A Perceptual Inference Mechanism for Hallucinations Linked to Striatal Dopamine

Highlights
- Auditory hallucinations are linked to a perceptual bias toward uncertain expectations
- Elevated striatal dopamine function relates to the same pattern of perceptual bias
- Volume of dorsal anterior cingulate relates to the same pattern of perceptual bias

Authors
Clifford M. Cassidy, Peter D. Balsam, Jodi J. Weinstein, ..., Nathaniel D. Daw, Anissa Abi-Dargham, Guillermo Horga

Correspondence
horgag@nyspi.columbia.edu

In Brief
Cassidy et al. induced auditory illusions to test a dopamine-dependent cognitive mechanism for hallucinations. Unmedicated schizophrenia patients with auditory hallucinations perceived tone durations in a way similar to what was expected, even when expectations were imprecise, and this perceptual bias related to excess dopamine function.
A Perceptual Inference Mechanism for Hallucinations Linked to Striatal Dopamine

Clifford M. Cassidy,1,5 Peter D. Balsam,1,3 Jodi J. Weinstein,1,4 Rachel J. Rosengard,1 Mark Slifstein,4 Nathaniel D. Daw,5 Anissa Abi-Dargham,1,4 and Guillermo Horga1,6,*

1Department of Psychiatry, New York State Psychiatric Institute, Columbia University Medical Center, 1051 Riverside Drive, New York, NY 10032, USA
2The Royal’s Institute of Mental Health Research, University of Ottawa, 1145 Carling Avenue, Ottawa, ON K1Z 7K4, Canada
3Department of Psychology, Columbia University, 3009 Broadway, New York, NY 10027, USA
4Department of Psychiatry, Stony Brook University, 100 Nicholls Road, Stony Brook, NY 11794, USA
5Department of Psychology, Princeton University, South Drive, Princeton, NJ 08540, USA
6Lead Contact
*Correspondence: horga@nyspi.columbia.edu

SUMMARY

Hallucinations, a cardinal feature of psychotic disorders such as schizophrenia, are known to depend on excessive striatal dopamine. However, an underlying cognitive mechanism linking dopamine dysregulation and the experience of hallucinatory percepts remains elusive. Bayesian models explain perception as an optimal combination of prior expectations and new sensory evidence, where perceptual distortions such as illusions and hallucinations may occur if prior expectations are afforded excessive weight. Such excessive weight of prior expectations, in turn, could stem from a gain-control process controlled by neuromodulators such as dopamine. To test for such a dopamine-dependent gain-control mechanism of hallucinations, we studied unmedicated patients with schizophrenia with varying degrees of hallucination severity and healthy individuals using molecular imaging with a pharmacological manipulation of dopamine, structural imaging, and a novel task designed to measure illusory changes in the perceived duration of auditory stimuli under different levels of uncertainty. Hallucinations correlated with a perceptual bias, reflecting disproportionate gain on expectations under uncertainty. This bias could be pharmacologically induced by amphetamine, strongly correlated with striatal dopamine release, and related to cortical volume of the dorsal anterior cingulate, a brain region involved in tracking environmental uncertainty. These findings outline a novel dopamine-dependent mechanism for perceptual modulation in physiological conditions and further suggest that this mechanism may confer vulnerability to hallucinations in hyper-dopaminergic states underlying psychosis.

INTRODUCTION

Perception is an inherently subjective process that is biased by beliefs acquired through experience [1]. Whereas these biases can adaptively facilitate disambiguation of noisy sensory stimuli, they can also confer a predisposition to perceptual distortions (for instance, the common perception of a cell phone vibrating in the pocket in the absence of true vibration) [2]. Patients with schizophrenia often experience extreme and maladaptive perceptual disturbances such as hearing voices in the absence of true speech stimuli. Such auditory hallucinations and other cardinal psychotic symptoms respond to antidopaminergic treatment [3], worsen with prodopaminergic drugs [4, 5], and their severity—beyond a categorical diagnosis of schizophrenia—correlates with excessive dopamine release in the associative striatum [6, 7]. However, the mechanism through which dopamine excess leads to hallucinations remains unknown [3].

Beyond their role in reinforcement learning [9–11], neuromodulators, including dopamine, have been proposed to contribute to experience-dependent sensory learning [12–14]. Specifically, Bayesian models posit that perception results from an optimal integration of bottom-up sensory evidence and top-down sensory predictions or priors [15]. Such integration depends on the precision of these top-down sensory predictions (mathematically defined as the inverse of the variance of the prior and more intuitively related to the confidence or certainty of expectations) [15–18], a key variable thought to be encoded by neuromodulators such as dopamine [18]. Under this Bayesian framework (Figures 1D and 1E), perceptual biases toward context-dependent predictions may explain sensory illusions [19, 20] and, in extreme cases, hallucinatory percepts [21, 22]: dopamine dysregulation could lead to faulty signaling of the precision of predictions, with systematic overconfidence in the predictions resulting in disproportionate perceptual biases toward expected states [17, 18, 23]. Importantly, under this model of hallucinations [17, 23–25], perceptual biases in psychosis would be even more apparent in highly uncertain contexts (i.e., in situations that should normally lead to imprecise predictions and hence weaker top-down predictions), an assumption that remains to be tested. Note that, according to some models, this pattern of...
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