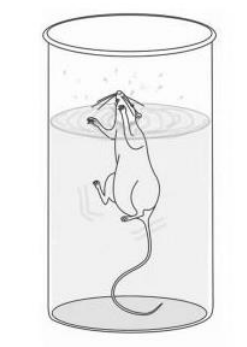


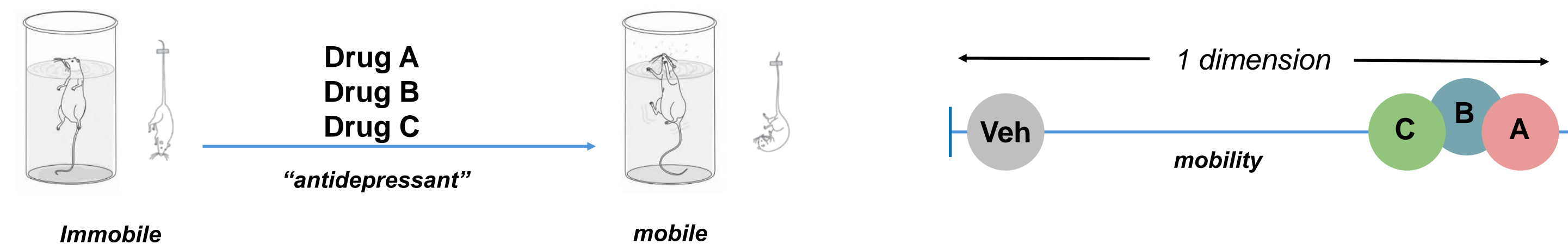
## Motivation

### Traditional behavioral assay

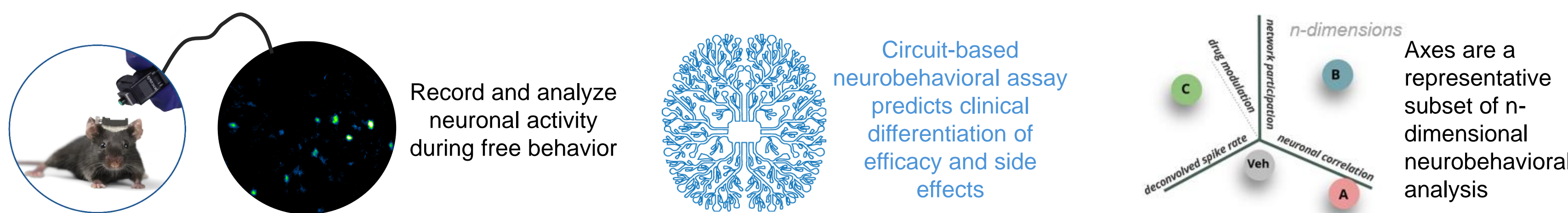
Traditional behavioral assays of "antidepressant efficacy" are **poorly predictive** of clinical performance



Traditional behavioral assays **cannot differentiate** effect based on mechanism or dose



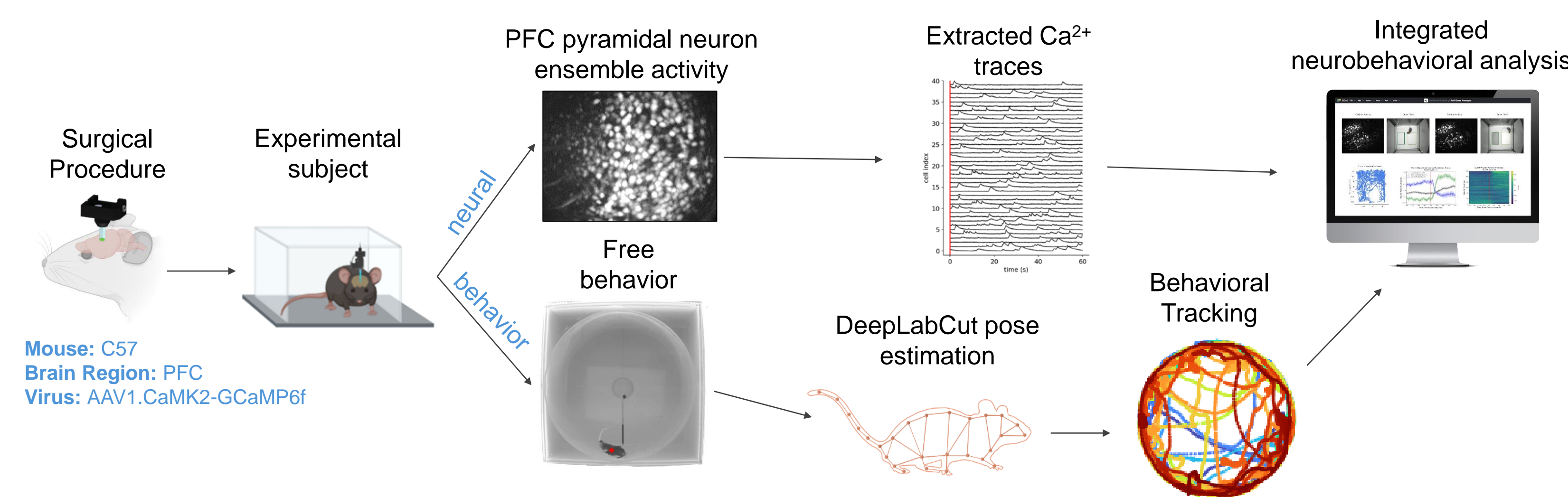
### Inscopix Integrated Neural Activity and Behavioral Assay



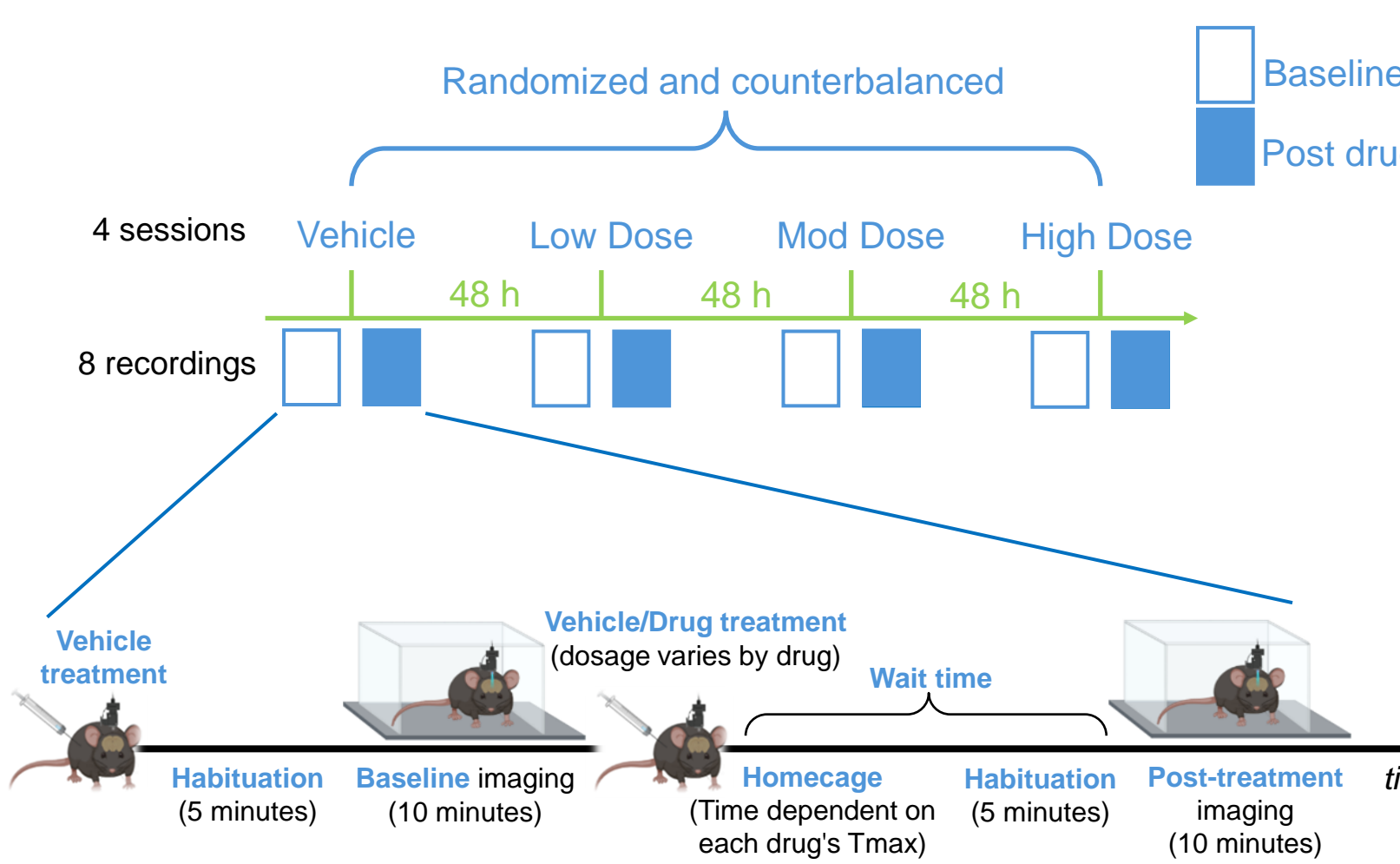
- Goals:**
- Establish a "high" throughput assay profiling the impact of antidepressants on ACC pyramidal neuron activity
  - Develop robust metrics for quantifying and comparing drug effects
  - Develop an unsupervised modeling approach to sensitively compare Mechanism Of Action (MoA) and dose

## Methods

### Experimental and computational workflow:



### Experimental design:

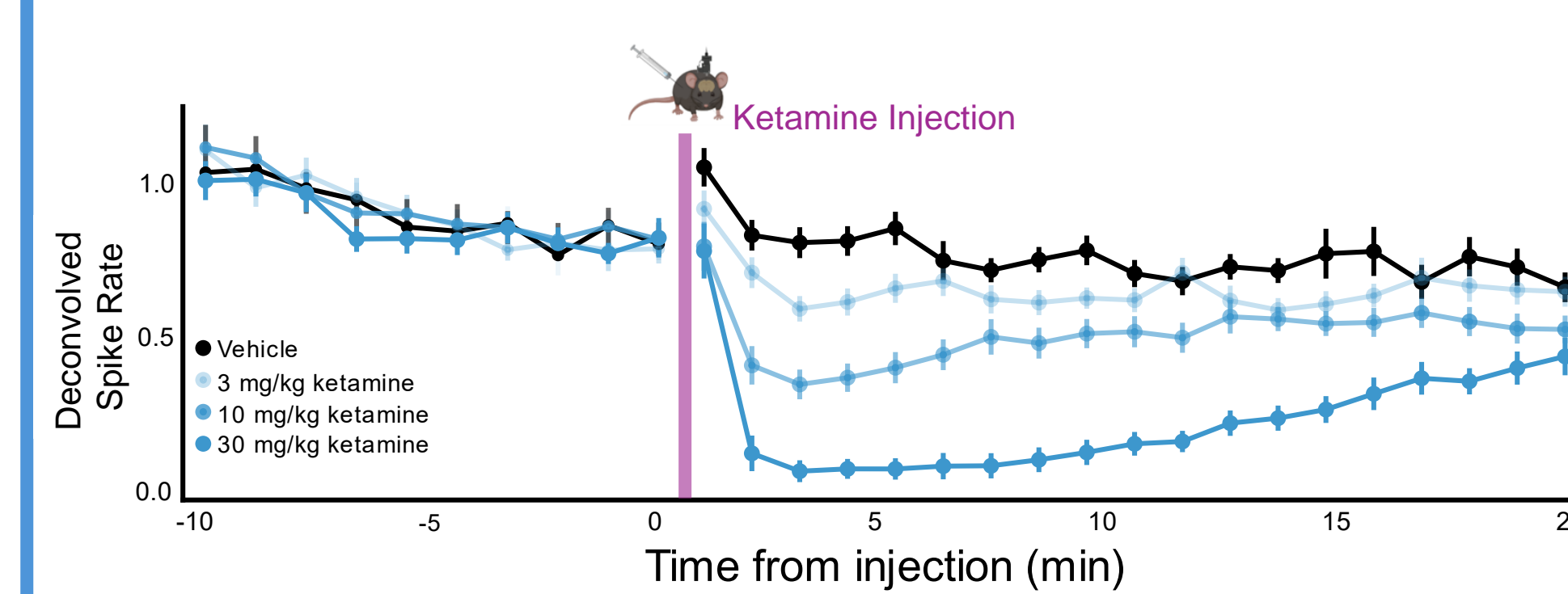


### Compounds profiled:

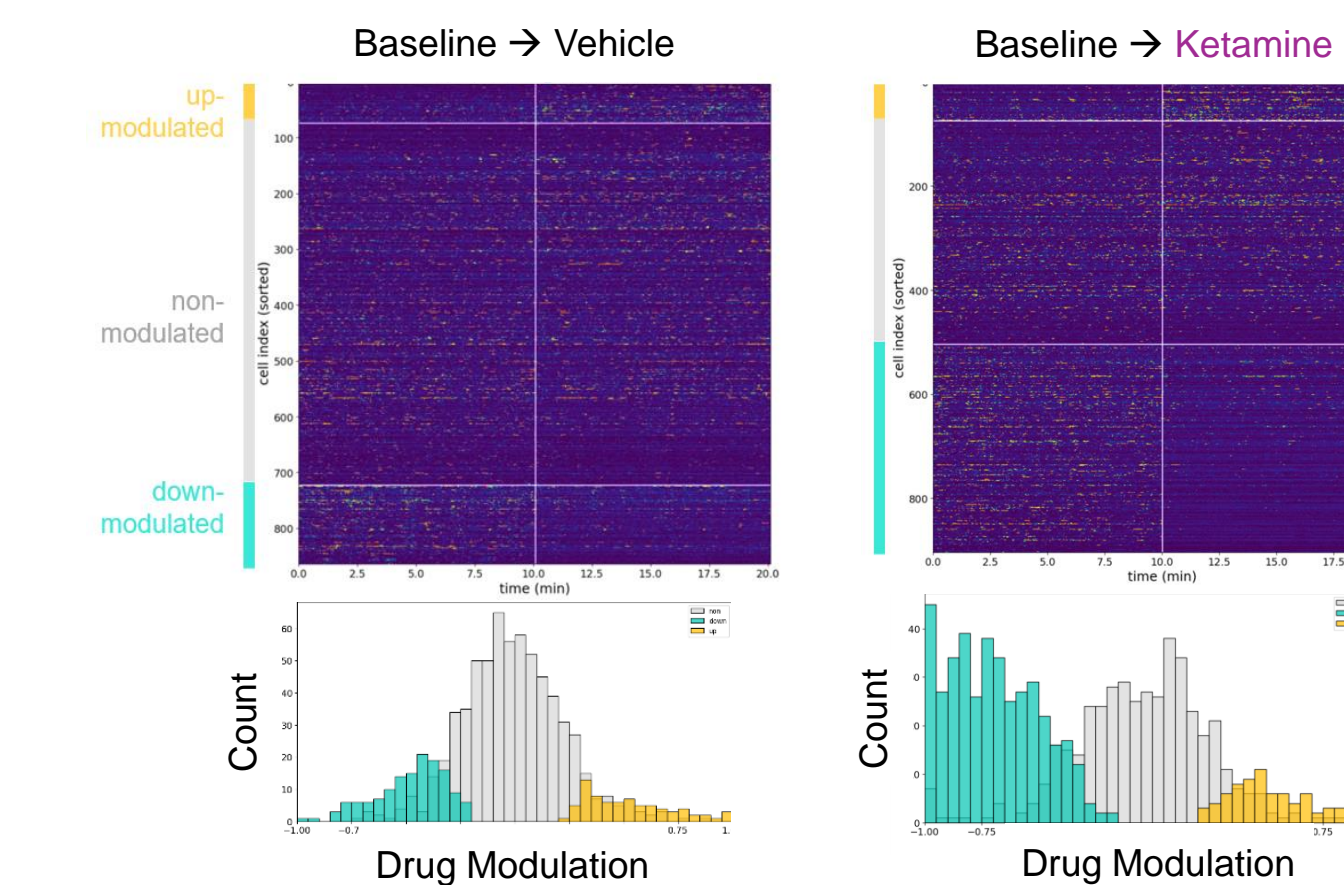
	Ketamine	Traxoprodil (CP-101, 606)	Rapastinel (GLYX-13)	N,N DMT
<b>MoA</b>	NMDAR Antagonist (med affinity pore blocker)	GIUN2B specific NMDAR antagonist (allosteric)	NMDAR glycine site partial agonist	5HT <sub>2A</sub> agonist (1A, 2A, 2C)
<b>Traditional behavior assay effect</b>	Reduction in immobility	Reduction in immobility	Reduction in immobility	Reduction in immobility
<b>Clinical effect in MDD</b>	Antidepressant	Antidepressant ?	Not antidepressant	Clinical trials ongoing

## Neural representation of rapid ketamine effects

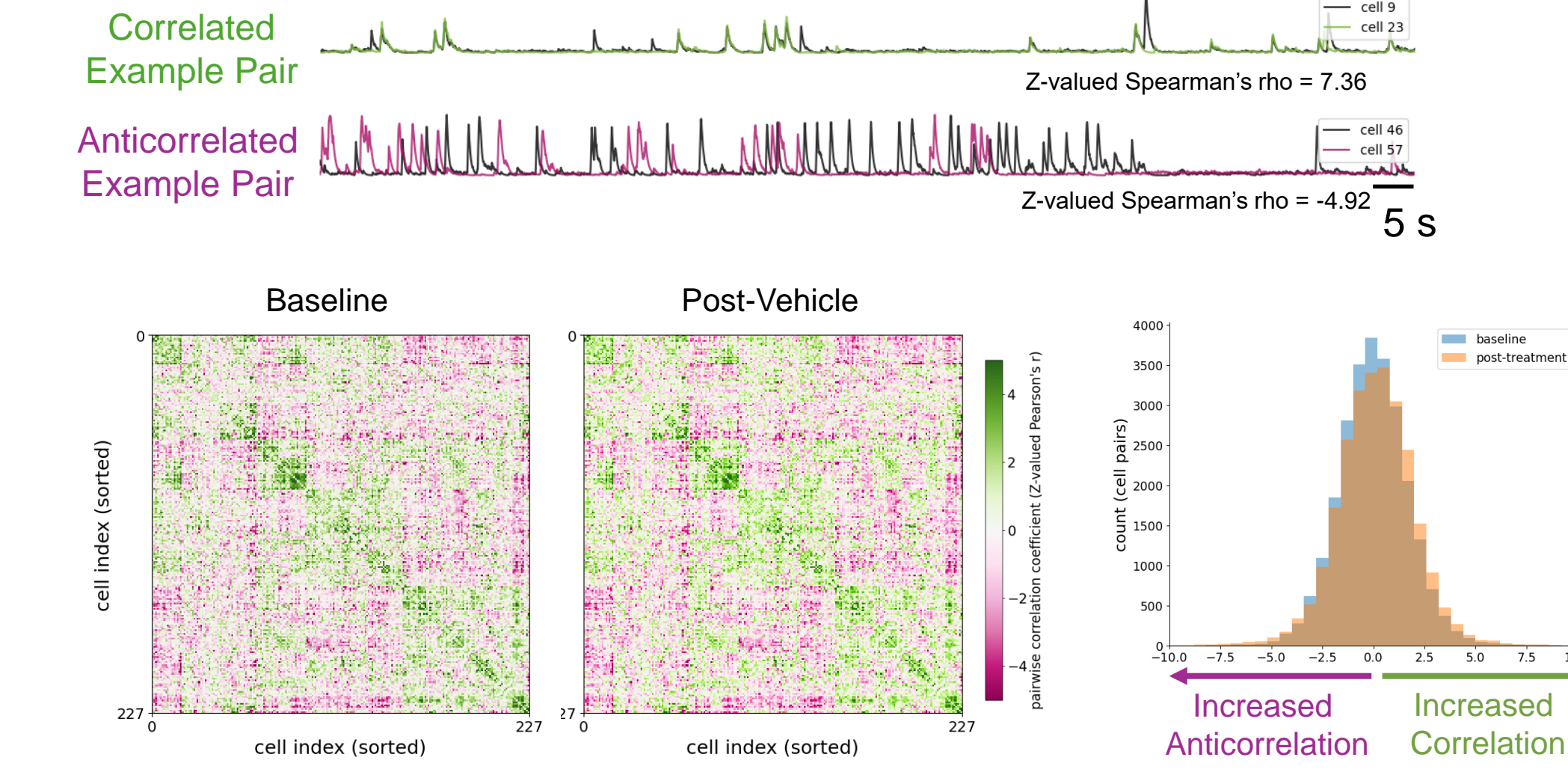
### Ketamine rapidly and dose-dependently suppresses ACC pyramidal neuron activity



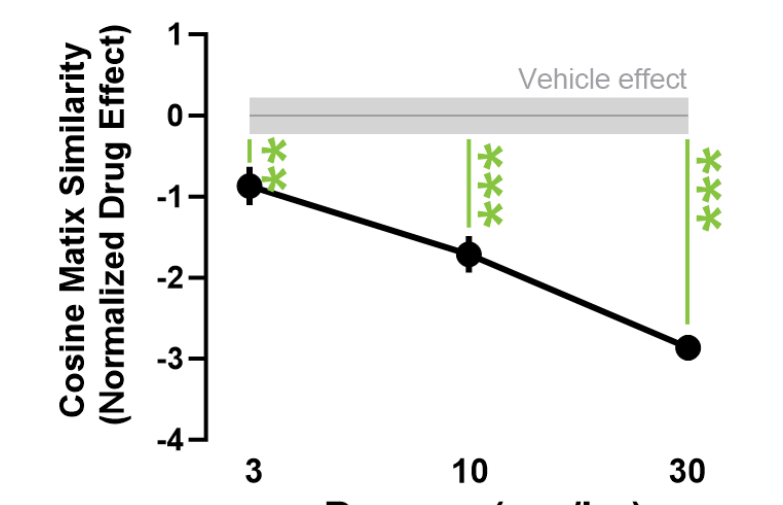
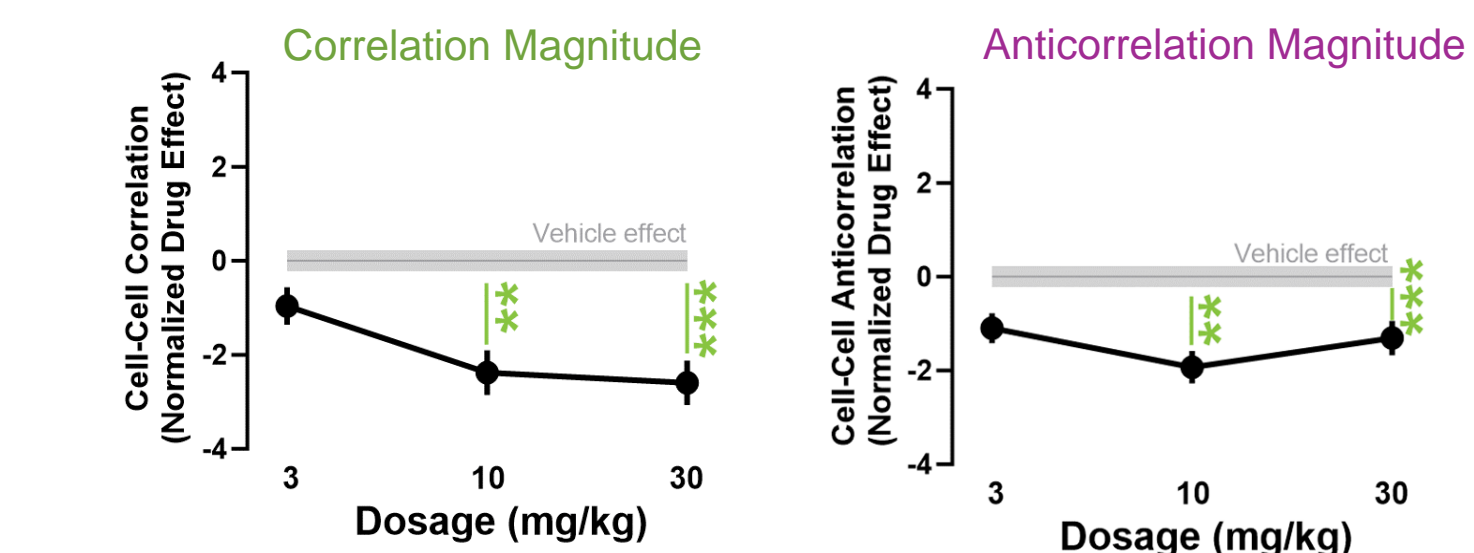
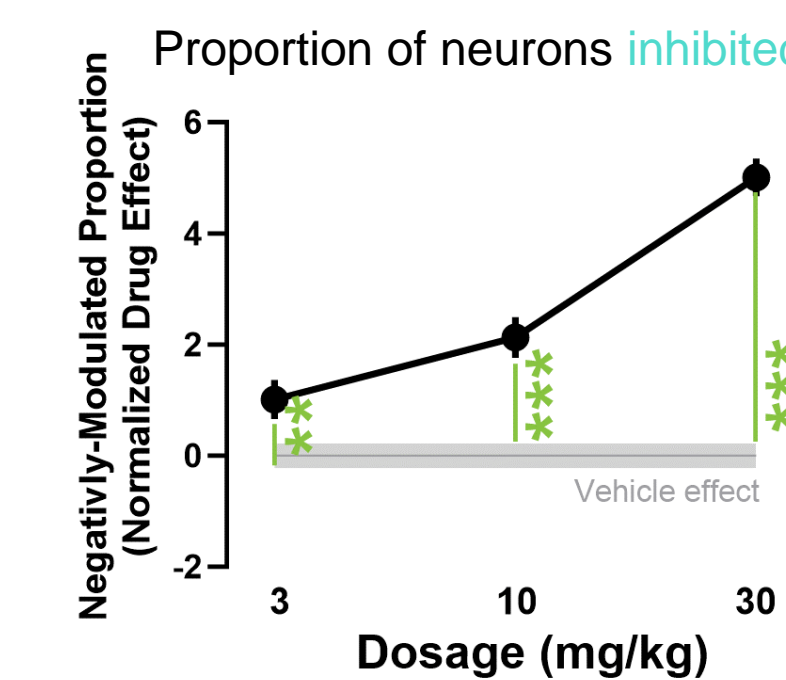
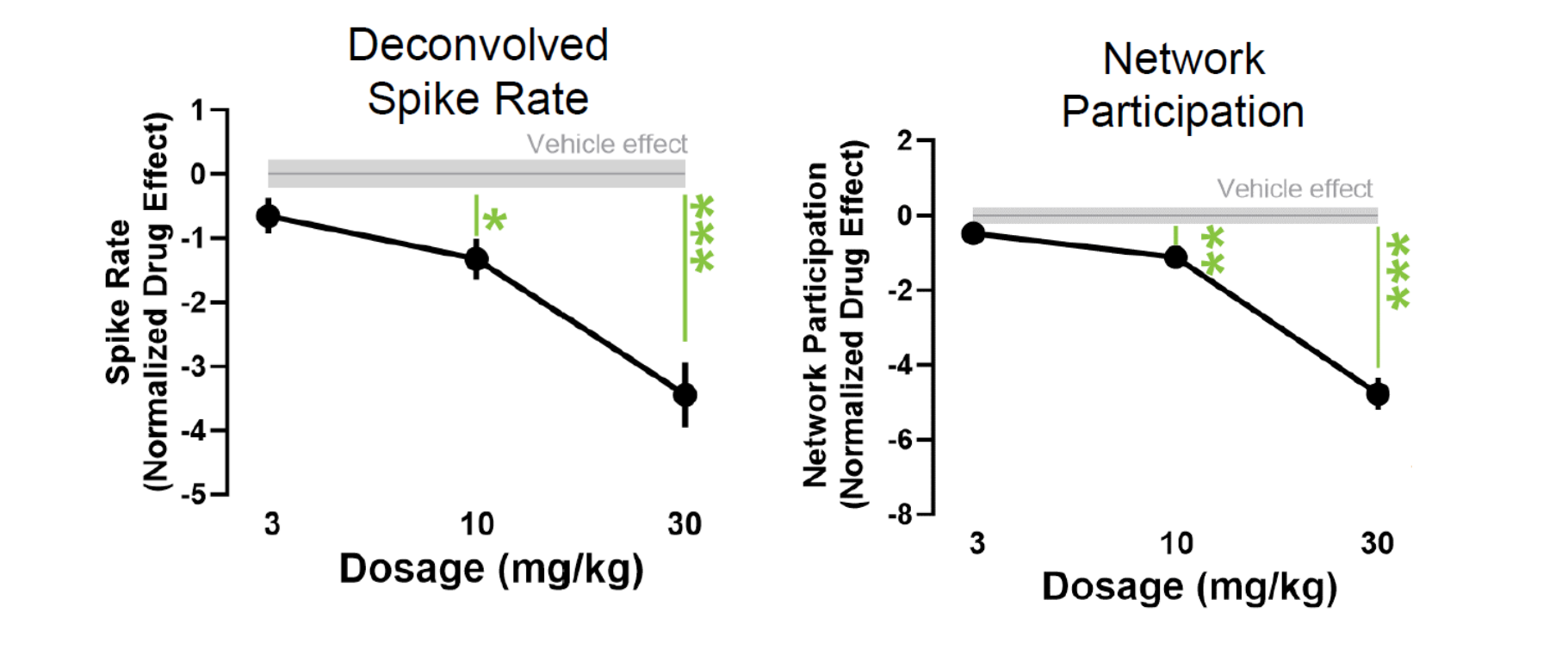
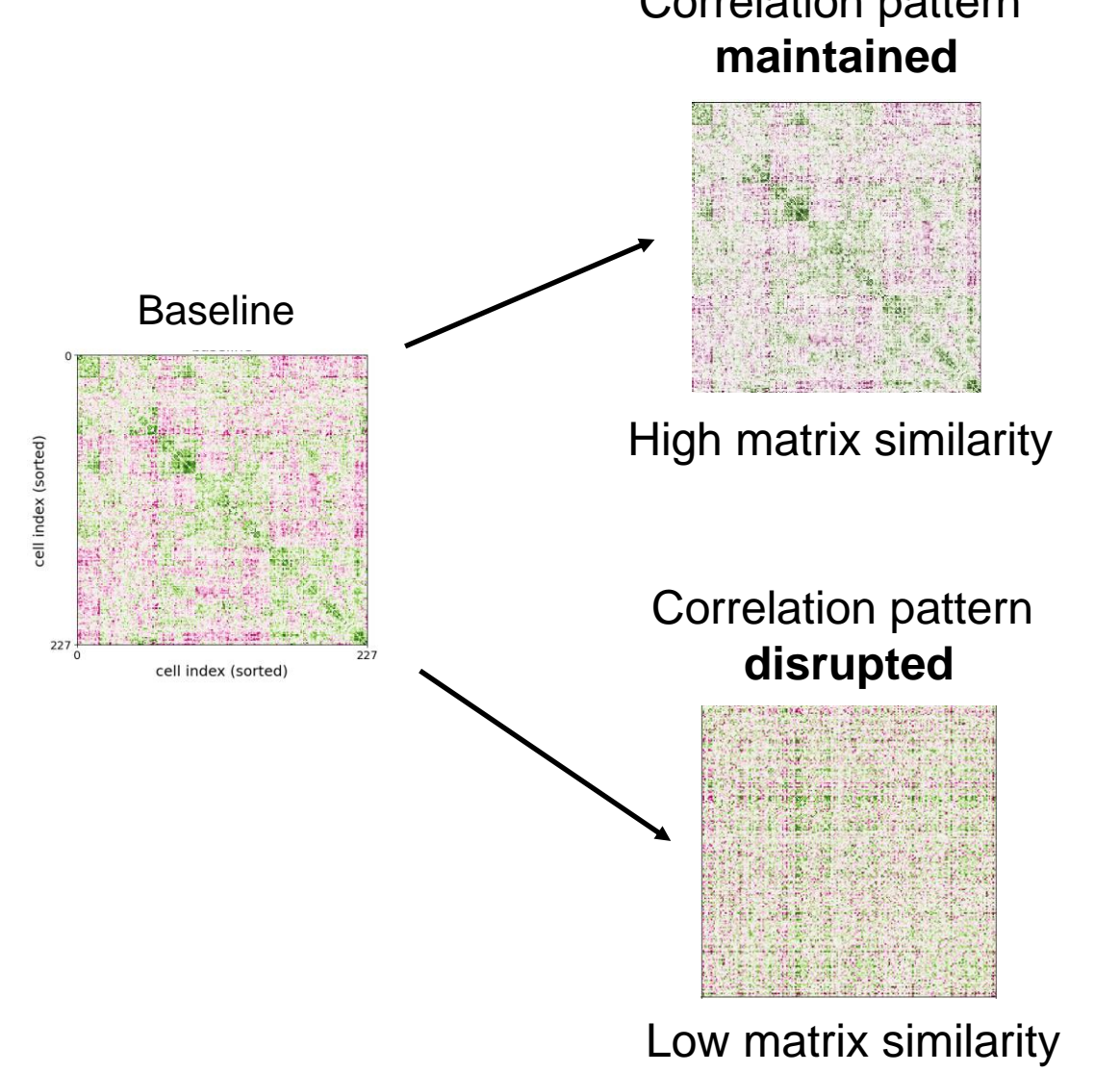
### Ketamine inhibits the majority of PFC pyramidal neurons



### Ketamine de-correlates prefrontal ensembles

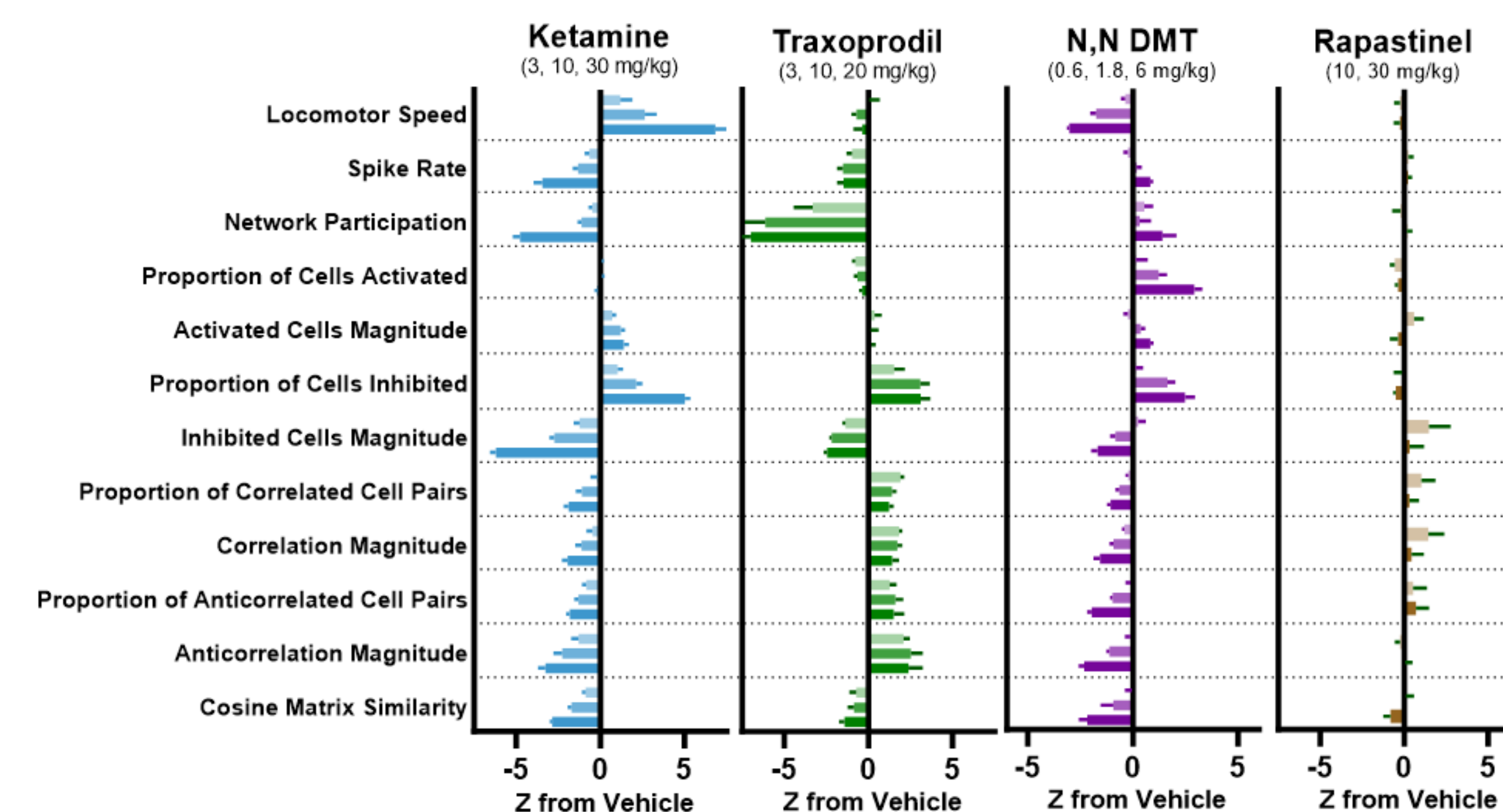


### Ketamine disrupts organization of correlated ensembles

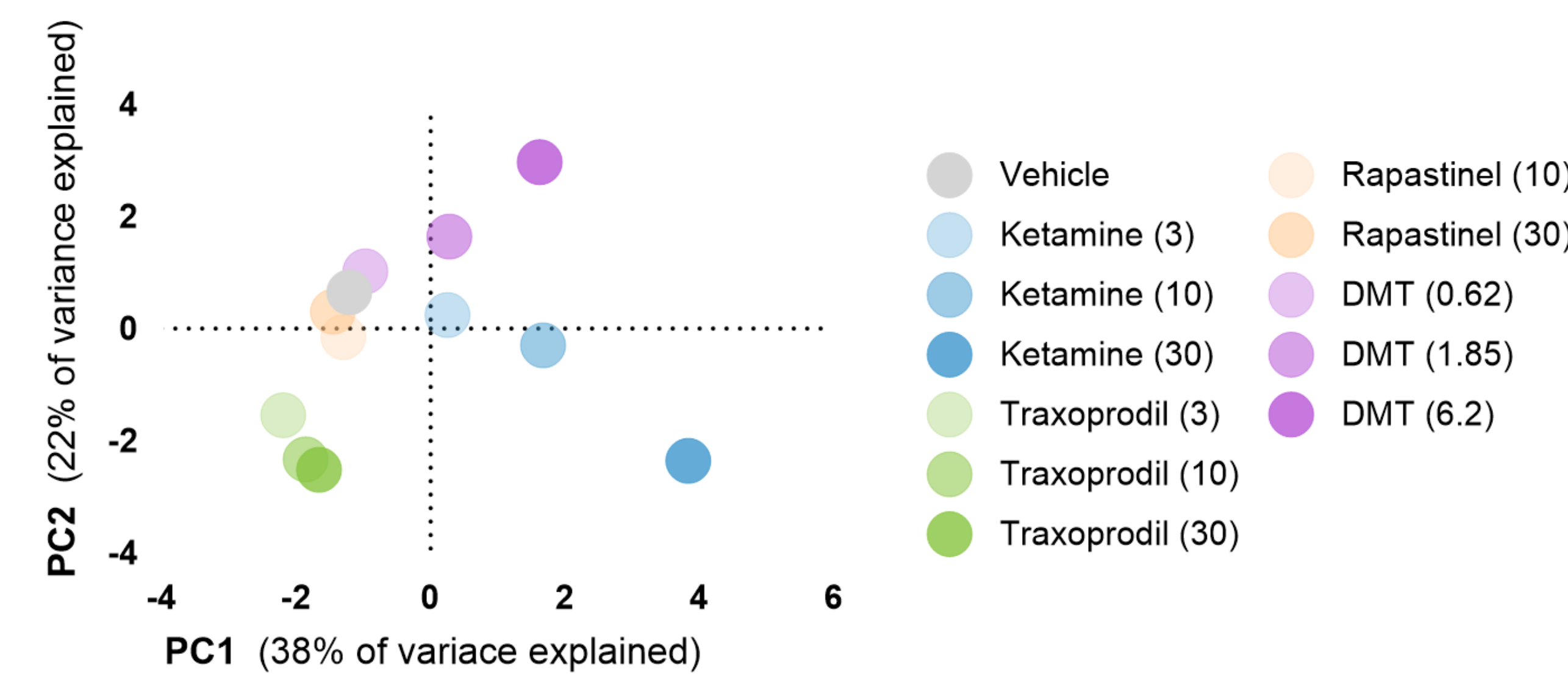


## Comparative drug profiling

### Neurobehavioral fingerprints

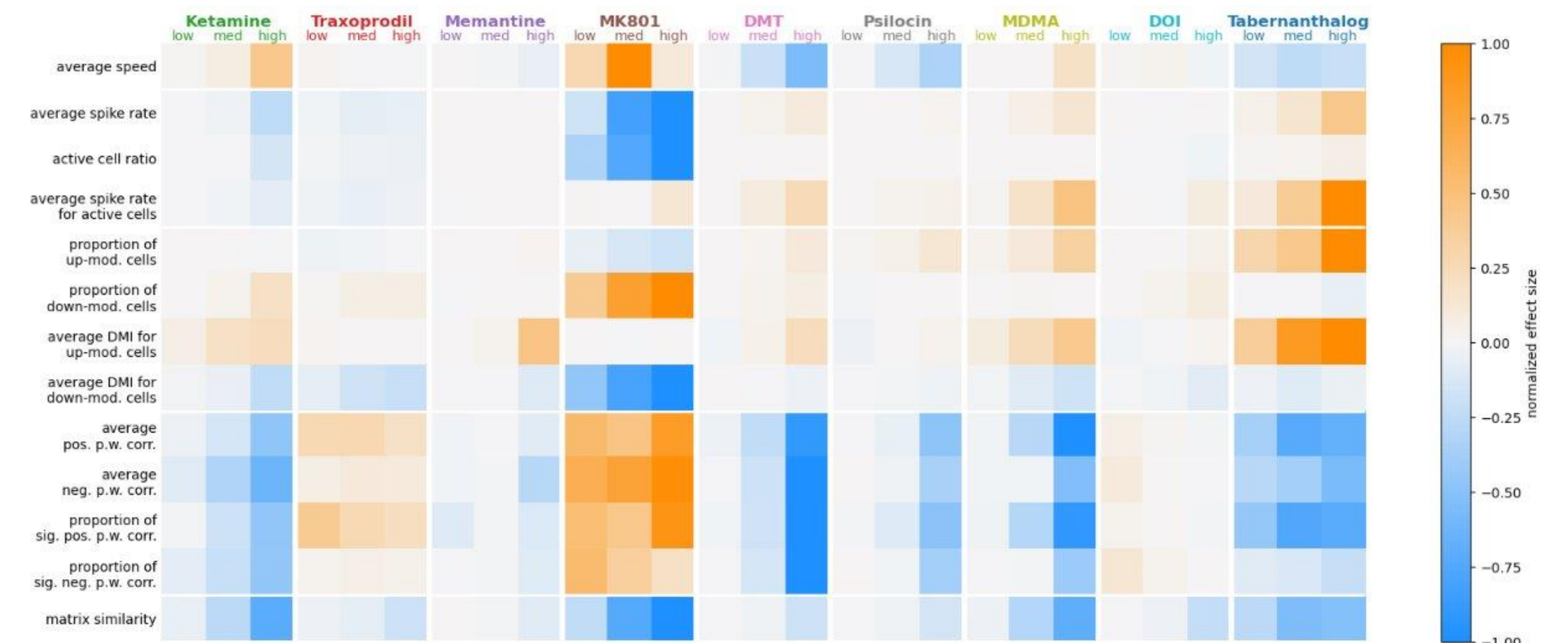


### Distinguishing Dose and MoA among compounds



## Compound reference library

### Effect size summary table of tested reference compounds



## Key findings and Research outlook

- Neurobehavioral fingerprint comparisons are more sensitive than traditional behavioral assays in distinguishing MoA and dose between different compounds.
- We have used these metrics as features for an unsupervised modeling approach with Principal Component Analysis. The PCA plot reveals distinct clustering patterns.
- The drugs form distinct clusters within the PCA space, with doses of the same drug, such as ketamine, showing a coherent trajectory, indicating a dose-dependent relationship in neural metric alteration.
- Conversely, Rapastinel's lack of separation from the vehicle control suggests negligible impact on the neural metrics, corroborating clinical trial findings.

