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Neurobiology

How does the brain orchestrate survival?

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ABSTRACT
Eating when hungry, drinking when thirsty and fear under threat are essential behaviors for animal survival produced by the long evolution of life. We found that the brain processes these simple survival behaviors in a surprisingly complex way. The brain encodes different survival behaviors using combinations of brain cell types, like the instruments in an orchestra playing different symphonies.

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We can think of the way the brain processes information as an orchestral ensemble. In the brain, information is mainly processed by a specialized type of brain cell called neurons, like individual instruments in the orchestra. Neurons use electrical signals to transmit information. These signals are called 'neuronal activity', and it is akin to an instrument playing different notes. Neurons can be classified into different subtypes, just as instruments can be categorized into wind and string instruments, etc.

A brain area called the paraventricular hypothalamus (PVH) is crucial for regulating hunger, thirst, and fear. The PVH has many different functions and contains various neuron subtypes. This made it challenging to systematically study how the different PVH neuron subtypes encode different behaviors. Previous studies examined neuron subtypes one-at-a-time, which gave the impression that the PVH acts as a behavioral state "switchboard", in which each neuron subtype influences a specific behavioral state as a "labeled-line". It is difficult to validate this model, because this requires examining neuronal activity of different subtypes at the same time.

We considered three possible models for the role of neuron subtypes to encode behavioral states. (1) Labeled-line coding model: Neurons of the same subtype respond similarly and are specialized for a specific behavioral state as a "labeled-line". (2) Full-ensemble coding model: Behavioral states are encoded irrespective of neuron subtypes. Individual neurons have their unique contributions to encode behavioral states. Neurons in the same subtype can have unrelated activity patterns. (3) Grouped-ensemble coding model: Neurons within the same subtypes have coordinated responses. Then, behavioral states are encoded based on specific combinations of these subtypes.

It has been extremely difficult to distinguish these models because they describe the relationship of neuron subtypes, their neuronal activity and neural coding of behaviors. This relationship is a long-standing question in neuroscience. To address this question, it requires simultaneously monitoring the neuronal activity across many behavioral states along with their subtype identities in the same animal. This is an unrealized "dream experiment" for neuroscientists. We made this dream come true by developing a new technique named CaRMA (Calcium and RNA Multiplexed Activity) imaging in mice. This technique aligns the activity of neurons with their subtype. First, we monitored the activity of individual PVH neurons without regard to subtypes during different survival tasks, including feeding, drinking and the experience of fear. Subsequently, we removed and sectioned the brain. Next, we aligned the neurons we studied when the animal was alive with the same neurons in the brain sections. Finally, we revealed the subtypes of these neurons by looking at their mRNA.

Using CaRMA imaging, we obtained neuronal activity in hundreds of PVH neurons across eleven behavioral states along with their subtypes. We first exhaustively searched for labeled-line neurons that only respond in a specific behavioral state. We could not find any labeled-line neurons in our dataset; all neurons were always involved in multiple behavioral states. Then, we classified these PVH neurons into ten different subtypes. We found that neurons within the same subtype often showed similar activity patterns. We could even predict the responses of individual neurons purely based on their subtype information. Using machine learning analysis, we found the neuronal activity of the PVH neuron subtypes supported the "grouped-ensemble coding" model of behavioral states. Using an orchestral ensemble as an analogy, PVH molecular subtypes are the instrument types with similar acoustic properties; each behavioral state is a symphony, but not a solo. An orchestra can play multiple symphonies, but the instruments need to be rearranged and cooperate in a different way for each symphony. Interestingly, we also found the "conductor" of the orchestra. We found that a particular receptor gene was the most predictive gene for neuronal activity and was expressed in multiple neuron subtypes, like the "conductor" of the PVH neuronal ensemble.

Our results confirmed that neuron subtypes are important information processing units in the PVH, and we provided an unprecedented view of the complex relationship between different neuron subtypes and how they encode different behavioral states related to survival. Do other brain regions use the same way to orchestrate different behavioral states? We don't know yet, but CaRMA imaging is a powerful tool that can help answer this question.