

Dispatch

Sensory Neuroscience: Linking Dopamine, Expectation, and Hallucinations

Psychosis is associated with a dysregulation of the brain's dopamine-mediated neurotransmitter system. Yet, specific mechanisms underlying psychotic symptoms are not well understood. A new study has now uncovered a dopamine-dependent mechanism that explains why psychotic patients experience hallucinations.

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Hallucinations — e.g., hearing voices or seeing objects that are not there — are a central characteristic of psychotic disorders such as schizophrenia. The fact that our perceptual systems are able to generate full-blown percepts in the absence of a causative stimulus is bewildering. Yet, insights about healthy brain function suggest that the potential to experience hallucinations is deeply rooted in how our perceptual systems work. Lay people often believe that the way in which we hear a sentence or see an object is analogous to a recorder registering sound or a camera taking pictures. Yet, registering sensory inputs is the mere starting point for perception. When you see a car driving by or hear your name being called out at a party, your eyes and ears feed highly ambiguous and underspecified information to your brain's visual and auditory systems. Before this input is transformed into a meaningful percept, it is fed through a host of information-processing stages and, critically, it is combined with the expectation about the world that you already hold

based on previous interactions with the environment. In short, the percepts we experience do not exclusively rely on sensory input but on a combination of input and already-existing expectation [1–3], an insight that sensory neuroscience often formalizes in Bayesian computational models. The relative contribution of sensory input and prior expectation to the final percept is determined by their respective reliability: when you have a very strong and reliable expectation about what to perceive, sensory information is weighted less strongly, and vice versa. Within this framework, hallucinations can be explained as an undue weighting of expectation, to an extreme point where a percept is solely determined by what one expects [4–7]. A recent, comprehensive study [8] reported in this issue of *Current Biology* by Cassidy *et al.* now links this undue reliance on prior expectation in hallucinations to a specific mechanism mediated by excessive amounts of the neurotransmitter dopamine in the striatum, a subcortical brain region.

Drugs that alleviate psychotic symptoms such as hallucinations — so-called antipsychotics — were discovered by serendipity, and it was research into how such drugs act on the brain that initially led to the dopamine hypothesis of psychosis: the idea that the underlying brain pathology in psychosis can be attributed to hyperactivity of dopamine mechanisms, in particular, in the striatum [9,10]. The dopamine hypothesis has been the leading explanatory framework for understanding psychosis for several decades, and it is one of the most enduring ideas in neuropsychiatry in general. Yet, despite decades of clinical research, and despite the link between excessive dopamine release in the striatum and psychosis being well-established, our understanding of the mechanisms that translate this

dopamine excess into specific symptoms such as hearing voices is, at best, patchy.

Hallucinations are exceedingly difficult to study in the lab because they are subjective by nature, and because their unpredictable occurrence makes it difficult to embed them in a well-balanced experimental design. Based on the above-mentioned framework of perception, Cassidy and colleagues [8] circumvented these difficulties by focusing on simple, perceptual phenomena that are closely linked to hallucination but are amenable to experimental manipulation. In their behavioral paradigm, participants were asked to judge the length of a target tone by clicking on a button to reproduce it (Figure 1). This target tone was preceded by a number of context tones, which, in three different conditions, were on average slightly shorter, the same length, or slightly longer than the target tone. The context tones thus set up an expectation in the participant of hearing tones of a certain length, which biases subsequent perception of the target tone. For instance, after having heard several short context tones, most participants perceived the target tone to be shorter compared to when they had heard several long context tones, and vice versa. Critically, as mentioned above, the influence of expectation on perception in health is dictated by how strong or reliable the expectation is. Cassidy and colleagues [8] manipulated this aspect by changing the variability of the context tones. In two conditions, context tones had the same average length but differed with respect to their variability: all context tones were either the same length or fluctuated around the mean. The resulting expectation is thus either reliable or, comparatively, less reliable, respectively. In healthy participants, the influence of expectation on perception was modulated by this manipulation: the perceptual bias

that was induced by the context tones was less strong in the condition with high variability compared to the one without. This finding indicates that when generating percepts, the auditory system of healthy individuals weights the influence of expectation on perception according to its reliability.

A different pattern emerged in (unmedicated) individuals with schizophrenia: the higher the patients' hallucination severity, the stronger was the biasing effect of expectation on perception; moreover, the reliability of the expectation had little or no modulatory influence on this bias. This finding suggests that hallucination severity is related to an overestimation of the reliability of expectation, which is thus given undue influence on perception. To study the role of dopamine in this process, a subsample of participants was given a low dose of amphetamine, which leads to an increase in the brain's dopamine levels and can, under some circumstances, induce experiences similar to some of those faced by individuals with schizophrenia [10].

Participants, whose perception had previously been sensitive to the reliability of their expectation, became less sensitive after this pharmacological challenge.

Moreover, the amount of striatal dopamine release as measured by Positron-Emission Tomography (PET) was related to a reduction in the sensitivity to the expectation's reliability. In other words, the more dopamine a participant's brain generated, the less their auditory system down-weighted the influence of expectation when its reliability was low. Together, the findings suggest that excess of striatal dopamine leads to an overestimation of the reliability of expectation. This process disturbs the flexible integration of expectations into perceptual experience, which might ultimately lead to hallucinatory percepts.

In both psychiatry and neurology, biologically heterogeneous syndromes with potentially different pathophysiological mechanisms are sometimes grouped into the same diagnostic category; this may hamper our attempts to understand the biological underpinnings of brain disorders **(Au: reference 11 seems to have been skipped)** [12]. As a response, there has been a general move within translational neuroscience in recent years to study pathophysiological mechanisms independent of, and beyond diagnostic labels. Cassidy and colleagues [8] follow this trend, demonstrating that their findings are specifically related to hallucinatory experiences rather than the categorical diagnosis of schizophrenia. This is an intriguing result because hallucinations are associated with a range of psychiatric, neurological, and ophthalmologic disorders [13]. It is therefore tempting to ask whether hallucinations in some or, potentially, in all of these diagnostic categories are underpinned by a similar mechanism.

A similarly intriguing question relates to the link between delusions and those mechanisms underlying hallucinations described by Cassidy and colleagues [8]. Delusions are beliefs that are often bizarre, held with strong conviction, and are resistant to change even in the face of compelling evidence to the contrary. Alongside hallucinations, they form the second core characteristic of psychosis. Interestingly, theories of delusions also invoke the role of striatal dopamine in coding confidence and uncertainty [14–16] — albeit during learning and belief formation, not perception — adopting explanations that appear similar on both a functional and neuro-pharmacological level to that proposed for hallucinations in the Cassidy study

[8]. A picture thus seems to emerge that highlights potentially important mechanistic relationships between hallucinations and delusions [15]. In fact, recent studies already provide evidence suggesting complex interactions between the mechanisms underlying these two symptom clusters [17,18].

Ultimately, it seems clear that no single mechanism will ever fully explain the unusual and distressing experiences faced by psychotic individuals [15,19]. Progress in our understanding and treatment of psychosis will necessarily have to span various explanatory levels including genetic, neuro-pharmacological, psychological, and social aspects. The study by Cassidy and colleagues [8] provides an important step in this direction by linking a psychological/functional model of hallucinations to a specific neuro-pharmacological mechanism.

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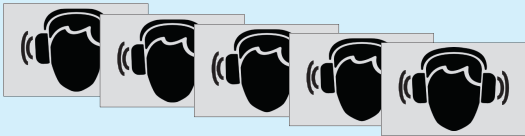
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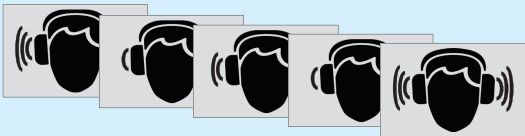
Figure 1. **(Au: Please add title for figure)**

In two conditions, participants heard context tones that were the same length on average but differed in their variability. A consistent context of short tones leads to a strong expectation to hear another short tone during test. This expectation biases perception such that a longer tone is perceived as shorter than it actually is. A variable context of tones (which are short on average) leads to a weak expectation, which has little or no biasing influence on perception during test.

Consistent context = strong expectation of short tone



Variable context = weak expectation of short tone



Test: long tone is perceived as shorter than it is



Test: long tone is perceived unbiased

