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Manuscript Title: Interviewing Mice and the Functions of Striatal Dopamine

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Schmack, K., Bosc, M., Ott, T., Sturgill, J. F. & Kepecs, A. Striatal dopamine mediates hallucination-like perception in mice. *Science.* 2021; DOI: https://doi.org/10.1126/science.abf4740

Clinical pharmacology indicates a role for dopaminergic neurotransmission in the pathophysiology of hallucinations, defined as perceptions without external stimuli. Schmack et al.[1] investigated dopaminergic modulation of perception with a clever task eliciting "hallucination-like percepts" (HALIPs) in mice. Trials consisted of light flashes that, on half of trials, were paired with variable intensity tones against a continuous white noise background. Mice reported tone presence or absence by nose-poking one of two ports to receive rewards. Responses to anticipated but absent stimuli had previously been used to model hallucinations in pre-clinical models. A critical insight by Schmack et al. was to deliver rewards at variable latencies, allowing them to estimate the mouse's confidence in false percepts. HALIPs were inferred as high-confidence "false alarms" – erroneous tone reporting with an extended wait for unforthcoming reward. Errors in which mice mistakenly reported the absence of a present tone were captured as "misses." Sub-anesthetic ketamine administration increased HALIPs, and a comparable human task showed correlations between hallucination frequency and high-confidence false alarms.

The background is a Bayesian model of expected outcomes (Priors) that are updated after each trial and may override sensory input. In a formal computational model, Schmack et al. distinguished two types of Priors – one for perception and one for reward. Strong perceptual vs reward Priors predicted different effects on "false alarms" and "misses."

Schmack et al. assessed dopaminergic neurotransmission in ventral (VS; reward region) and posterior striatum (PS; perception region) using $GRAB_{DA}$. $GRAB_{DA}$ is a conjugate of a human dopamine receptor with a green fluorescent protein (GFP) derivative, which fluoresces upon dopamine binding. The investigators measured dopamine-induced $GRAB_{DA}$ fluorescence on a subsecond timescale through an optical fiber implanted in VS or PS ("fiber photometry"). Elevated pre-trial VS dopamine corresponded with increased "misses" and HALIPs, consistent with over-riding reward expectation - overconfidence in tone absence or presence. Pre-trial PS dopamine elevation was associated with decreased misses and increased HALIPs, consistent with over-riding perceptual expectation - overconfidence in tone presence. Optogenetic stimulation of PS dopamine release confirmed a causal role for PS dopamine in HALIP generation.

Pioneering work from Wolfram Schultz and others indicates that stimulus-reward locked phasic dopamine release signals reward prediction errors (RPEs) for reinforcement learning[2]. Recent work indicates that dopaminergic signals also update internal representations for motor control[3]. In contrast to canonical RPE signals, Schmack et al. observed gradual pre-trial striatal dopamine increases that signal information about Priors. Similarly, VS dopamine "ramps" are associated with reward expectation during instrumental tasks[4]. These data indicate the importance of non-phasic dopaminergic

signaling and suggest that dopamine has parallel roles across cognitive, motor, and sensory domains.

What information does non-phasic dopamine signaling convey across striatal subregions? Can these functions be condensed into a single dopamine "law"[5]? Can differences be leveraged to selectively modulate dopaminergic influences across behavioral domains? Can motor function be improved without worsening psychosis, and vice versa? Schmack et al. provide an essential tool for exploring these questions – a model in which mice can be asked reliably if they are "hearing things."

1. Schmack K, Bosc M, Ott T, Sturgill JF, Kepecs A. Striatal dopamine mediates hallucination-like perception in mice. Science 2021; **372**
2. Schultz W. Recent advances in understanding the role of phasic dopamine activity. F1000Res 2019; **8**
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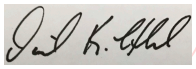

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Exhibit A

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