COASTERCHASE

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Proposer's Day
7 July 2025

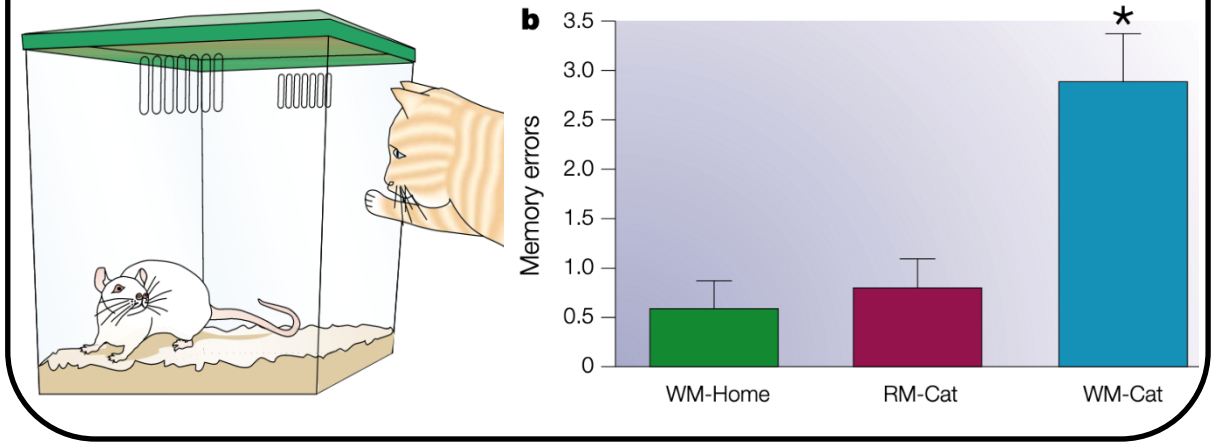
COASTERCHASE

DoD Problem: Warfighters under stress make poor decisions with immediate and also lasting consequences

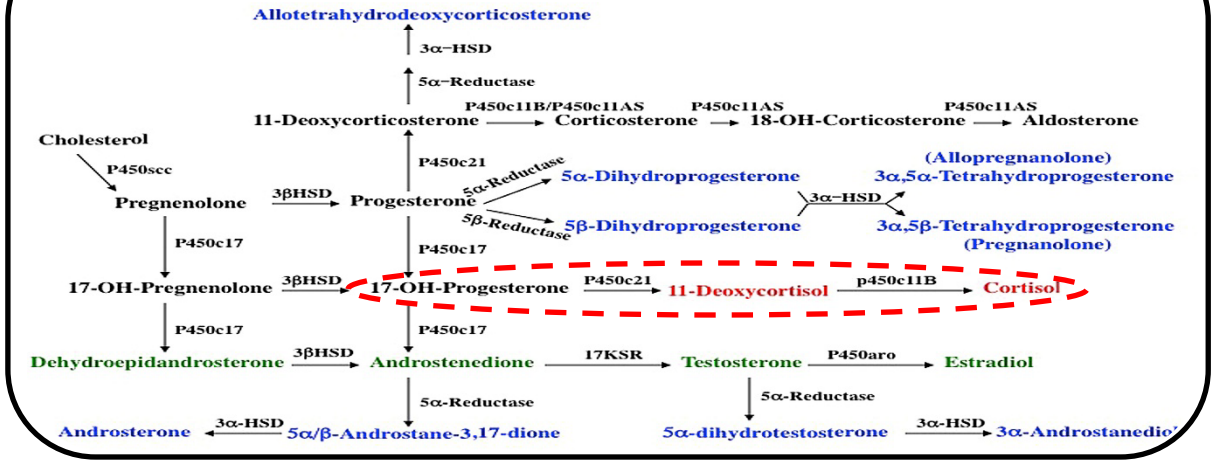
Program vision: A platform for enteric neuro-modulation to optimize warfighter psychology in extremis

H1: the enteric nervous system (ENS) modulates…

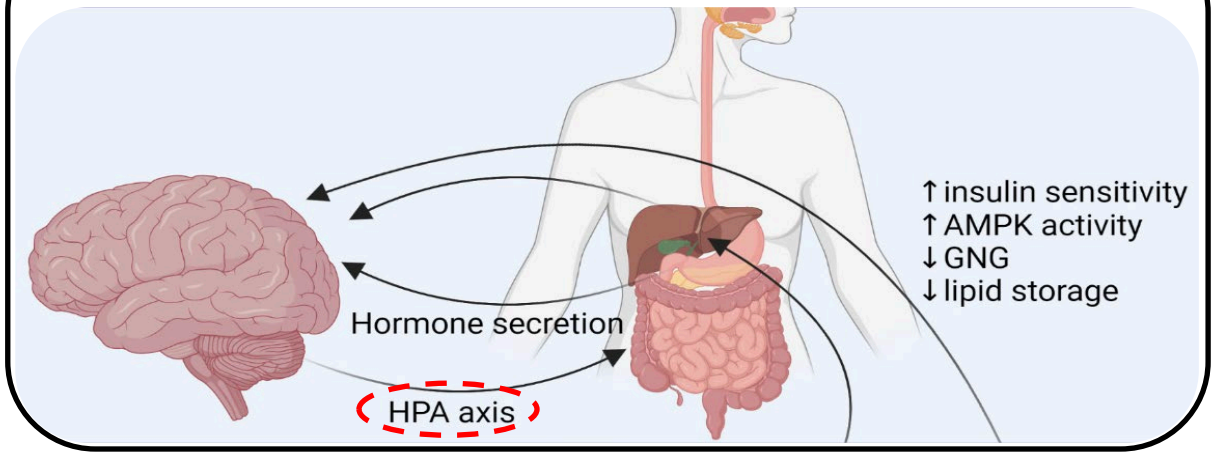
Memory (formation and retrieval)



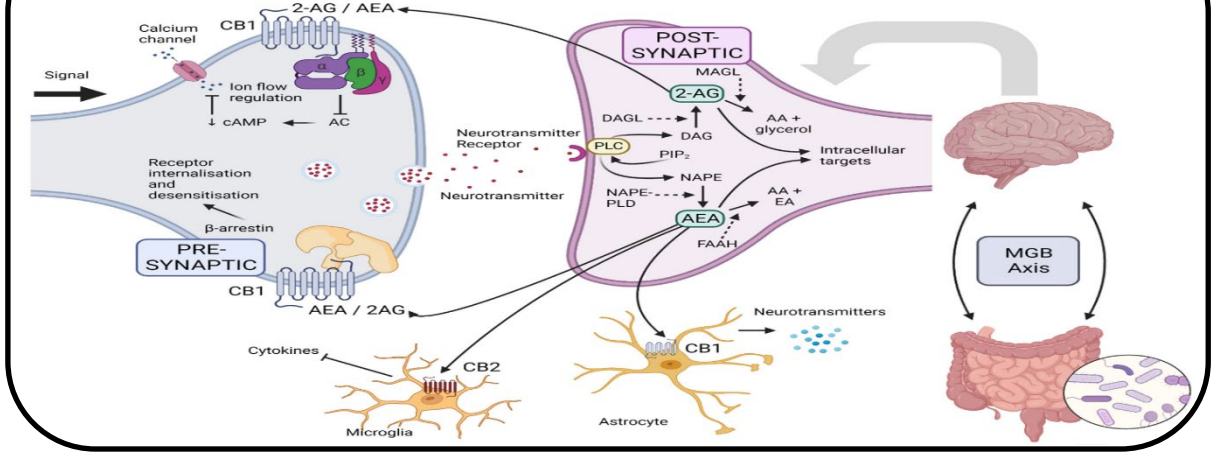
PTSD (and neuroactive steroids)



Metabolism



Immunological defense

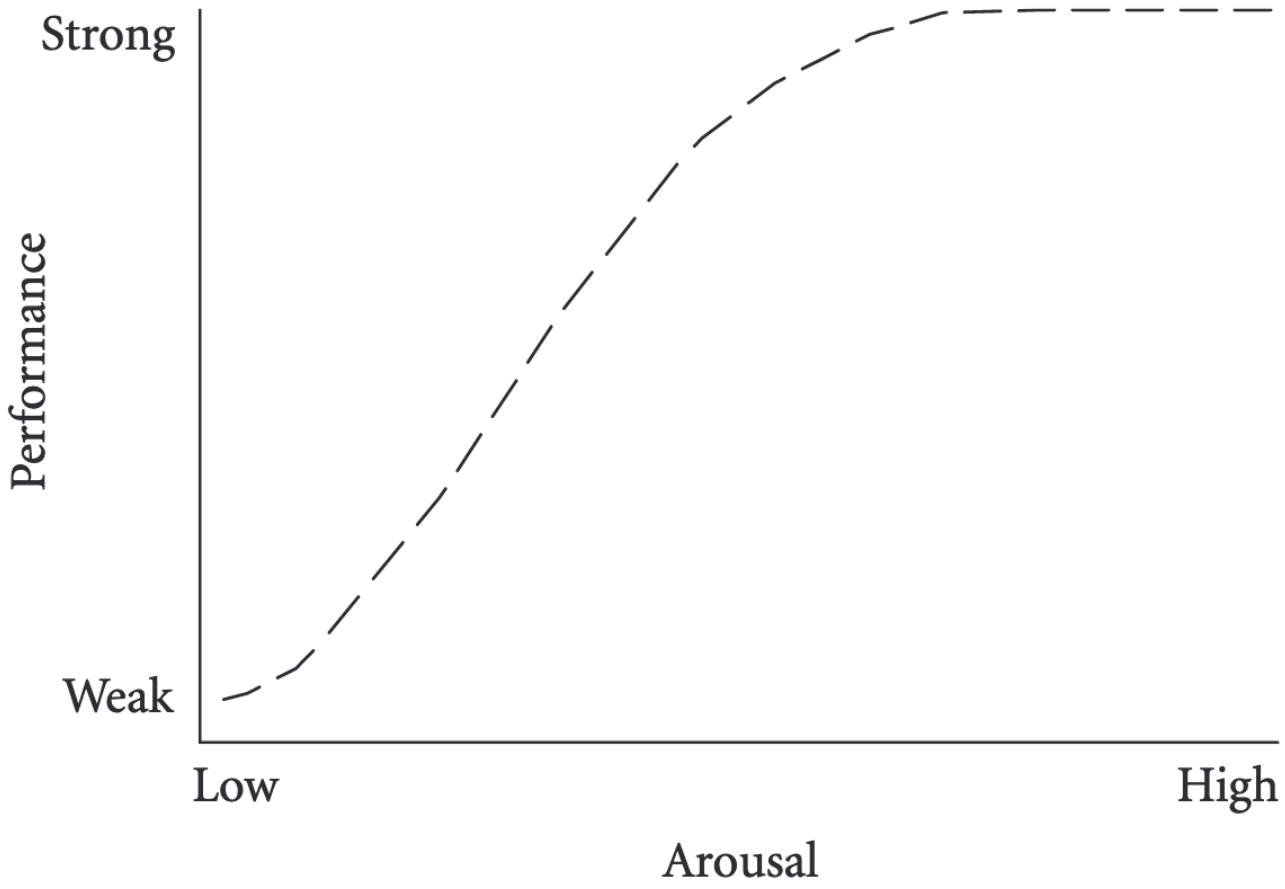


Today: ENS operates as an independent control unit for myriad critical warfighter physiological functions

ENS = Enteric Nervous System; WM = Working Memory; RM = Reference Memory
AMPK = Adenosine Monophosphate-activated Protein Kinase; GNG = Gluconeogenesis;

PTSD = Post Traumatic Stress Disorder; HPA = Hypothalamic-Pituitary-Adrenal axis;
MGB = Microbiota-Gut-Brain axis

H1: the CoasterChase MVP problem



Sense
- Gut biomarkers (e.g. Cortisol, NPY)

Integrate
- Ground truth

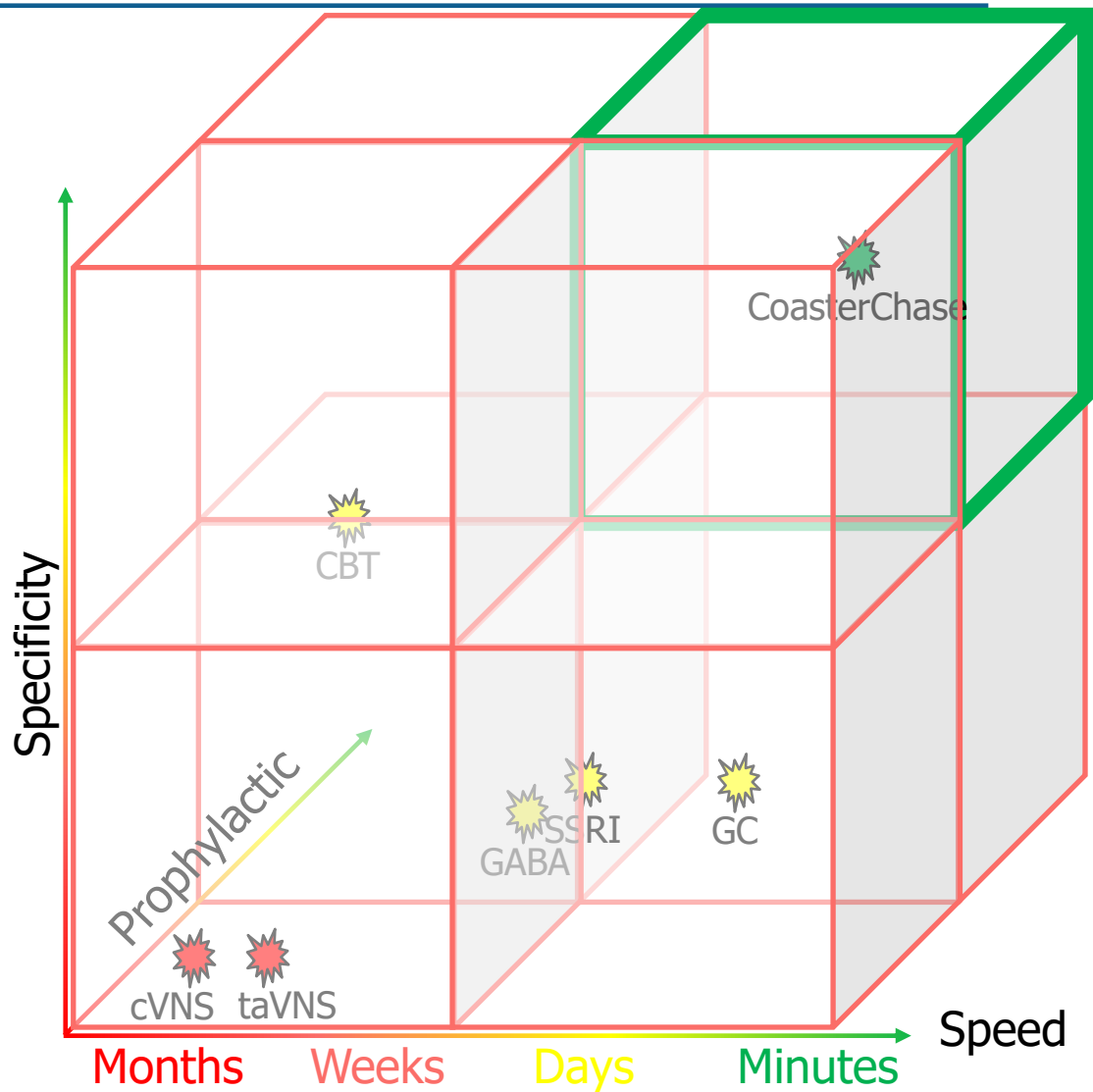
Actuate
- Personalized fine control of the arousal response

Goal: a closed-loop stimulation and sensing platform for fine cortisol control leading to optimal performance

NPY = Neuropeptide Y

H2: the broader standard-of-care lacks specificity, is slow, and reactive

	Specificity	Speed	Prophylactic
CBT	Mid	Low	Mid
cVNS	Low	Low	Low
taVNS	Low	Mid-low	Low
GABA agonists	Mid-low	Mid	Mid-low
SSRI	Mid-low	Mid	Mid
GC	Mid-low	High	Mid
Coaster Chase	High	High	High



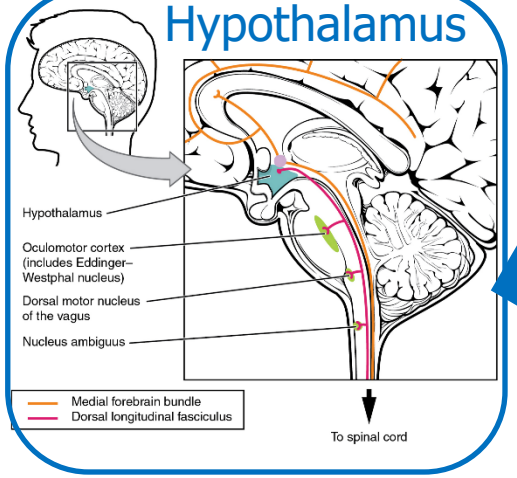
Today: therapies are non-specific (∴ side-effects), slow to act, and do not lend themselves to prevention

CBT = Cognitive Behavioral Therapy; cVNS = cervical vagus nerve stim; taVNS = trans-auricular VNS; GABA = gamma-aminobutyric acid; SSRI = Selective Serotonin Reuptake Inhib.; GC = Glucocorticoids

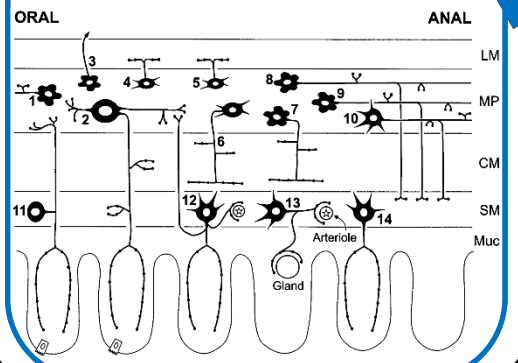
H3: the hypothalamic-pituitary-adrenal axis at the heart of our MVP

Neuropeptide Y

Hypothalamus



Small intestine

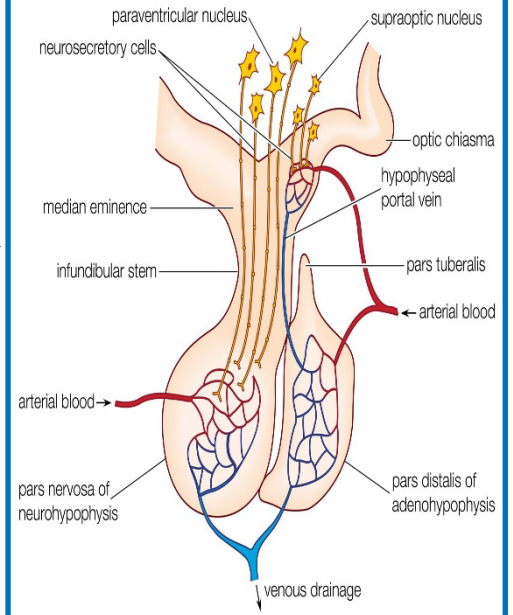


Corticotropin Releasing Hormone

Paraventricular n.

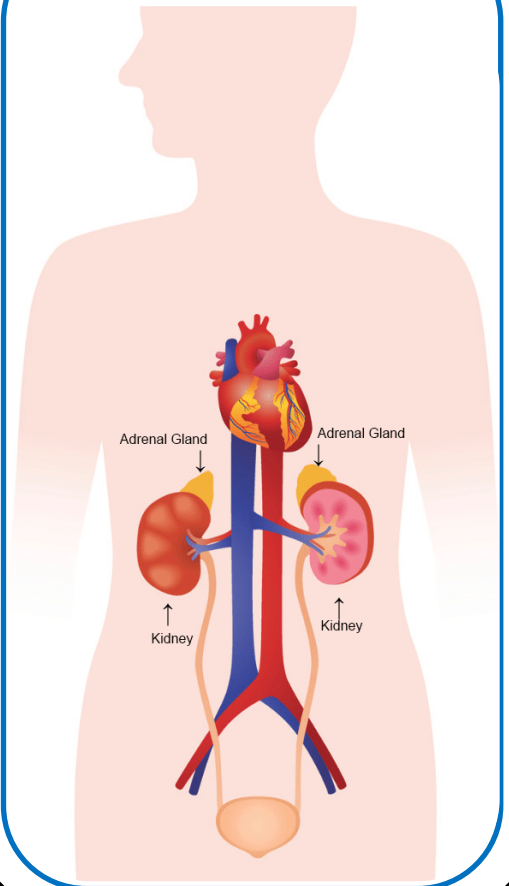
Adrenocorticotropic Hormone

Pituitary



Cortisol

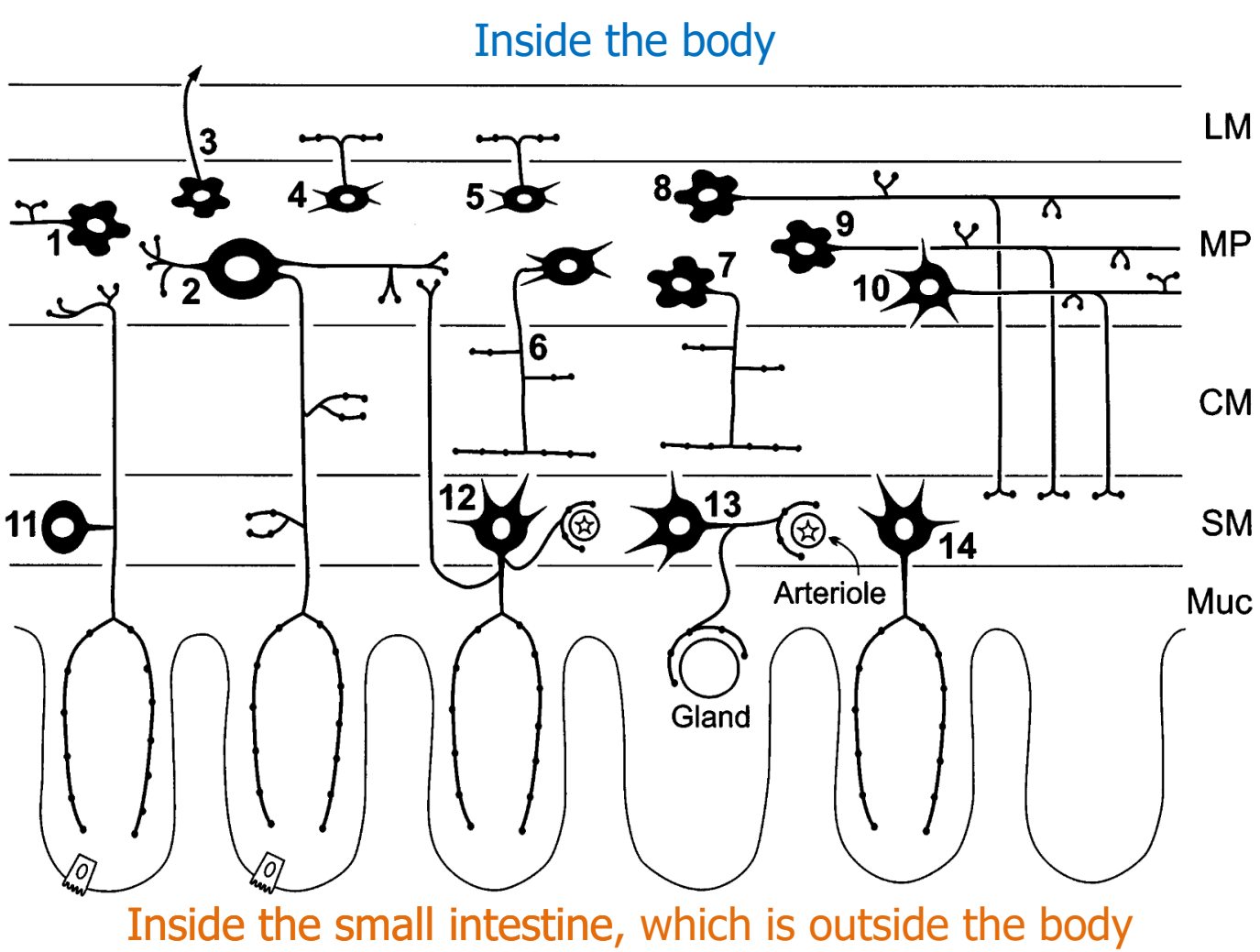
Adrenal glands



Enabling observation: systemic cortisol can be regulated by modulating NPY release in the small intestine

NPY = Neuropeptide Y; LM = Longitudinal Muscle; MP = Myenteric Plexus; CM = Circular Muscle; SM = Submucosal Plexus; Muc = Mucosa;
CRH = Corticotropin-Releasing Hormone; CNS = Central Nervous System; IV = Intra-Vascular

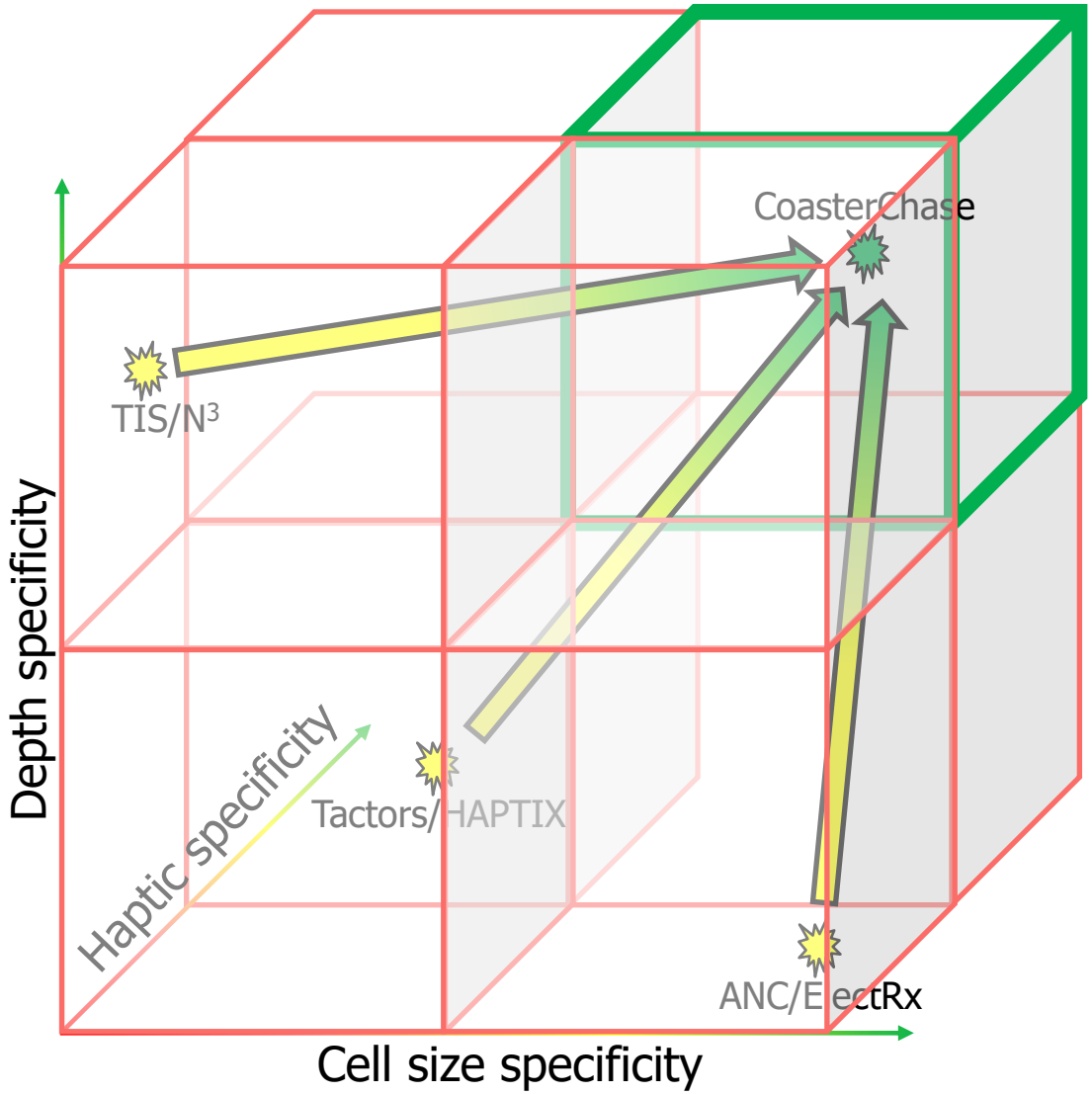
H3: enteric neurons selectively controlled from "outside" the body



Enabling Deliverable: A platform for wearable, responsive neuromodulation, of the enteric "second brain"

LM = Longitudinal Muscle; MP = Myenteric Plexus; CM = Circular Muscle;
SM = Submucosal Plexus; Muc = Mucosa

H3: optimal performance depends on selective enteric neuron stimulation

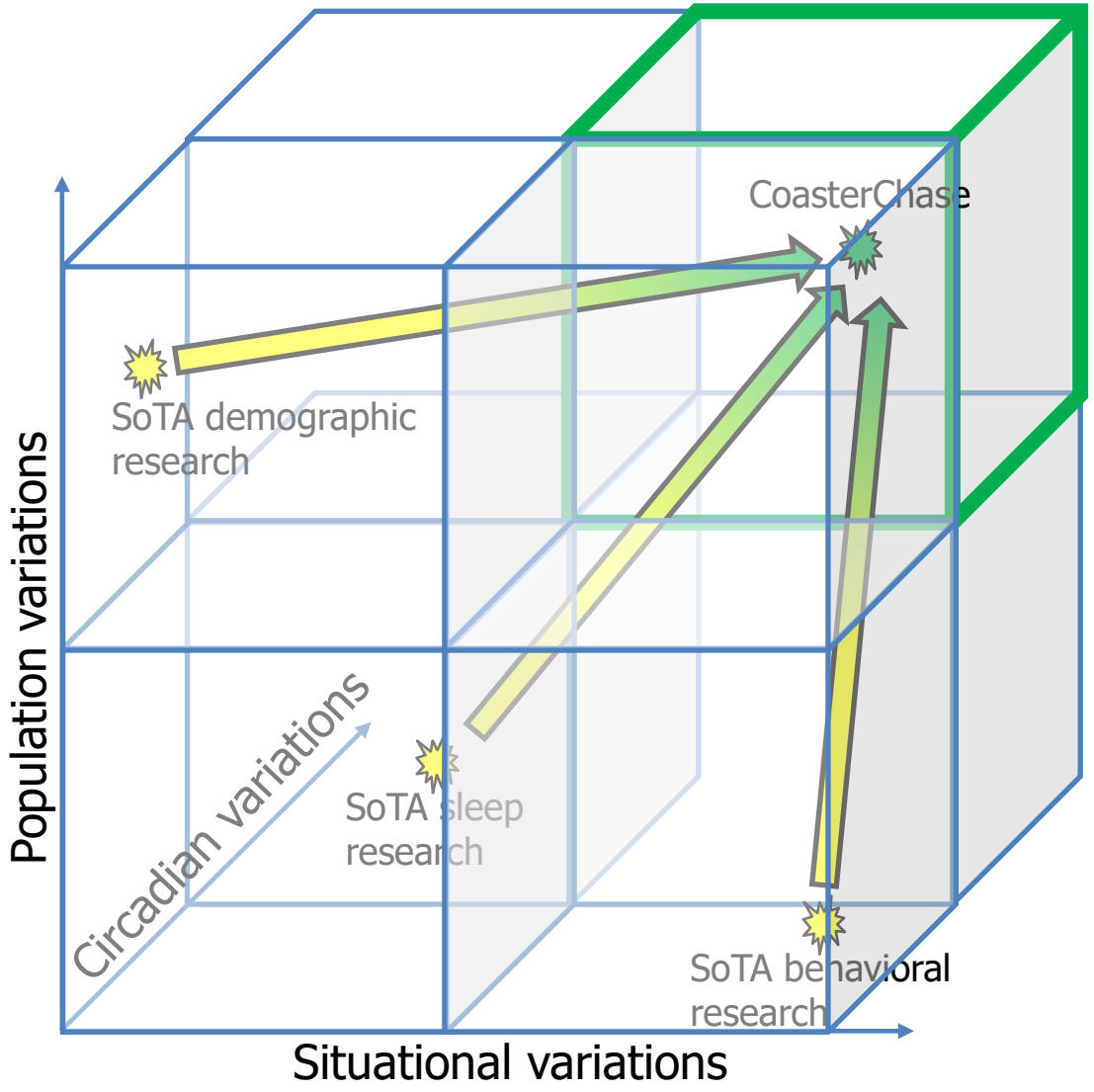


Enabling Deliverable: A platform for wearable, stimulation of the enteric "second brain"

TIS = Temporal Interference Stimulation; N3 = Next-Generation Nonsurgical Neurotechnology; ANC = Autonomous Neural Control; ElectRx = Electrical Prescriptions

HAPTIX = Hand Proprioception and Touch Interfaces;

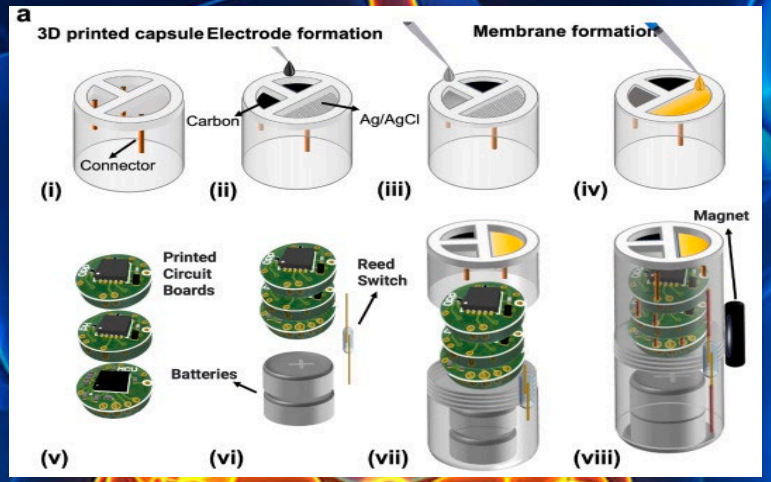
H3: optimal performance requires enteric nervous system sensing



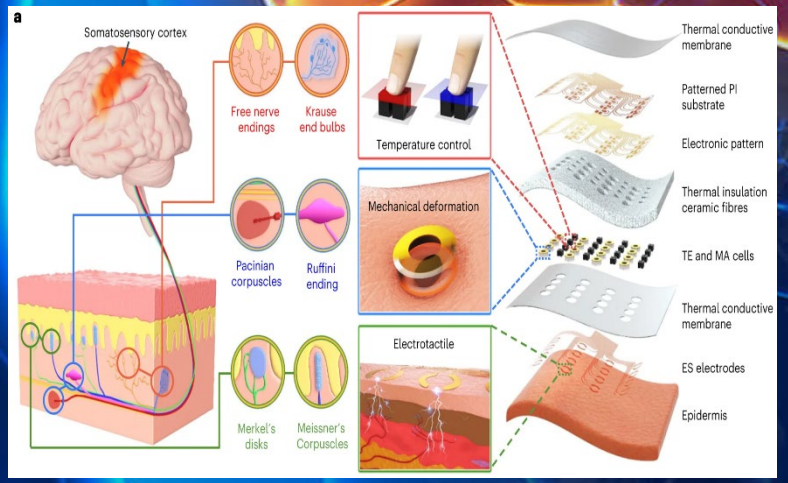
Enabling Deliverable: A platform for wearable, sensing of the enteric "second brain"

H3: sense to actuate to fine control, all from a single ingestible platform

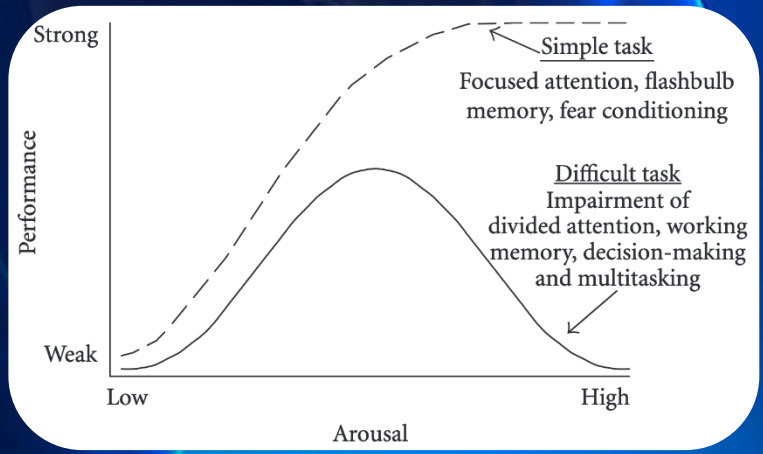
1. Sense



2. Actuate



3. Fine tune



H3 - Phase 1: questions to be answered with this MVP platform

Phase & year 1	FA1: Animal Physiology Research	FA2: Electroceutical Development
	Q: How can we isolate and stimulate NPY-expressing ENS neurons (or other ENS neurons with stress performance relevance)? **Deliverable:** Stimulation sensitivity results of targeted intestinal neurons for 2 stimulation modalities. **Q:** How much of the small intestine needs to be stimulated *in vivo* to evoke significant changes to measured biomarkers of stress (such as NPY and cortisol)? Is this location dependent? **Deliverables:** - A range of small intestine lengths that produce significant changes to measured biomarkers of stress (such as NPY and cortisol). - Input-output curve for the NPY-cortisol (or other stress biomarkers, with justification) relationship as a function of stimulation dosage. **Q:** Can we sense both circulating and localized biomarker concentration dynamics? **Deliverables:** - Circulating and local concentration dynamics for neuromodulation-stress relationship during stimulation. **Deliverable**: Proposal of appropriate induced stress behavioral paradigm for chronic experiments.	**Q:** Can we build a stimulation benchtop capable of electrical actuation within the full range of parameters? **Deliverable:** Benchtop test results. **Q:** Can we build a stimulation benchtop capable of a second actuation modality within the full range of parameters? **Deliverable:** Benchtop test results. **Q:** Can we develop ability to sense identified biomarkers within the full range of parameters? **Deliverable**: Benchtop test results. **Q:** Can we combine both stimulation modalities on a single platform? **Deliverable:** Demo of pill capsule stimulation platform. **Q:** Can we miniaturize this platform and encapsulate it? **Deliverable:** Initial capsule for stimulation platform.

FA = Functional Area; NPY = Neuropeptide Y; ENS= Enteric Nervous System; GI = Gastrointestinal

H3 - Phase 2: questions to be answered with this MVP platform

Phase & year 2	FA1: Animal Physiology Research	FA2: Electroceutical Development
	Q: Can we use gold-standard neuromodulation biomarker sampling to explore cognitive performance in *in vivo* tests? **Deliverable:** Plots/data/diagrams of cortisol (or other biomarkers of stress) vs. cognitive performance vs. stimulation. **Q:** If one population variable (age, sex, etc…) is changed for the above study, does the zone change significantly? **Deliverable:** Notional zone comparisons with demographical variations **Q:** If one situation variable (e.g. acute stress vs. chronic intermittent stress; predator-related stress vs. water-restriction stress) is changed, does the zone change significantly? **Deliverable:** Notional zone comparisons with situational variations. **Q:** If one innate variable (e.g. circadian rhythm, estrous cycle) is changed, does the zone change significantly? **Deliverable:** Notional zone comparisons with innate variations. **Q:** If two variables are modulated (e.g. population, situation, innate), does the zone change significantly? **Deliverable:** Notional zone comparisons with two variations. **Q:** Will the platform persist 5 days in the small intestine? **Deliverable:** Benchtop test results.	**Q:** Can we integrate both stimulation and sensing modalities on a single ingestible platform? **Deliverable:** Demo of integrated pill capsule platform. **Q**: Can this combined platform withstand the pressurized and acidic environment of the GI tract? **Deliverable**: GI-transit test results **Q:** Will this combined platform chronically persist in the small intestine of a large animal model? **Deliverable:** Data-driven proof of chronic persistence. **Q.** Can the dynamic platform use sensing inputs to drive stimulation outputs with closed-loop control? **Deliverable:** Results from closed-loop control testing. **Final Deliverable:** An ingestible, persistent sensing and stimulating platform for use in enteric neuromodulation.

.

FA = Functional Area; NPY = Neuropeptide Y; GI = Gastrointestinal

H4: Who cares?

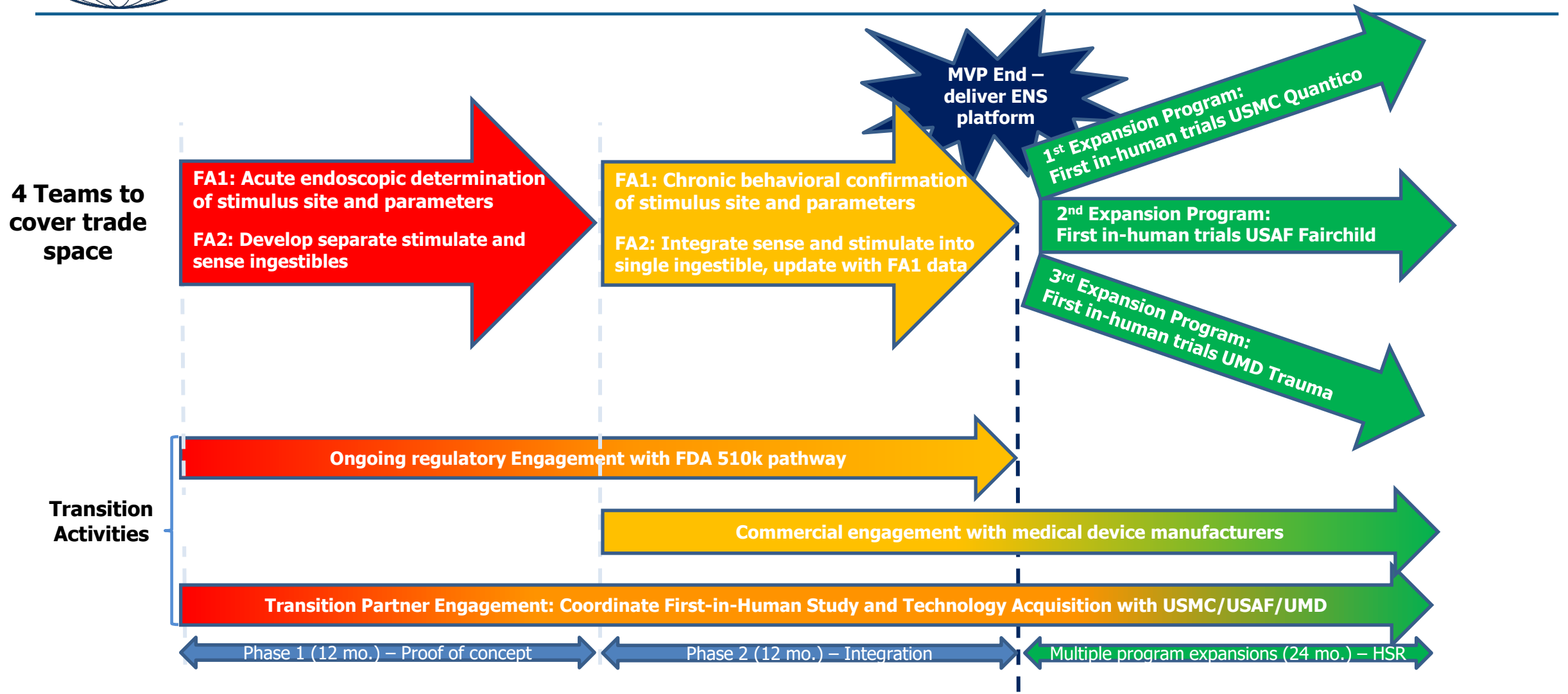
Warriors

Pilots

Survivors

Beneficiaries: every DoD and civilian individual performing complex tasks in a high-stress environment

CoasterChase timeline



Timeline: Proof of concept platform and exploration of ENS neuromodulation → first HSR → transition

FA = Functional Area; ENS = Enteric Nervous System; USMC = U.S. Marine Corps; USAF = U.S. Air Force; UMD = University of Maryland; FDA = U.S. Food and Drug Administration; HSR = Human Subjects Research

Phase 1: milestones and metrics

Animal Physiology Research Milestones

1: Identification and stimulation sensitivity results of targeted intestinal neurons for 2 stimulation modalities

2: Input-output curve for the neuromodulation-stress relationship as a function of stimulation dosage for **1 cm** length of small intestine (2 modalities)

3: Input-output curve for the neuromodulation-stress relationship as a function of stimulation dosage for **up to 20 cm** length of small intestine (2 modalities)

4: Local and circulating biomarker concentration dynamics as a function of stimulation

5: Proposal of appropriate induced stress behavioral paradigm for chronic *in vivo* experiments

Electroceutical Metrics

Demonstrate ability to stimulate (up to 20 cm):

- 1 Hz – 10 kHz e-stim
- 100 µA – 5 mA e-stim
- 1 Hz – 300 Hz m-stim
- 2 µm – 20 µm m-stim

Demonstrate ability to sense intra-luminal NPY with:

- 1 pg/mL sensitivity
- 1-100 pg range
- 5 min refresh frequency

Phase 1 deliverables:

- Characterization of ENS (such as NPY-producing) stress-modulating neurons with proposed minimum sensitivity and ranges of detection for measured biomarkers of stress (such as NPY and cortisol)
- Defined range of intestinal length activation needed to produce significant changes to measured biomarkers of stress (such as NPY, cortisol)
- Input-output curves for neuromodulation-stress relationship for stimulus modality and stimulus dosage
- Circulating/local concentration dynamics for measured biomarkers of stress during stimulation (such as NPY and cortisol)
- Design for combined multi-modal stimulation platform for ENS neuron modulation in ingestible capsule format
- Performance testing of platform in GI tract facsimile
- Initial encapsulated sensing platform for Phase 2 behavioral testing
- Chronic-ready multi-modal stimulation capsules for Phase 2 behavioral testing

NPY = Neuropeptide Y; ENS = Enteric Nervous System; GI = Gastrointestinal; m-stim = Mechanical Stimulation (i.e. vibrational); pg = Picogram

Hz = Hertz (i.e. cycles/second); e-stim = Electrical Stimulation;

Phase 2: milestones and metrics

Animal Physiology Research Milestones	Electroceutical Metrics
6: Finding the responsiveness of stress biomarker (e.g. cortisol) production that underlies the optimal range of performance for the behavioral paradigm. **7:** Variability testing of modulated biomarker responsiveness with the introduction of a demographic variable. **8:** Variability testing of modulated biomarker responsiveness with the introduction of a situational variable. **9:** Variability testing of modulated biomarker responsiveness with the introduction of an innate variable. **10:** Initial FDA engagement for 510K pathway	**Integrated capsule platform with 2 stimulation modalities and 1 sensing modality NTE:** - Diameter < 1.3 cm - Weight: < 5 g **Demonstrate persistence :** - Stable in simulated gastric fluid for 1 day - Withstands ~ 1000 cycles/day at 50g/cm^2 pressure - In small intestine at least 5 days, no more than 21 days

Phase 2 deliverables:

- Exploration of optimal zone for paradigm
- Optimal zone variability plots across a) population variables, b) situational variables, c) innate variables, and d) combined variables
- Integrated sensing + stimulation capsules in ingestible form factor
- Performance test results in pressure and simulated gastric fluid studies
- Proof of persistence in the small intestine for 5 days in animal model

FDA = Food and Drug Administration; NTE = Not to Exceed

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