

Offline Prefrontal Cortical Dynamics Underlines Odor-based Transitive Inference Emergence in Mice

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Transitive inference (TI) is deductive reasoning that derives relations between items in the absence of direct evidence. TI is conserved across species and is clinically relevant because relational-reasoning deficits, sleep disruption and prefrontal dysfunction occur in schizophrenia. Although sleep “idling brain” activity has been implicated in inference, the neural mechanisms by which sleep organizes memories into structured knowledge remain unclear. To address this, we developed a head-fixed, olfactory TI paradigm with controlled sensory input. Mice first learned operant Go/No-Go odor discrimination and were then trained on four premise pairs (A>B, B>C, C>D, D>E). Animals discriminated premises and, when tested on the novel BD pair, preferred B over D, mirroring performance on the end-anchor AE pair, indicating construction of the entire hierarchy A>B>C>D>E. Chemogenetic inhibition of prefrontal cortex (PFC) idling activity before test selectively impaired BD inference, whereas comparable inhibition of hippocampus did not. We next recorded PFC neural activity across wake and sleep using Neuropixels 2.0 electrophysiological recording. Principal component analysis (PCA) and uniform manifold approximation and projection (UMAP) trajectories of neural activity suggest that PFC neurons encode inference outcomes categorically by valence, independent of odor identity. Ongoing work applies a novel Transformer-based POYO-input/CEBRA-output framework to large-scale neural activity data and combines Neuropixels recordings with automated closed-loop 6-hour sleep deprivation to causally test sleep dynamics to TI. These analyses will link sleep information processing to behavioral inference. Together, our study enables mechanistic dissection of how sleep-dependent prefrontal dynamics support inference and abstraction, with implications for neuropsychiatric disorders and biologically inspired artificial intelligence.

(1936/2000 characters)