HHS Public Access

Author manuscript

JAMA Psychiatry. Author manuscript; available in PMC 2023 July 28.

Published in final edited form as:

JAMA Psychiatry. 2022 January 01; 79(1): 75–76. doi:10.1001/jamapsychiatry.2021.3200.

Computational Psychiatry Across Species to Study the Biology of Hallucinations

Katharina Schmack, MD, PhD,
Francis Crick Institute, London, United Kingdom

Division of Psychiatry, University College London, London, United Kingdom

Torben Ott, PhD,
Department of Psychiatry, Washington University School of Medicine in St Louis, St Louis, Missouri

Department of Neuroscience, Washington University School of Medicine in St Louis, St Louis, Missouri

Adam Kepecs, PhD
Department of Psychiatry, Washington University School of Medicine in St Louis, St Louis, Missouri

Department of Neuroscience, Washington University School of Medicine in St Louis, St Louis, Missouri

Challenges in the Biological Study of Psychiatric Disorders

Progress in the treatment of severe psychiatric disorders has been slow, despite remendous advances in neuroscience. In other fields of medicine, the prognosis of many previously devastating disorders has improved thanks to new treatments that were developed based on biological insights gained in animal models. In breast cancer, for example, the study of estrogen receptors in tumors growing in rodents paved the way to novel hormonal therapies. Modeling disease in animals starts with a hypothesized biological dysfunction (eg, uncontrolled cell proliferation) that is inducible by experimental manipulations (eg, carcinogen exposure) and results in quantifiable manifestations (eg, tumor growth). Psychiatric disorders, however, have been challenging to model in animals.

Psychiatric disorders are hypothesized to arise from biological dysfunctions in neural circuits, and neural circuits are increasingly amenable to experimental manipulations in animals. However, psychiatric disorders manifest themselves primarily through subjective experiences that are challenging to objectively quantify. The challenge of objectively capturing subjective experiences, especially across species, remains a critical gap for progress on new treatments for psychiatric disorders.

Corresponding Author: Katharina Schmack, MD, PhD, Francis Crick Institute, One Midland Road, London NW1 1AT, United Kingdom (katharina.schmack@crick.ac.uk).
Additional Contributions: We thank Anissa Abi-Dargham, MD, Stony Brook University, and Daniel Mamah, MD, MPE, Washington University, for their comments. They were not compensated for their contributions.

Animals cannot verbally report their subjective experiences; thus, researchers must infer them through observation of behavior. Rodent studies in psychiatry have typically inferred psychiatric symptoms from low-dimensional phenotypes that are impaired in human patients (eg, decreased prepulse inhibition) or altered through interventions known to induce symptoms in humans (eg, phencyclidine-induced hyperlocomotion).While these phenotypes can be successful for screening drug candidates,[1,2] they do not connect subjectively experienced symptoms with a hypothesized neural circuit process. Consequently, these phenotypes may probe auxiliary processes not directly relevant to the psychiatric condition, and it is unclear how to move on from translational failures other than by trial and error.

We argue that these limitations of translational psychiatric research can be overcome using a computational approach to psychiatry.[3] Our approach rests on the idea that neural circuits instantiate computations that underlie both subjective experience and observable behavior. Consequently, neural circuit dysfunctions lead to maladaptive computations that manifest as both altered behavior and altered subjective experience, including psychiatric symptoms(Figure, A). Appropriately designed behavioral tasks combined with principled computational models can capture neural circuit computations across species. We can then associate behavioral-computational measures with psychiatric symptoms in humans and probe the underlying neural circuits in animals. We propose that this computational approach to psychiatry can provide a path forward for scientific inquiry. We will illustrate this approach using our recent study[4] that modeled hallucination-like experiences in humans and mice (Figure, B).

A Computational Psychiatry Approach to Capture Hallucinations Across Species

Hallucinations are false percepts that are typically experienced with similar confidence as true percepts. We reasoned that hallucinations result from a dysfunction in neural circuits that transform sensory stimuli into percepts with confidence.[4] We designed a perceptual detection task with confidence reports that can be similarly performed by humans[5] and rodents.[6] In this task, humans and mice report whether they hear an auditory signal embedded in noise and indicate how confident they are in their decision. Humans press 1 of 2 buttons to report whether they heard a signal, whereas mice poke into 1 of 2 choice ports. Humans report their confidence by positioning a cursor on a slider; mice express their confidence by investing variable time durations to earn a reward.[6] We defined hallucination-like percepts (HALIPs) as high-confidence incorrect reports that a signal was present.

Our rationale was that experimentally controlled HALIPs are produced by a neural circuit shared with spontaneously experienced hallucinations in psychosis and can therefore be used as a translational measure of psychotic symptoms. Importantly, this computational psychiatry approach is amenable to systematic testing. If overlapping neural circuit computations mediate spontaneous hallucinations and HALIPs, these 2 should be correlated with each other and inducible by the same manipulations. We found in humans HALIPs that were specifically correlated with the self-reported tendency for hallucinations outside

the task (Figure, B) and in mice HALIPs that were selectively increased by ketamine, a drug known to induce psychosis-like experiences. We also established HALIPs were quantitatively explained by the same computational algorithm in humans and mice, supporting its use as a translational marker across species.

In mice, we could use state-of-the-art technologies for monitoring and controlling neural circuits to understand what happens during HALIPs. We delivered genetic sensors and actuators for dopamine and implanted optical fibers into different regions of the striatum. In the sensory striatum, we found that dopamine levels rose just before HALIPs; optogenetically stimulating dopamine release led to more HALIPs, and this was reversed by the antipsychotic drug haloperidol (Figure, B). Our computational model showed that HALIPs occur when expectations about upcoming sensory signals are high. We suggest that increased striatal dopamine biases perception to rely more on expectations, conveyed by auditory cortex, compared with sensory input, signaled by thalamic inputs, thereby producing hallucinations.

Caveats and Future Directions for Biological Study of Hallucinations

It is natural to wonder whether mice subjectively experience hallucinations. We think that while this question is intellectually fascinating, it is not a fruitful subject of scientific inquiry because it is unresolvable in principle. Hallucinations are by definition private experiences: even in people, one can never be certain whether another individual is hallucinating. In our view, the critical question is whether our measure of hallucination-like perception in mice will be useful for advancing the treatment of hallucinations in patients. While only future studies can answer this question, we are excited about the clear path opened by our new cross-species approach. The next critical steps will be to test whether our approach anticipates hallucinations and treatment responses in patients with psychosis.

One might further argue that the role of dopamine in psychosis was already known based on the dopamine-antagonistic properties of antipsychotic drugs and molecular imaging studies in patients.[7] Indeed, the well-established role of dopamine in psychosis is precisely the reason why we selected striatal dopamine as an entrypoint for our circuit studies of hallucinations. However, it has been unclear by what mechanisms dopamine could give rise to hallucinations. The approach we presented unlocks the arsenal of neuroscience to generate and test hypotheses. By probing neural circuit mechanisms of how changes in dopamine produce hallucinations, we hope to pave the way for mechanistic antipsychotic treatments, improving on the limitations of dopamine-antagonistic drugs.

Conflict of Interest Disclosures:

The authors report support from Leopoldina-German Academy of Sciences (fellowship LDPS 2010-03 [Dr Schmack]), German Research Foundation (grant OT 562/1-1 [Dr Ott]), and the National Institutes of Health (grants MH097061 and DA038209 [Dr Kepecs]).

REFERENCES

1. Dedic N, Jones PG, Hopkins SC, et al. SEP-363856, a novel psychotropic agent with a unique, non-D_2 receptor mechanism of action. J Pharmacol Exp Ther. 2019;371(1):1–14. doi:10.1124/jpet.119.260281 [PubMed: 31371483]
2. Koblan KS, Kent J, Hopkins SC, et al. A non-D2-receptor-binding drug for the treatment of schizophrenia. N Engl J Med. 2020;382(16): 1497–1506. doi:10.1056/NEJMoa1911772 [PubMed: 32294346]
3. Montague PR, Dolan RJ, Friston KJ, Dayan P. Computational psychiatry. Trends Cogn Sci. 2012;16(1):72–80. doi:10.1016/j.tics.2011.11.018 [PubMed: 22177032]
4. Schmack K, Bosc M, Ott T, Sturgill JF, Kepecs A. Striatal dopamine mediates hallucination-like perception in mice. Science. 2021;372(6537): eabf4740. doi:10.1126/science.abf4740
5. Sanders JI, Hangya B, Kepecs A. Signatures of a statistical computation in the human sense of confidence. Neuron. 2016;90(3):499–506. doi:10.1016/j.neuron.2016.03.025 [PubMed: 27151640]
6. Masset P, Ott T, Lak A, Hirokawa J, Kepecs A. Behavior- and modality-general representation of confidence in orbitofrontal cortex. Cell. 2020;182 (1):112–126.e18. doi:10.1016/j.cell.2020.05.022 [PubMed: 32504542]
7. Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, Abi-Dargham A. Pathway-specific dopamine abnormalities in schizophrenia. Biol Psychiatry. 2017;81(1):31–42. doi:10.1016/j.biopsych.2016.03.2104 [PubMed: 27206569]

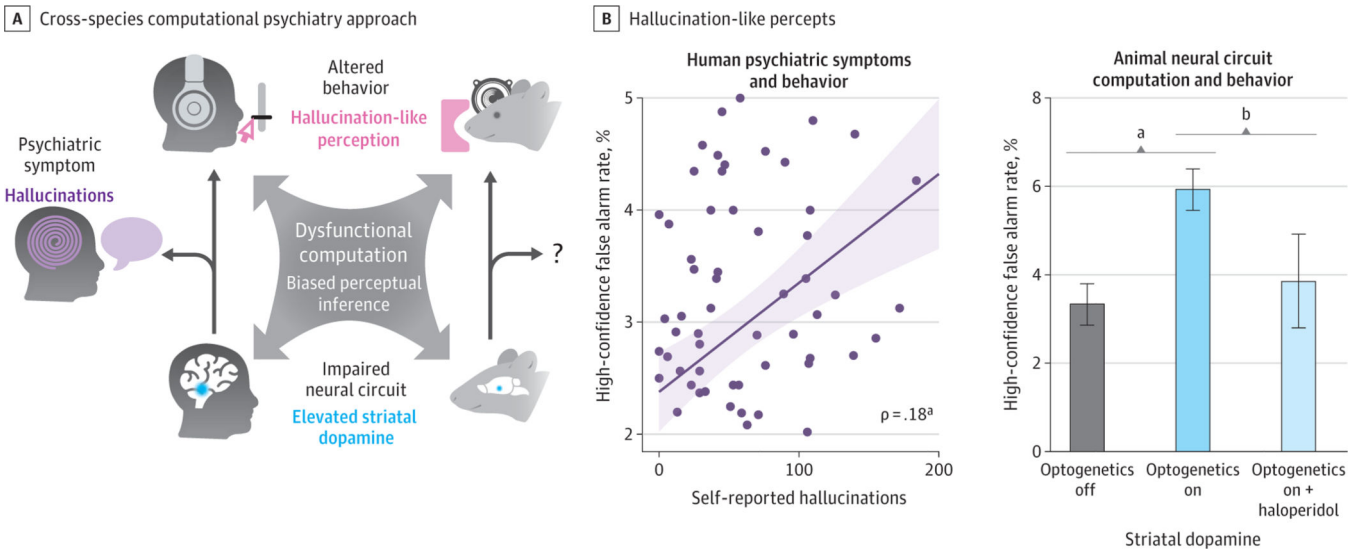

Figure.

Computational Psychiatry Across Species to Probe the Neural Circuitry Underlying Hallucinations

A, Cross-species computational psychiatry approach connects psychiatric symptoms with neural circuits. Impaired neural circuits perform dysfunctional computations that give rise to psychiatric symptoms as well as to altered observable behavior. Appropriately designed, task-based behaviors (hallucination-like perception) can identify dysfunctional computations (perceptual inference) underlying psychiatric symptoms in humans (hallucinations) and enable access to the underlying neural circuit across species (striatal dopamine). B, Hallucination-like percepts are defined as high-confidence false alarms in a detection task for humans and mice (middle). Hallucination-like percepts are associated with hallucinations in humans and mediated by increased striatal dopamine in mice.

[a] $P < .01$.

[b] $P < .05$.