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Title: Decoding of Thirst States in the Mammalian Brain

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Abstract: The motivation to drink is triggered by two distinct thirst states. Increased internal osmolality induces osmotic thirst that drives animals to drink pure water. Conversely, loss of body fluid volume induces hypovolaemic thirst, in which animals drink both water and minerals to recover blood volume and electrolyte composition. Sensory nuclei in the Lamina terminalis (LT) including the subfornical organ (SFO) and organum vasculosum of lamina terminalis (OVLT) are critical for sensing both types of thirst-inducing stimuli. However, how different thirst modalities are encoded in the brain and how the thirst need state is decoded in higher order brain centers remains unknown. Here we employed single cell RNA-seq based stimulus-to-cell-type mapping to identify cellular substrates that detect the two kinds of physiological thirst states as well as thirst need signal decoding cellular populations in downstream hypothalamic nuclei. These studies revealed diverse types of excitatory and inhibitory neuron in each sensory LT nuclei SFO and OVLT. We show that unique combinations of these neuron types are activated under osmotic and hypovolaemic stresses. These results elucidate the cellular logic that underlies the detection of distinct thirst modalities. Furthermore, optogenetic gain of function in thirst-modality-specific cell types in the SFO and OVLT recapitulated water-specific and non-specific fluid appetite caused by the two distinct dipsogenic stimuli. Furthermore, we identified neural populations downstream of SFO and OVLT that orchestrate thirst motivation and endocrine responses in response to the thirst need state. Together, these results outline a robust and rapid strategy to map out cellular substrates for motivated behaviors and reveal that thirst is a multimodal physiological state that is mediated by specific neuron types in the mammalian brain.