The effect of systemic ketamine on working memory history dependencies

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Working memory (WM) representations in humans and monkeys are attracted to the immediate prior stimuli (serial dependence) but repulsed away from the long-term distribution of stimuli (history dependence). Recently, it has been shown that WM attractive serial dependence is reduced in patients with schizophrenia or autoimmune anti-NMDA receptor encephalitis - two symptomatically related diseases linked to hypofunctional NMDA receptors[1,2]. In contrast, people with dyslexia show a reduction in history biases while serial dependence is unaffected[3]. These distinct patterns across disorders offer valuable insights into the neural and biophysical mechanisms underlying WM processes, which remain unclear.

Here, we study the mechanisms underlying WM serial and history dependence in four male and female macaque monkeys performing a biased oculomotor delayed response task (biased-ODR). In each session, stimuli followed a bimodal Gaussian distribution, with two diametrically opposed reference locations, which changed from session to session. We recorded the neural activity of prefrontal neurons in two monkeys using acute recordings (with 128-contact Diagnostic Biochips probes). In some sessions, monkeys were administered ketamine, an NMDA receptor antagonist.

We used linear models to assess the serial and history dependence of the monkeys' saccadic responses, and their dependence on ketamine. Surprisingly, monkeys did not exhibit attractive, but mostly repulsive serial and history biases when these were combined. Ketamine reduced repulsive serial dependence but increased repulsive history bias. Moreover, we used neural population decoders to predict the stimulus location from prefrontal neural activity and analyzed the relationship between the decoded locations and the responses of the monkeys. Our analyses suggest that different mechanisms underlie serial dependence and history biases in the prefrontal cortex, based on their inverse modulation by systemic NMDAR disruption, and the close correspondence between decoding errors from prefrontal populations and behavioral errors in the task. These results have strong implications for attractor model simulations that implement serial dependence[1] and history effects[4] based on biophysically plausible NMDAR-dependent mechanisms.

Refs:

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