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HOT TOPICS

Linking cell types to behavior in the vertebrate hypothalamus

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Neurons can be categorized according to a variety of different attributes, including their anatomy, genetics, connectivity, or activity. However, it is unclear how these different categorizations relate to one another [1], especially in brain regions like the vertebrate hypothalamus, where it is challenging to measure the molecular identity and activity patterns of the same neurons.

Two recent studies have overcome these challenges in mice, using single-cell RNA-sequencing to jointly measure the molecular identity of neurons and the expression of activity-dependent genes after specific behavioral experiences [2, 3]. Moffitt et al. [2] used spatial transcriptomics to classify neurons in the medial preoptic region of the hypothalamus, and concluded that different social behaviors recruit different molecular subclasses of neurons. Using a complementary approach, Kim et al. [3] analyzed gene expression and axonal projections in the ventromedial hypothalamus, but found that neurons expressing activity-dependent genes after social behaviors included cells of many molecular and projection-defined subclasses. Despite the substantial insights gained from these studies, the fast-timescale activity patterns of neurons are not captured by activity-dependent gene expression, preventing detailed characterization of neurons based on their activity.

To jointly measure the fast-timescale activity and expression of multiple genes in the same neurons, we developed a method to merge live-brain calcium imaging and fixed-brain multiplexed gene expression labeling, across large populations at single-cell resolution [4, 5]. We applied this to the hypothalamus of larval zebrafish; like mammals, the fish hypothalamus is composed of conserved peptidergic cell types and directs multiple innate behaviors, but is accessible for non-invasive neural activity imaging during behavior [6]. We recorded from neuropeptide-expressing cell types in the zebrafish homolog of the paraventricular hypothalamus, where we had observed that different threats (sudden increases in heat, acidity, or salinity) would recruit different neural populations [5]. To determine if differences in functional responses corresponded to differences in neuropeptide expression, we simultaneously imaged the activity of neurons that express genes for *oxytocin*, *vasopressin*, *corticotropin-releasing factor*, *somatostatin*, *vasointestinal polypeptide*, and *neuropeptide-Y*.

Rather than finding a clear correspondence between the functional and molecular identity of neurons, we found that cells responsive to different behavioral features (i.e., heat, salinity, acidity, movement, and combinations thereof) were distributed across multiple sets of peptidergic cell types [5]. Specific manipulations of different genetic cell types, including *oxytocin*- and *corticotropin-releasing factor*-expressing neurons, revealed that distinct cell types can play overlapping roles in threat avoidance, owing to common glutamate co-release and innervation of spinal-projecting premotor neurons in the lateral brainstem [5].

Together, these findings in the rodent [2, 3] and zebrafish [5] hypothalamus suggest that grouping neurons by single attributes can be misleading—knowledge of a neuron's genetic identity may not necessarily inform its functional identity, and vice versa. Instead, the functional organization of the brain may be better understood by finding common ground across multiple methods of categorization (thousands of genes, complete connectivity, and activity across multiple behaviors and internal states), or searching for new organizational principles altogether.

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