PAPER OF THE YEAR 2023

TRR 295 ReTune

Integrated cardio-behavioral responses to threat define defensive states.

Signoret-Genest J*, Schukraft N*, Reis SL, Segebarth D, Deisseroth K, Tovote P.

*equal contribution

Nat Neurosci. 2023 Mar; 26(3): 447-457. doi: 10.1038/s41593-022-01252-w. PMID: 36759559.

The defense response to threat involves complex behavioral and autonomic adjustments, however the integrated nature of these responses remain poorly understood. In particular, although threat has been associated with various cardiac changes, there is no clear consensus regarding the relevance of these changes for the integrated defense reaction.We re-addressed this issue by delineating a conceptual framework for defensive states based on their associated autonomic and behavioral co-adaptations. We first generated a large dataset of combined behavioral and cardiac readouts in mice. To this end, we placed mice in contexts that elicited distinct emotional states by varying threat intensity and acuteness.

We focused on the strong association between immobility (often referred to as freezing) and a decrease in heart rate under threat conditions, which we defined as a 'microstate' because of its short-lasting on/off characteristics. However, we realized that slow latent processes were influencing this defensive state. One such process, which we called 'rigidity', was constraining the range of heart rate values. In contrast to microstates, we defined this higher order process as a 'macrostate'. Factoring this into our analysis revealed that different behaviors, regardless of their physical demands, were associated with different average heart rate levels, such as a time-locked decrease or increase in heart rate or a general stabilization around a given average. The influence of the context proved to be decisive, in that higher contextual threat level led to more constrained heart rate changes.

We then used optogenetics to characterize a crucial circuit element, Chx10-expressing neurons in the midbrain periaqueductal gray region that mediate the freezing-bradycardia microstate. Strikingly, the evoked cardiac response was similarly influenced by rigidity, as observed during spontaneous defensive states. This showcased the usefulness of our integrated cardio-behavioral approach for characterization of multimodal states and their neural substrates.

The reconciliation of threat-induced cardiac dynamics restores heart rate as a valuable tool in systems neuroscience and shows how it can reveal otherwise hidden, latent macrostates. Similar to how integrating state phenomena such as rigidity unravelled some unforeseen cardio-behavioral relations, other macrostates have yet to be uncovered. These include so called "pathostates", caused by neurodegenerative processes in the course of PD, which encompass behavioral and autonomic dysfunction among many other symptoms. Through characterization of the interrelationship of motor and non-motor state components, our work presents a new angle for a better understanding of highly dynamic neural network diseases.

Dr. Jérémy Signoret-Genest

He is a postdoctoral research fellow in Prof. Tovote's lab. His research is based on the computational analysis of multi-dimensional read-outs displayed during fear and anxiety in order to identify integrated defensive states.

Nina Schuhkraft

Nina Schukraft is a PhD student in Prof. Tovote's lab with a focus on identifying neural brain circuitries underlying integrated defensive states.

Prof. Dr. Philip Tovote

He is the head of Systems Neurobiology and Co-director of the Institute of Clinical Neurobiology in Würzburg. His group aims at a better understanding of the neuronal circuits that underlie brain-body interactions in health and disease and to develop models for targeted 'circuit therapy' with enhanced specificity to treat systems neuropsychiatric disorders.

RETUNE

CRC TRR 295 Berlin–Würzburg