The effect of systemic ketamine on working memory history dependencies

Working memory (WM) responses in primates are attracted to immediate prior stimuli (serial dependence) and to the mean of the long-term distribution of stimuli (long-term history dependence). It has been shown that WM attractive serial dependence is reduced in people with schizophrenia or autoimmune anti-NMDAR encephalitis, diseases linked to hypofunctional NMDARs[1,2], and in autism, while people with dyslexia show instead a reduction in long-term history dependence[3]. These distinct patterns across brain disorders underscore the relevance of understanding the mechanisms of WM history-dependent biases.

Here, we study the mechanisms underlying WM serial and long-term history dependence in four macaque monkeys performing a biased visuospatial oculomotor delayed response task. In each session, stimuli followed a bimodal Gaussian distribution, with two diametrically opposed mode locations, which varied by session. In some sessions, monkeys were administered ketamine, an NMDAR antagonist, systemically.

We used linear models to assess the serial and long-term history dependence of the monkeys' responses. Surprisingly, monkeys exhibited mostly repulsive serial and long-term history biases. Ketamine reduced repulsive serial dependence but increased repulsive long-term history bias, suggesting distinct mechanisms for the two processes.

Moreover, to investigate candidate circuit mechanisms, we trained excitatory–inhibitory recurrent neural network models to perform the same task under identical stimulus statistics. The models incorporated biophysically motivated mechanisms, including adaptation, synaptic plasticity, and NMDA receptor–mediated currents. To mimic the effects of ketamine, we perturbed the trained networks by removing NMDA currents and reducing adaptation. Simulations of the behavioral task with these perturbed networks reproduced the differential effects of ketamine on serial and long-term history dependence, providing a mechanistic hypothesis for the distinct effects of ketamine on these two forms of working memory bias.

1 Stein, H. *et al. Nat. Commun.* 11, 4250 (2020).

2 Bansal, S. et al. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* (2023)

3 Lieder, I. et al. *Nat. Neurosci.* 22, 256–264 (2019)

Working memory (WM) responses in primates are biased toward recent stimuli (serial dependence) and toward the mean of the long-term stimulus distribution (long-term history dependence). In humans, attractive serial dependence is reduced in schizophrenia and autoimmune anti-NMDAR encephalitis, conditions linked to NMDAR hypofunction, and in autism, whereas dyslexia is associated with reduced long-term history dependence. These distinct

patterns highlight the importance of identifying the mechanisms underlying WM history-dependent biases.

Here, we study the mechanisms underlying WM history dependence in four macaque monkeys performing a biased visuospatial oculomotor delayed response task. Within each session, stimuli were drawn from a bimodal Gaussian distribution with two diametrically opposed modes that varied across sessions. In a subset of sessions, monkeys received systemic ketamine, an NMDAR antagonist.

Using linear models, we quantified serial and long-term history dependence in behavioral responses. Contrary to prior findings in humans, monkeys exhibited predominantly repulsive serial and long-term history biases. Ketamine reduced repulsive serial dependence while increasing repulsive long-term history bias, indicating that these two forms of WM history dependence rely on distinct mechanisms.

To probe candidate circuit mechanisms, we trained excitatory–inhibitory recurrent neural network models to perform the same task under identical stimulus statistics. The models incorporated biophysically motivated mechanisms, including neuronal adaptation, synaptic plasticity, and NMDA receptor–mediated currents. To mimic ketamine, we perturbed trained networks by removing NMDA currents and reducing adaptation. Simulations reproduced the opposing effects of ketamine on serial and long-term history dependence, providing a mechanistic account of how NMDAR hypofunction differentially alters these two WM biases.