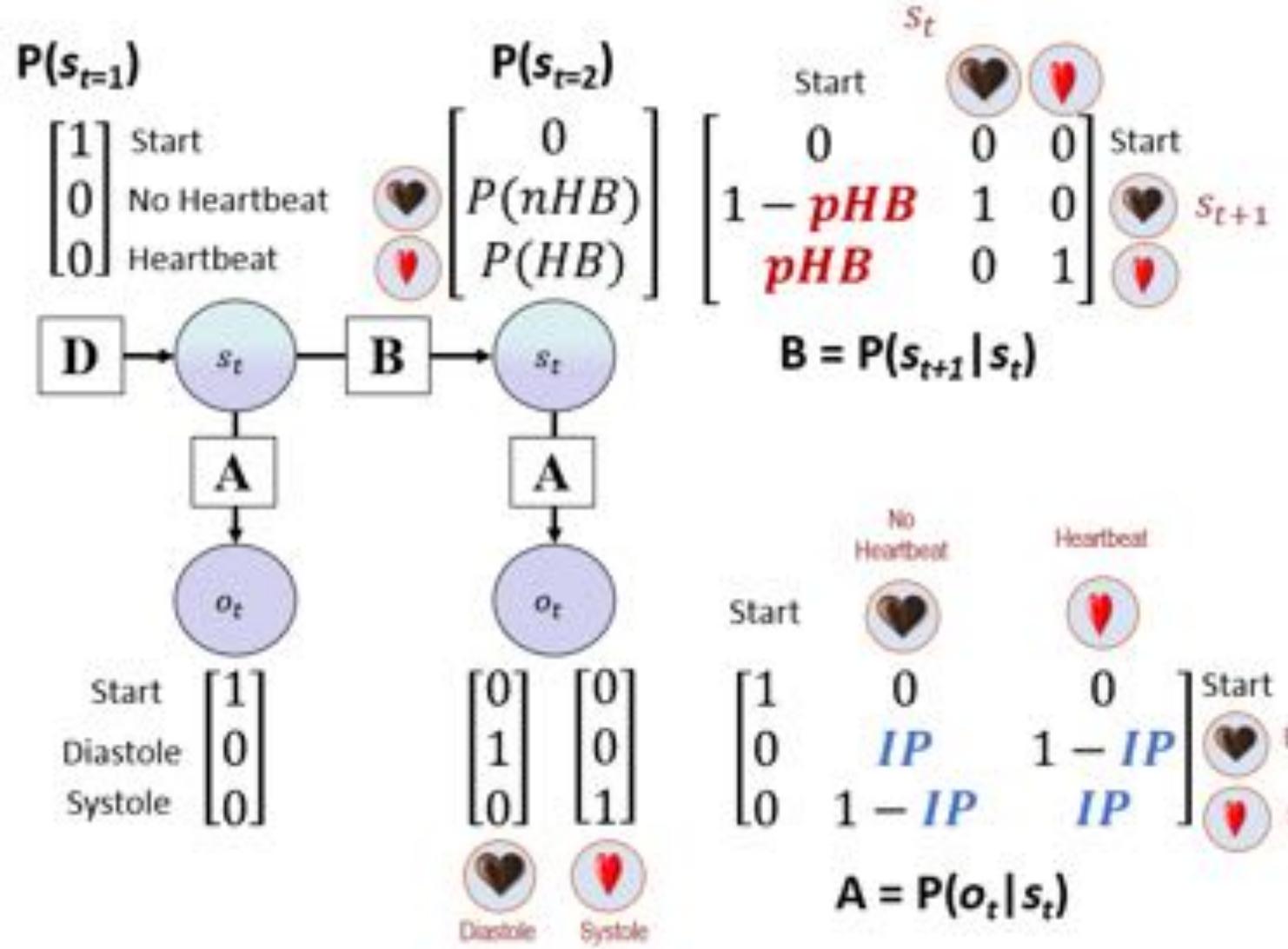
Individual difference variable	Healthy comparisons (N = 52)	Anxiety disorder (N = 15)	Depressive disorder (N = 69)	Depression + anxiety (N = 153)	Eating disorder (N = 14)	Substance use disorder (N = 131)	p-value
Age (years)	32.0 (11.1)	36.4 (10.0)	37.1 (11.8)	35.3 (11.2)	27.4 (9.8)	34.0 (8.9)	0.012
Sex	50% male	33% male	30% male	26% male	14% male	45% male	0.001
PHQ-9 - depression	0.8 (1.3)	7.5 (5.8)	13.5 (4.7)	13.1 (5.2)	12.9 (7.9)	6.7 (5.9)	<0.001
OASIS - anxiety	1.4 (1.9)	10.6 (2.2)	7.6 (3.3)	10.5 (3.1)	9.5 (4.9)	5.9 (4.8)	<0.001
DAST-10 - addiction	0.1 (0.3)	0.3 (0.5)	0.7 (1.7)	0.6 (1.1)	1.2 (2.6)	7.6 (2.1)	<0.001
Pulse Transit Time (seconds)	0.20 (0.02)	0.20 (0.01)	0.19 (0.01)	0.20 (0.02)	0.20 (0.02)	0.20 (0.02)	0.261
Body mass index	27.6 (5.5)	27.1 (6.0)	28.5 (5.5)	28.8 (5.5)	22.3 (4.4)	28.2 (4.6)	0.001

QC: removed 19 individuals for pulse taking; 3 individuals didn't complete the task; 13 individuals had poor EKG signals across all trials. An additional 31 individuals were removed due to being outliers when performing the tone task (using Iterative Grubb's with $p < 0.01$). Diagnosis verified via structured clinical interview using DSM-5 criteria, with groupings according to Aupperle et al. (2020) *JMIR Ment Health*



Blue = diastole
Purple = systole
Light Red = no tap
Dark Green = tap

Green vertical lines = R-wave + 200ms
Red vertical lines = tap location



IP = interoceptive precision
pHB = prior expectation for heartbeat

Blue = diastole
Purple = systole
Light Red = no tap
Dark Green = tap

Green vertical lines = R-wave + 200ms
Red vertical lines = tap location

Heartbeat perception:

$$\bar{s}_{t=1} = \sigma \left(\frac{1}{2} (\ln D + \ln B \cdot s_{t+1}) + \ln A \cdot o_t \right)$$

$$\bar{s}_{t=2} = \sigma (\ln B \cdot s_{t-1} + \ln A \cdot o_t)$$

Model Variables

Model variable	General Definition	Model-specific specification
o_t	Observable outcomes at time t	Outcome modalities: 1. Diastole vs. systole
s_t	Hidden states at time t	Hidden state factors: 1. Feel heartbeat vs. no heartbeat
A matrix $p(o_t s_t)$	A matrix encoding beliefs about the relationship between hidden states and observable outcomes (i.e., the probability that specific outcomes will be observed given specific hidden states).	Encodes beliefs about the relationship between felt heartbeats and diastole vs. systole. The precision of the relationship between heartbeats and diastole/systole was controlled by a parameter IP , which specified how much evidence systole provides for a heartbeat and how much evidence diastole provides for the absence of a heartbeat.
B matrix $p(s_{t+1} s_t)$	A matrix encoding beliefs about how hidden states will evolve over time (transition probabilities).	Encodes the prior expectation that either a heartbeat or no heartbeat would occur on each trial, as controlled by a parameter pHB .
D vector $p(s_1)$	A matrix encoding beliefs about (a probability distribution over) initial hidden states.	Ensures the individual always begins in an initial starting state.

More complex learning model

$$b(\text{heartbeats}) = P(s_{t+1}|s_t) = \begin{bmatrix} 0 & 0 & 0 \\ 1 - pHB & 1 & 0 \\ pHB & 0 & 1 \end{bmatrix} \times b_0$$

$$b_t = b_{t-1} + \sum_t s_t \otimes s_{t-1}$$

- This just says that **prior expectations** for feeling a heartbeat go up after every time you **think you felt one**, and **vice-versa** when you **don't think you felt one**
- The larger b_0 is the **more slowly** you update prior expectations – **rigid priors**.

Final Model Parameters

- **b₀** – inverse learning rate (in learning model)
- **pHB** – prior expectations to feel a heartbeat (e.g., faster heart rate)
- The “raw” IP parameter values were transformed to correctly capture 2 distinct constructs of interest.

$$IP = |IP_{raw} - 0.5|$$

- This means that **IP** has a minimum value of 0 and a maximum value of 0.5. (reliable anticipatory or reactive tapping)

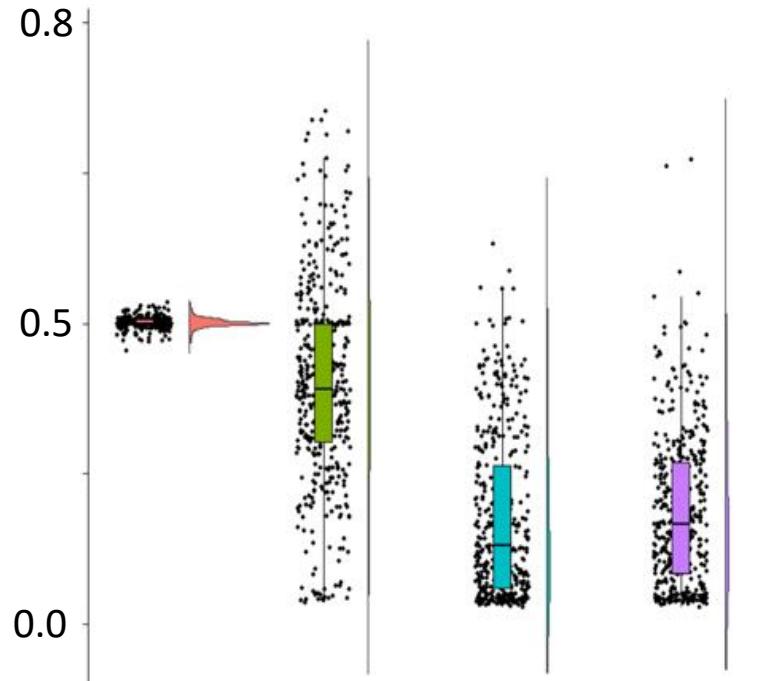
$$AvR = IP_{raw}$$

- Higher **AvR** values (> 0.5) thus indicated a stronger tendency to **reactively** tap in response to a heartbeat as opposed to tapping in an **anticipatory** fashion (< 0.5).

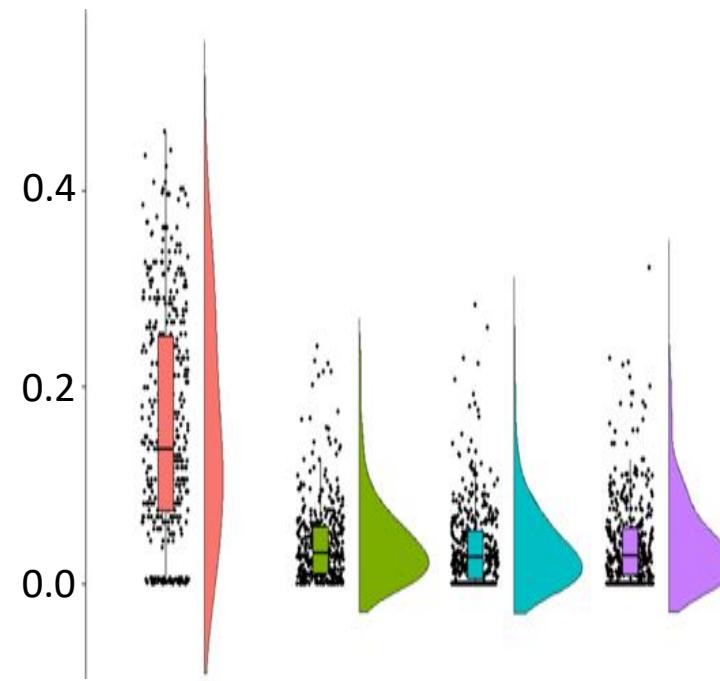
Model comparison

- Overall, there was more evidence for the model without learning
- The “**perception only**” model was better than the model that included learning prior expectations for the **no-guessing and breath-hold** conditions (protected exceedance probability = 1)
- There was **not a significantly better model for the guessing condition** (protected exceedance probabilities = .46 vs. .54, slightly favoring the learning model).
- The **learning model was better in the tone condition** (protected exceedance probability = 1).
- No group differences were observed when comparing model fits between groups.

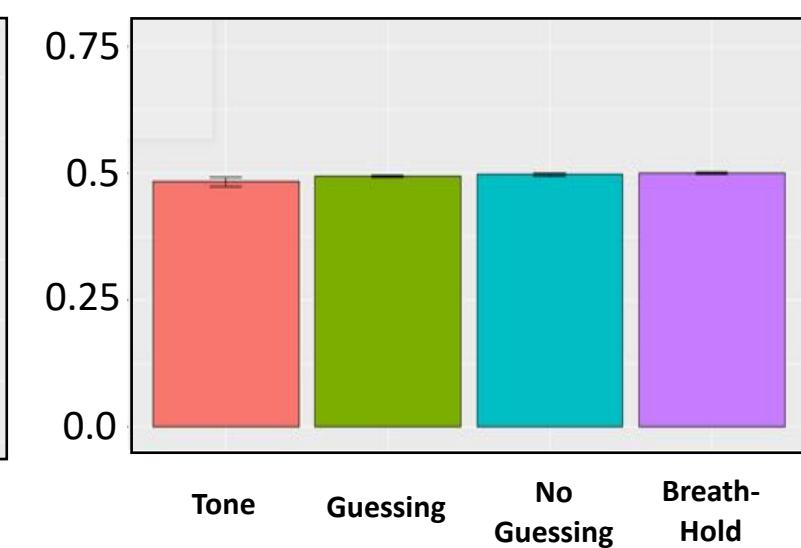
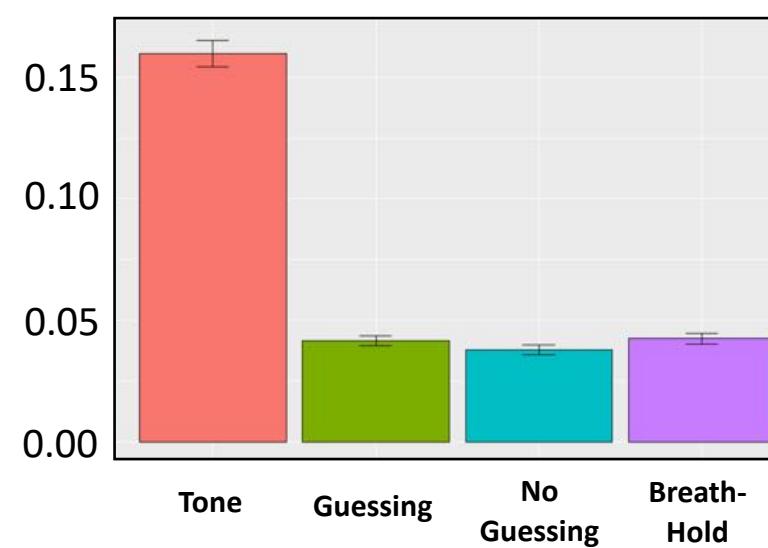
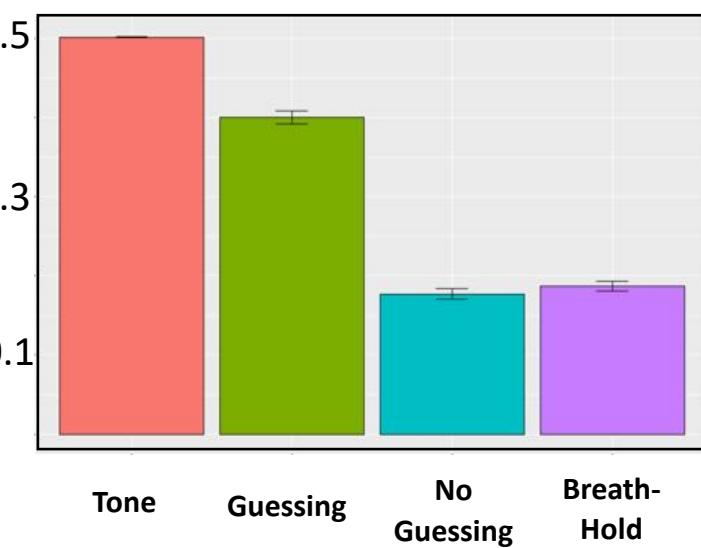
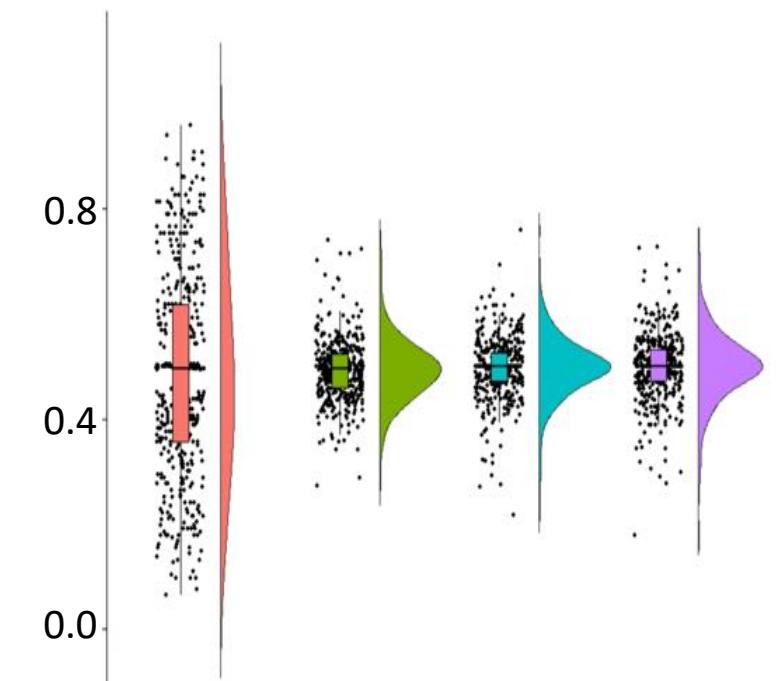
Prior Expectation for Heartbeat or Tone



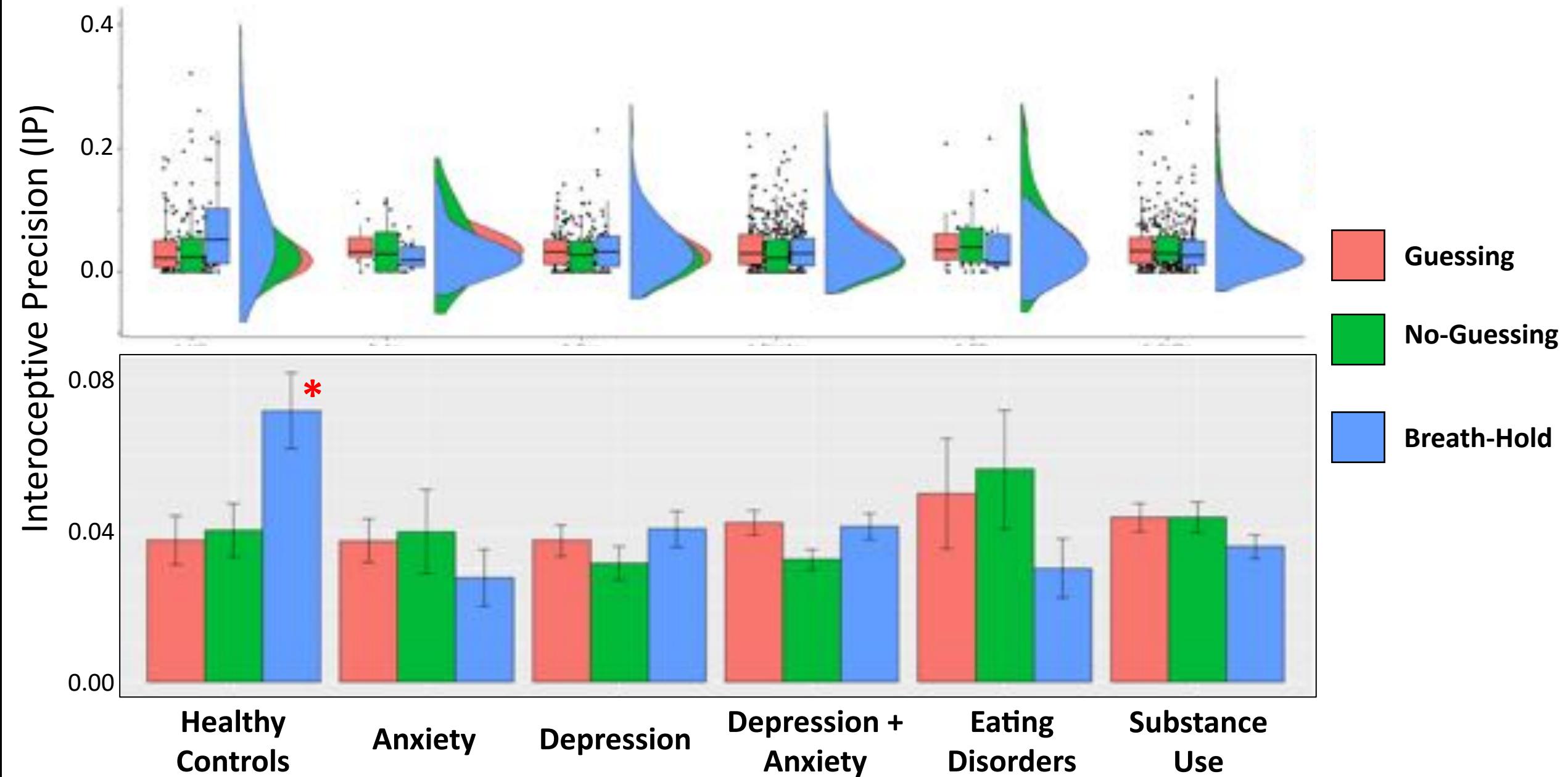
Sensory Precision



Anticipate vs. React



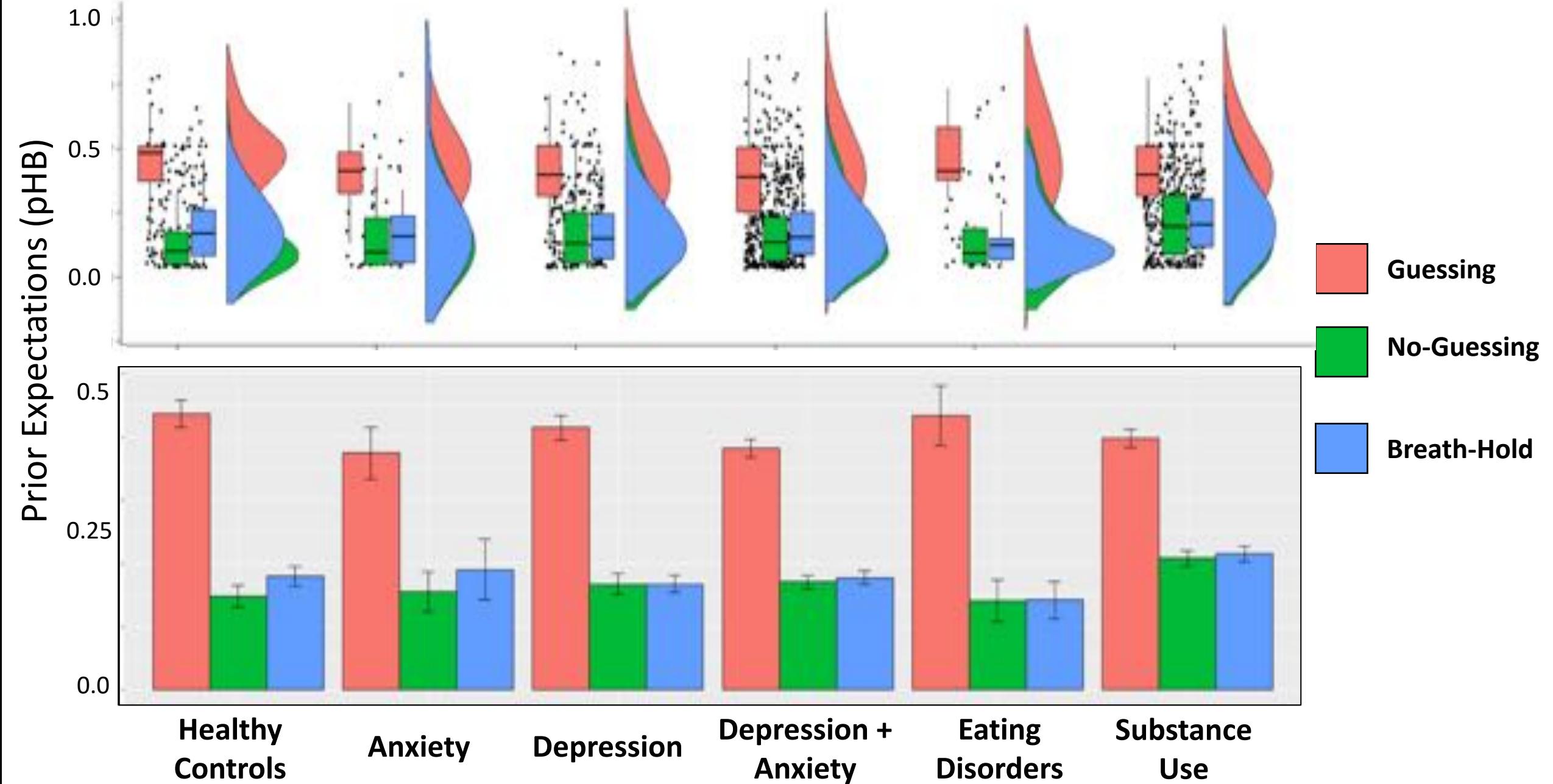
Cardiac Interoceptive Precision Estimates by Group and Trial Type



Group by condition ANOVAs (Interoceptive Precision)

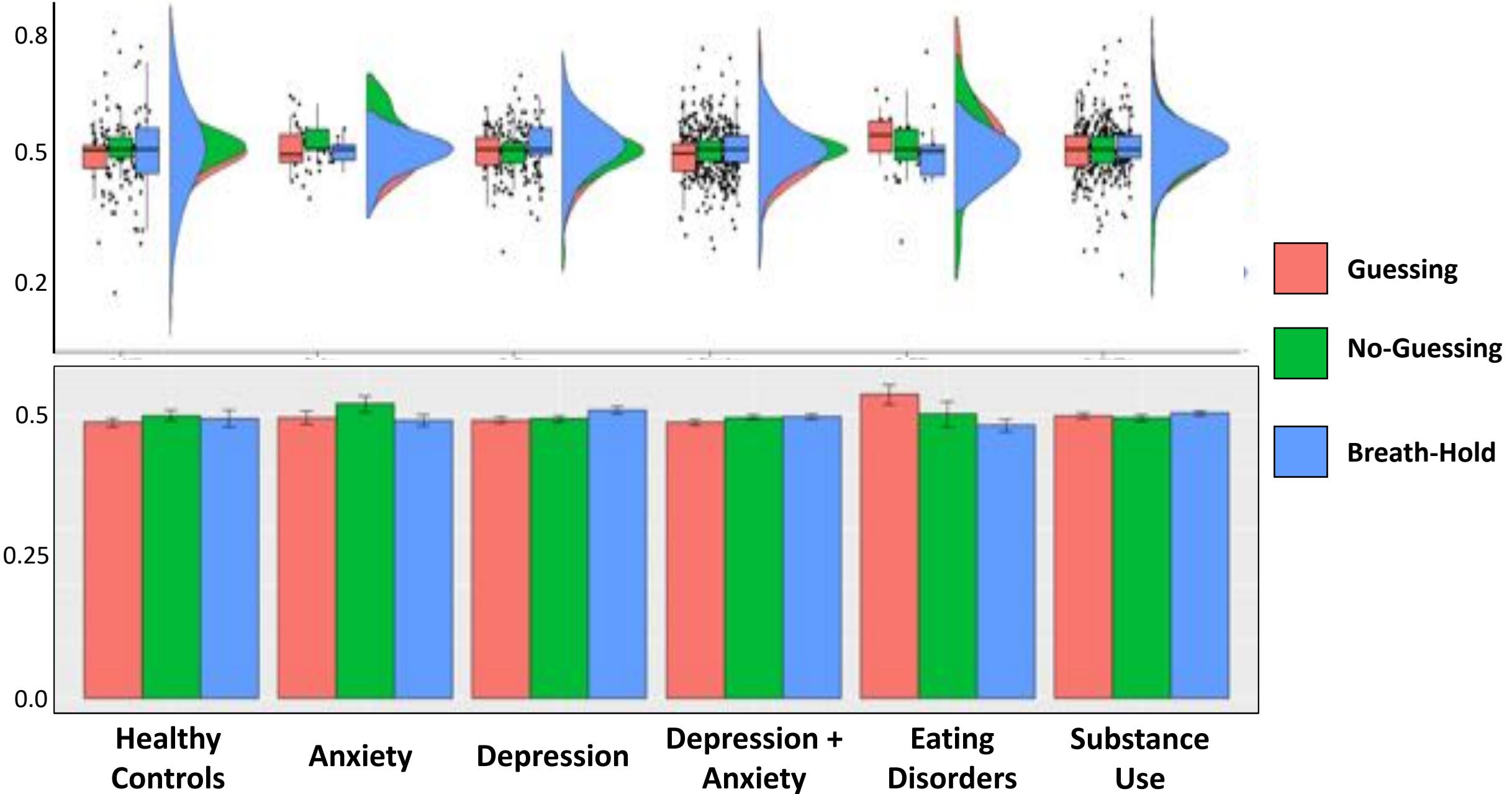
- **Main effect of group** ($F(5,1273) = 2.35, p = .04$)
- **Group by condition interaction** ($F(10,1273) = 3.10, p < .001$);
- Post-hoc Tukey comparisons indicated:
 - **Greater IP in HCs than DEP/ANX** ($p = .05$) and **DEP** ($p = .04$)
 - **Greater IP in the breath-hold condition than in the guessing ($p = .005$) and no-guessing ($p = .02$) conditions in HCs**
 - but not in any of the other clinical groups
 - HCs had **greater IP** than ANX, DEP, DEP+ANX, and SUDs in the **breath-hold condition** ($p = .04, p = .008, p = .001$, and $p < .001$, respectively).
- The **group by condition interaction remained significant** ($F(10,1114) = 2.7, p = .003$) when also including age, sex, BMI, median PTT, precision within the tone condition, number of heartbeats (and its interaction with condition), and medication status within the model.

Cardiac Prior Expectation Estimates by Group and Trial Type

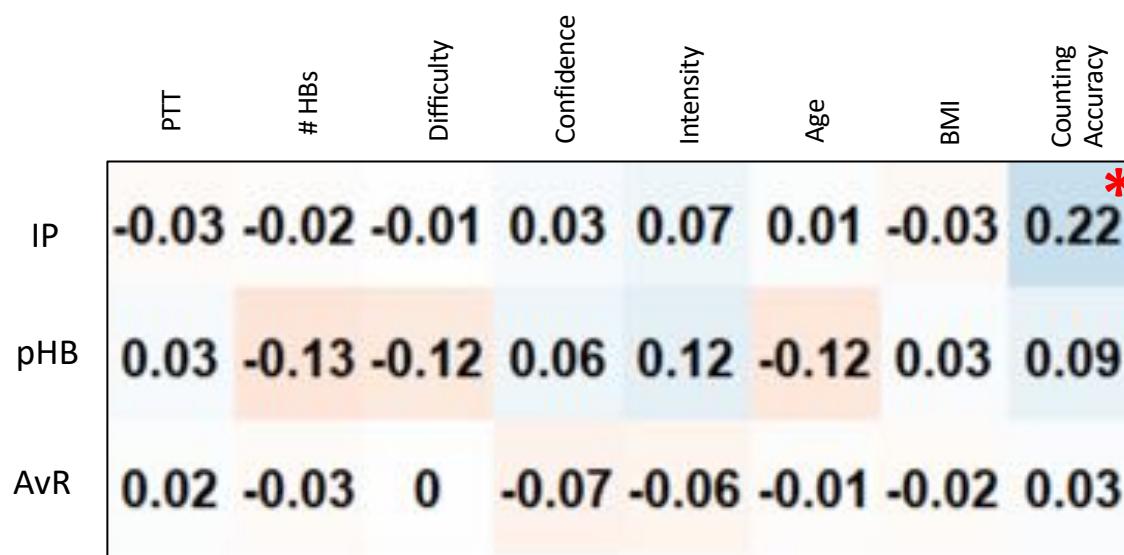


Anticipate vs. React Estimates by Group and Trial Type

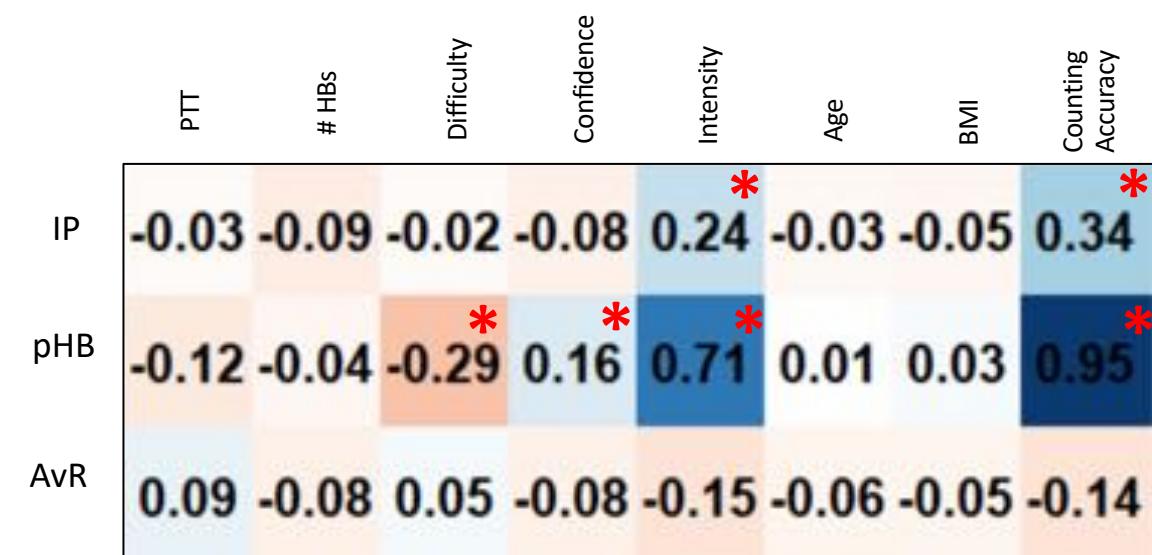
Anticipate vs. React (AvR)



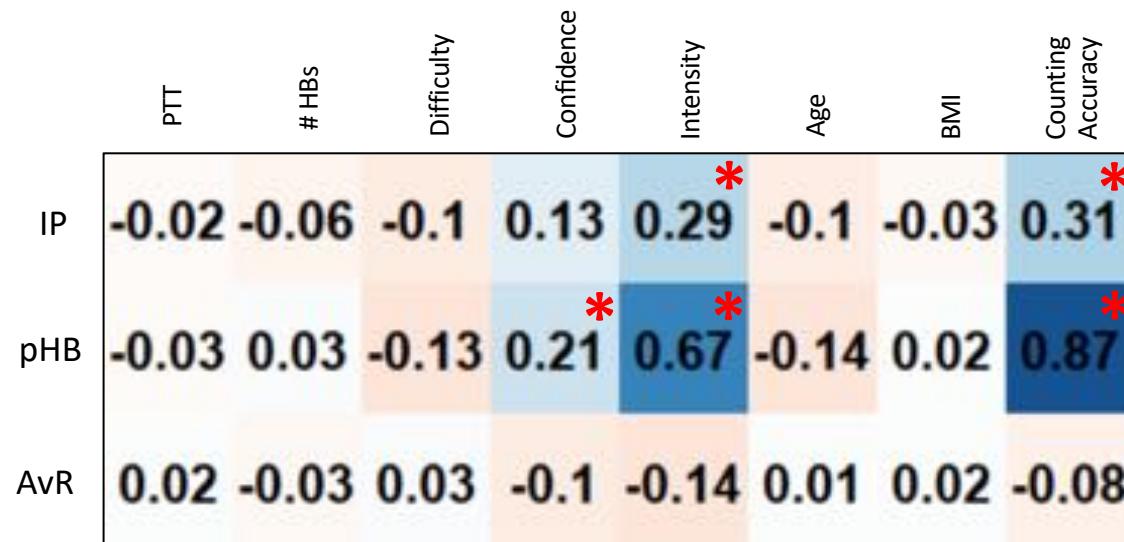
Guessing



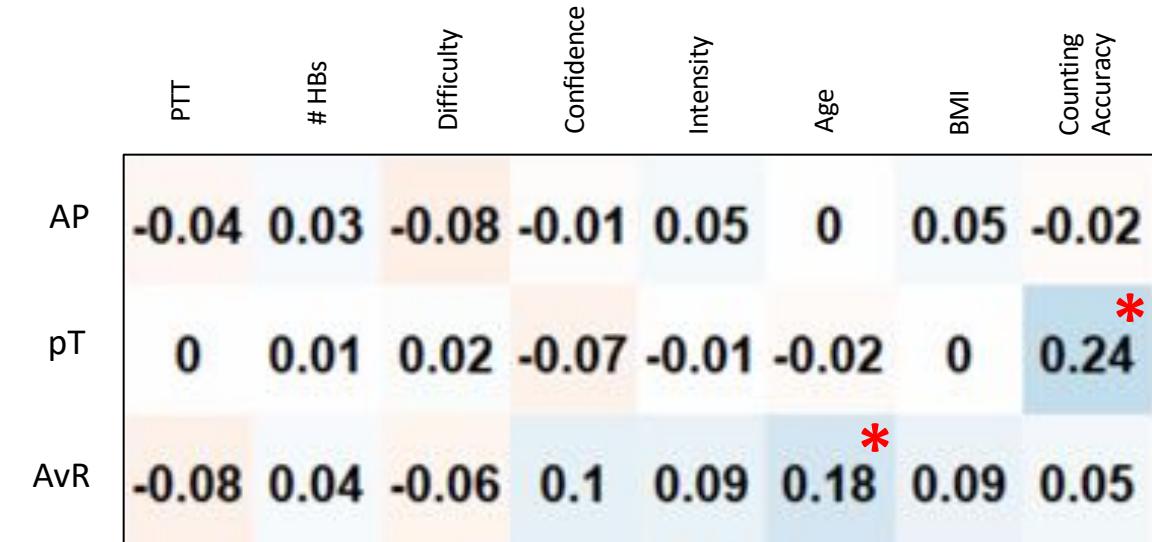
No Guessing



Breath-Hold



Tone



Summary

- Cardiac interoceptive precision **at rest was equally poor** in HCs and psychiatric patients with depression, anxiety, substance use and eating disorders
- A breath-hold perturbation (aimed at amplifying afferent signal) **increased interoceptive precision in HCs but not in any patient groups**
- **Prior expectations** were modulated by task condition, but **did not differ** in the psychiatric patient groups
- **Learning does not appear to be involved** (likely due to poor signal)
- Anticipatory vs. reactive **strategies were not different** between groups
- The traditional **heartbeat counting accuracy** measure primarily **tracks prior expectations** about the heartbeat

Conclusion

- These computational modeling results suggest the possibility that individuals with depression, anxiety, eating, and substance use disorders **cannot update precision estimates** when afferent interoceptive signals change, at least with respect to the cardiac signal
- The inability to adjust sensory precision when signals from the body change could play a role in **visceral dysregulation** observed in psychiatric disorders during high arousal states
- Future directions:
 - Replication in an independent healthy sample
 - Replication in 2nd patient cohort of Tulsa 1000 dataset
 - Integrate the model with neural measurements
 - Examine influence of other physiological perturbations



How well do you understand the concept of interoception?

- A. Not very well
- B. A little
- C. Moderately
- D. Quite well

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